W22: Management of Fecal Incontinence from Bench to Bedside

Workshop Chair: Donna Bliss, United States
12 September 2017 15:30 - 17:00

Start	End	Topic	Speakers
15:30	15:35	Welcome and Overview	Donna Bliss
15:35	15:50	Conservative/Lifestyle/Self Management	Donna Bliss
15:50	16:05	Behavioural Therapies	Julia Herbert
16:05	16:10	Questions	Donna Bliss Julia Herbert
16:10	16:30	Surgical Approaches	Holly E. Richter
16:30	16:50	Cell-Based Therapies	Massarat Zutshi
16:50	17:00	Questions	Holly E. Richter Massarat Zutshi

Speaker Powerpoint Slides

Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website www.ics.org/2017/programme Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

This workshop will provide a comprehensive overview of current approaches for managing fecal incontinence (FI) from bench to bedside. It will explain progress in developing cutting-edge cell-based therapies for FI and provide the latest evidence about behavioral and conservative management strategies as well as surgical modalities. The session will focus on adults and incorporate findings and recommendations of the ICI6-ICS consultation.

Learning Objectives

At the end of the session, the participant will be able to:
1. Examine the different types of behavioral therapies and conservative and self management strategies for fecal incontinence (including devices such as an anal plug, anal insert, and vaginal bowel device). Review their evidence, strengths, and limitations, and impact of managing FI on daily life.
2. Discuss the indications and efficacy of surgical procedures in treating fecal incontinence, including sphincter repair, sacral neuromodulation, sphincter replacement and implantable sphincter enhancement device-good with this.
3. Discuss advances in cell-based therapies for fecal incontinence and consequences of their use.

Learning Outcomes

1. Understand the impact of managing fecal incontinence (FI) on daily life.
2. Understand that conservative/self management and behavioral therapy (i.e., non-surgical approaches) of FI are the initial strategies.
3. Understand the role of surgery including sphincter repair and sacral neuromodulation (SNM) as well as other new modalities such as an implantable sphincter and a new device to enhance sphincter function in the treatment of FI.
4. Appreciate the exciting new cell-based therapy approach for FI and future possibilities for their use in treatment.

Target Audience

Physicians, Nurses and Physiotherapists interested in the latest evidence about comprehensive therapies for fecal incontinence

Advanced/Basic

Basic

Suggested Reading

Bliss DZ, Mimura T, Berghmans B, Bharucha A, Chiarioni, G, Emmanuel, A, Maeda Y, Peden-McAlpine, C, Northwood, M., Rafiee H, Rockwood T, Santoro, G, Taylor S, Whitehead W. Assessment and conservative management of faecal incontinence and quality of life in adults. In P. Abrams, L. Cardoso, S. Khoury, & A. Wein (Eds.), Incontinence (6th ed.). In press. Bristol, UK: International Continence Society.

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Salcedo L, Penn M, Balog B, Damaser, Zutshi M. Functional outcome after anal sphincter injury and treatment with mesenchymal stem cells. Stem Cell Trans Med. 3:760-777.

Thaha MA, Abukar AA, Thin NN, Ramsanahie A, Knowles CH. Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database Systematic Reviews. 2015;8.Art. No.: CD004464. DOI: 10.1002/14651858.CD004464.pub3.

This workshop will provide a comprehensive overview of current approaches for managing fecal incontinence (FI) from conservative management and behavioral therapies to surgical approaches. It will also review the latest work in cellular therapies targeted to fecal incontinence.

Conservative Management: Lifestyle

Donna Z. Bliss, PhD, RN, FGSA, FAAN, Professor of Nursing and Nursing Research, University of Minnesota School of Nursing, United States

Fecal incontinence is a type of bowel leakage associated with emotional distress, reduced quality of life, and often other problems such as odor and skin damage. Management of fecal incontinence among community-living adults begins with conservative or symptom management approaches unless surgery is indicated. Central to conservative management is a focused assessment of lifestyle and previous self-management activities to assess whether they improve or exacerbate leakage and need modification. This session will review the latest evidence, recommendations and algorithm for conservative management of fecal incontinence of adults living in the community per the recent ICS-ICI6 review. Content is applicable to primary care or generalist healthcare providers who are frequently the first contact for conservative management.

Conservative management of fecal incontinence includes ascertaining a patient's goals for therapy, inquiring about self-management strategies tried, and potentially lifestyle modifications. Studies have revealed a need for improved incontinence-related literacy for the patient and possibly a family caregiver; therefore, education about bowel function, leakage, and available interventions is important part to engage the patient in the conservative management plan. Patients also need information about advances in and selecting absorbent products aimed at containing bowel leakage while reducing associated skin problems. Studies have tested patient education strategies to improve knowledge and use of recommended therapies.

Regarding lifestylefocused strategies, recent studies have reported beneficial effects of diet/dietary fiber and rectal emptying after intra-anal irrigation. Although weight loss has been successful in lessening urinary incontinence, results of weight loss studies for fecal incontinence are mixed and inconclusive. Establishing regular bowel habits, using anti-diarrheal medications, and cautioning about unpredictable effects of complementary therapies are other recommendations. Conservative management includes options for use of intra-anal or intra-vaginal devices. Qualitative studies have identified areas for practical suggestions to support self-management and promote emotional and psychological coping, and the need to increase a sense of control and a sense of a normal life.

Conservative Management: Behavioural Therapies

Julia H Herbert, Consultant Physiotherapist, Grad Dip Phys. MSc. MCSP, MPOGP, United Kingdom

The management of faecal/anal incontinence in the adult population is multifactorial. The first line therapeutic approach is dietary and lifestyle modifications. The International Consultation on Incontinence recommends patient education

about the causes of faecal incontinence and a systematic effort to remove barriers to effective toileting is an intervention likely to be beneficial based on the consensus of experts. This is often followed by or given in association with a form of behavioural therapy. In order to change the behaviours associated with faecal incontinence many therapists will use Biofeedback which has also been described as operant conditioning therapy. Biofeedback can take many forms and this can make review of the literature difficult as studies use different protocols cannot be directly compared. The American College of Gastroenterology and the American Gasrotrenterological Association both recommend biofeedback for the treatment of faecal incontinence. Biofeedback gives the subject immediate feedback about subconscious body processes. Equipment is used to detect and amplify a physiological response. Three main modalities are described in the literature, with many variations and adjunctive measures.

1. Improvement of anal sphincter function – power, endurance co-ordination
- Intra anal surface Electromyography
- Intra anal manometry
- Trans perineal ultrasound

2. Re-training co-ordination of rectal filling sensation with voluntary contraction of anal sphincter
- Double balloon catheter to evoke rectal sensation and re-train sphincter co-ordination

3. Rectal sensation re-training4
- Use of rectal balloon catheter

Biofeedback is often offered in conjunction with pelvic floor muscle training. In association with Behavioural therapy, the consistency of the stool must also be considered and may require further modification of dietary intake or stool consistency modification via the use of medication as used in the CAPABle study.

This presentation will review the current evidence regarding behavioural therapy for faecal/anal incontinence in adults and will examine recommendations from the ICS/ICI-6 for this therapeutic area.

Evolving Surgical Treatments for the Treatment of Fecal Incontinence: An Evidence and Case-Based Approach

Holly E. Richter PhD, MD, FACOG, FACS, J Marion Sims Professor Obstetrics and Gynecology and Director, Division Urogynecology and Pelvic Reconstructive Surgery, University of Alabama at Birmingham, United States

Significant innovative approaches for the surgical treatment of fecal incontinence (FI) have emerged in the past 10 years. In general, surgery should be offered to women who have failed a credible attempt of conservative therapies and viewed as an adjunct to conservative therapies. Surgical therapies include repair of anal sphincter disruption. For most women, sphincter injuries are caused by obstetric trauma in the anterior segment. The etiologies for chronic sphincter disruptions can be due to either unrecognized injuries at the time of childbirth, from a perineal repair breakdown, or persistent injuries after the primary repair. Short-term continence rates have been reasonably good with up to 75% of patients becoming continent to liquid/solid stool. Longer-term results suggest that these results are not robust.

Other surgical modalities include neosphincter approaches such as graciloplasty and artificial bowel sphincter (ABS). Graciloplasty success rates of 38-90% have been reported. However, gracilis muscle transfer has drawbacks; deterioration in effectiveness over time, a long learning curve for surgeons, and high morbidity. Complications include infection and problems related to the defecatory dysfunction. Existing data on ABS success rates and safety vary considerably. Device erosion and infection are the most common reasons for explantation.

Sacral Neurostimulation (SNS) was first introduced in Europe in 1994 as a minimally invasive treatment for FI.[7] The InterStim® (Medtronic, Inc., Minneapolis, MN) was approved by the US Food and Drug Administration (FDA) for chronic refractory FI in April, 2011. In the 2010 pivotal US multicenter trial including 133 patients undergoing InterStim®, 83% achieved therapeutic success of 50% reduction of FI episodes at 12 months, and 41% had complete continence. Common device-related adverse events are implant site pain (28%), paresthesia (15%), and changes in the sensation of stimulation (12%).

Posterior tibial nerve stimulation (PTNS) for FI has been approved in Europe, but is still under investigation in the US. PTNS treatment uses a 34-gauge needle to stimulate the posterior tibial nerve near the medial malleolus to achieve effects via L4 – S3 nerve roots. PTNS is a minimally invasive outpatient therapy with almost no associated morbidity. Estimated cost is less than 1/10th compared to that of SNS.

Bulking materials into the submucosa or intersphincteric space increase the tissue volume in the high-pressure zone, especially in the proximal sphincter canal, creating a greater seal at rest. In 2011, non-animal stabilized hyaluronic acid/dextranomer (NASHA Dx) was approved by the FDA for the treatment of FI refractory to conservative therapy. Although complete continence may not be achieved, perianal bulking therapy may be an effective and safe option to alleviate symptoms especially in patients with mild to moderate passive FI.

Diversion by colostomy or ileostomy is considered a definitive therapy yet the last option when other treatments have failed. One study reported that both general and disease specific QOL were better in patients with colostomy where higher scores on social function on the SF-36 as well as the coping, embarrassment, lifestyle, and depression scales on the FIQoL compared to patients with FI were noted. Other evolving surgical approaches will also be discussed.

Cell-Based Therapies

Massarat Zutshi, MD, Staff Surgeon; Associate Professor of Surgery Department of Colorectal Surgery
Cleveland Clinic Foundation, United States

Cell-based therapies for injury and inflammatory diseases are an emerging area of interest. A major reason why cellular therapy has become attractive for these diseases is that treatment must be multi-focal and include the ability to stimulate repair, dampen inflammation and minimize opportunistic infection. Fecal incontinence is one such disorder that has attracted various researchers to study cell-based therapies. Mesenchymal stem cells (MSCs) have been utilized for this purpose due to their ability to differentiate into multiple cell types within a variety of organs as well as suppress immune functions. Early clinical trials with MSCs have yielded some exciting therapeutic potential and had good results in animal models. Other cells that have been used are adipose derived stem cells (ADSC's) and muscle derived stem cells (MDSC's). Most studies have evaluated regeneration after an acute injury. Fecal incontinence most often presents many years after an injury. This talk explores all cell based option and some non-cellular ones to heal a dysfunctional anal sphincter.

All preclinical animal research involving anal sphincter regeneration have used the model of an acute injury to evaluate cell based therapies including studies that demonstrated an increase in EMG and healing of the defect with muscle; a decrease in anal pressures then an increase after muscle progenitor cell transplant in a rabbit model; and an increase in the muscle fraction area in the groups treated with MSC and also an increase in EMG contraction compared to control but not to the sham. Pathi et al evaluated neurophysiological studies 21 days after injury and reported full recovery in rats treated with direct MSC injection and partial recovery with those treated with an IV injection. Fitzwater et al. did not demonstrate increase in muscle volume between cell and sham treated animals. They reported histological findings but did not quantify the muscle mass. They also reported no beneficial effect in animals where the cut ends were not repaired. We have demonstrated that the sphincterotomy in rats heals at 4 weeks and therefore have used a model which excises part of the anal sphincter which does not heal spontaneously.

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Schedule

1530-35	Welcome and Overview	Bliss
1535-50	Conservative/Lifestyle/Self Manage	Bliss
1550-1605	Behavioural Therapies	Herbert
1605-10	Questions	Bliss & Herbert
1610-30	Surgical Approaches	Richter
1630-50	Cell-Based Therapies	Zutshi
1650-1700	Questions	Richter & Zutshi

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Fecal Incontinence
Conservative Management: Lifestyle

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Donna Bliss

Affiliations to disclose:

- Consulting agreement with Domtar
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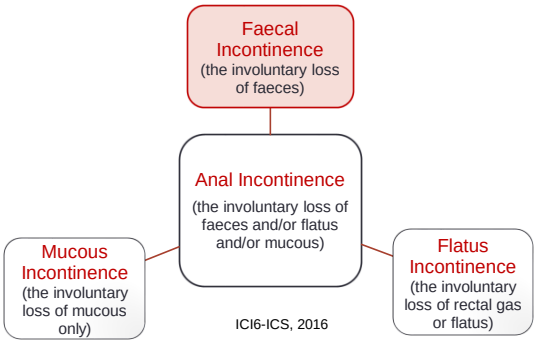
Definitions of Bowel Incontinence

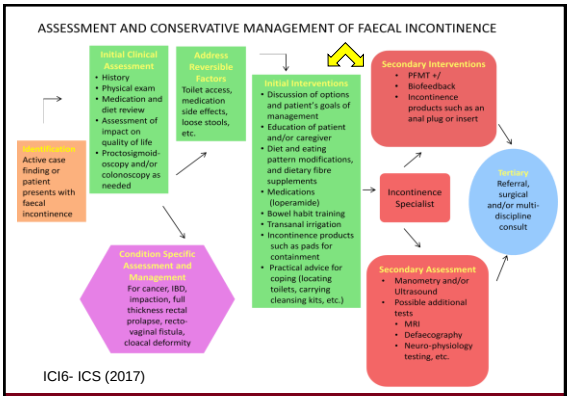


Clinical Assessment
AI or FI Severity Scales/Scores

8 Common Severity Scales

- 7 score severity of AI or AI+QoL
  - Pescatori
  - Wexner or Cleveland Clinic Scoring Scale
  - Vaizey or St. Mark's Score
  - Fecal Incontinence Severity Index (FISI)
  - Modified Manchester Health Questionnaire
  - Fecal Incontinence and Constipation Assessment (FICA) (now Fecal Incontinence Symptom Severity Scale (FISS))
  - ICI questionnaire for Bowel (ICIQ-B)
- 1 scores severity of FI + QoL
  - Revised Fecal Incontinence Scale (RFIS)
- None score FI severity only or FI separate from AI

(Bliss et al, ICI6-ICS 2017)



ICI6- ICS (2017)

Conservative Management

- Educate patient and/or caregiver
  - Individuals with FI and family caregivers have many incontinence literacy needs (B/C)
  - Normal bowel function, alterations in fecal incontinence, management options, absorbent product types, skin care
  - Use of a mnemonic (RELIEF) vs. standard counselling for FI to assist women to remember treatment plan – no differences

(Bliss et al.,ICI6-ICS 2017)

Consider Patients' Goals of Management

If complete cure is not possible…top goals:

- Decrease frequency of leakage
- Decrease leakage of loose or liquid stool
- Greater confidence in controlling fecal incontinence

(Manthey et al. *Western J Nurs Res* 2010)

Modify Diet Intake

Avoid Aggravating or Gas-Forming Foods

- Spicy, ethnic foods
- Fatty, greasy foods, eggs
- Caffeinated coffee, chocolate
- Dairy products
- Fresh apricots, strawberries, citrus
- Popcorn, nuts, seeds
- Onions, beans
- Cabbage, broccoli
- Alcohol

(Hansen et al. *JWOCN* 2006; *Croswell et al. JWOCN 2010)*

Initial Interventions

- Dietary fiber supplements -- Psyllium
  - Moderately fermentable and soluble
  - Start at lower amount and increase as needed (3-16 g/d)
  - Mixed with adequate fluid, in baked goods, take with extra fluid
  - Supported by RCTs

(Bliss et al. *RINAH*, 2014; ICI6-ICS 2017; Markland et al. *Dis Colon Rec*, 2015)

- Medications -- Antimotility (Loperamide)
  - 1-2 tablets (2 mg/tablet) before each meal and bedtime up to 16 tablets/d
  - Effects not improved by supplementing dietary fiber

(Lauti et al., *Colorectal Disease* 2008; Bliss et al.,ICI6-ICS 2017)

Lifestyle Modifications

- Smoking Cessation
  - Recommended for general health but limited and inconclusive evidence for reducing FI
- Weight loss
  - Observational studies in FI (mostly women)
    - More women with FI (26%) were overweight vs. women without FI (19%)
    - Obese women with FI had higher ARM baseline anal resting tone and squeeze pressures vs. normal weight
  - Improvements in UI with weight loss

(Bussen et al. *Gastrointestinal Med Surg*. 2012; Bliss et al. ICI6-ICS 2017)

Weight Loss -- inconclusive

- No difference in FI after weight loss from dieting
  - Dieting program with higher fiber content (10 g/d) vs. controls (education program)
  - women on program with dual incontinence lost weight and UI improved
- After bariatric surgery
  - Mixed results after surgical weight loss
  - 1 study: Anal incontinence increased 12.5% 5.6 months after surgery despite weight loss of 40 kg on average
- Recommended for general health but inconclusive for FI

(Markland et al. *Int Urogynecol J Pelvic Floor Dysfunct* 2011; *Am J Obstet Gynecol* 2009; Burgio et al., *Obstet Gynecol* 2007; Roberson et al. *Digest Dis Sci* 2010; Scozzari et al. *Obes Surg.*2013)

Establish Bowel Pattern and Bowel Training

- Try to establish regular bowel pattern/habits
  - Eat at consistent times
  - Modify cooking practices depending on diet tolerance -- no frying, mild spices
- Bowel Training
  - Behaviors to achieve a controlled response to urge to defecate
  - Procedure similar to bladder training
  - Progressive delay, reduce anxiety, and build confidence (Cognitive and relaxation techniques)
  - Consensus Best Practice recommendations by ICS Nursing Committee underway

Rectal Emptying

- Purpose: empty rectum, more complete elimination, prevent involuntary leakage
  - Transanal irrigation systems

mbh-international.com/product/qufora-mini-system/

http://www.medicalexpo.com/prod/coloplast/product-78838-489466.html

  - Suppository, abdominal massage, digital stimulation, senna, prunes – less evidence

(Collins & Norton, Br J Nurs 2013; Rosen et al. Colorectal Dis. 2011; Bliss et al., ICI6-ICS 2016)

Complementary Therapies

- No recommendation (Bliss et al. ICI6-ICS, 2017)
- Patients use a variety -- inquire about & evaluate
- Most common: herbs, probiotics (acidophilus)
- Others: acupuncture, massage, homeopathy, kinesiology, relaxation, reflexology, Chinese medicine
- Users: consider them safe, natural, allow control

2 FI case reports (women)
- opposite results

1. Cured FI, ↓ liquid stools, urgency ↓
   - antimicrobial herbs + Lactobacillus probiotic then herbs + bioceutical
   - (Aloe vera, Ulmus rubra, Citrus bioflavonoids, apple pectin, Pisacia lemtiscus, glutamine and Curcuma longa) (Lorback et al., *Aust J Herbal Med* 2015)
2. FI developed after bilateral needling of trigger-point acupuncture for pain in MS (McDowell et al, *Med Acupunct* 2015)

Practical Advice for Coping

- Incontinence absorbent products
  - Types of products
    - Pads, pantiliners, briefs, etc
    - For light to heavy leakage
  - Day vs night

Bliss et al., *JWOCN* 2013

  - Hard copy guide on ICS Nursing Committee "Library" of resources webpage

https://www.ics.org/Documents/Documents.aspx?FolderID=317

  - Website for assistance with selecting options

Continence Products Advisor http://www.continenceproductadvisor.org/

(Hansen et al. *JWOCN* 2006; Croswell et al. *JWOCN* 2010)

Design Changes for Absorbent Products FI

- ~ 1/3 absorbent products users not satisfied with product design for FI

- Recommended Changes
  - Materials that can protect skin from more solid/softer feces or particulate irritants in liquid feces
  - Better/more absorption in back with low bulking
  - Decrease odor
  - Easier on and off (w/o removing pants), make flushable
  - Decrease leaking of bigger leaks
    - Raised gathers along inside, around legs
    - Package with wipes
  - Trial sampler packs of different types

(Bliss et al. *JWOCN* 2011)

Practical Advice for Coping

- Locating or mapping public toilets -- apps

- Carrying small kits for cleansing and change
- Eat less or skip meal before going out or when in public
- Ask to be seated nearer restrooms
- Use continence aids (C)

(Bliss et al. ICI6-ICS 2017; Peden-McAlpine et al, *WJNR* 2008)

Secondary Interventions

Anal plugs, anal inserts, vaginal bowel device

(Continence Products Advisor http://www.continenceproductadvisor.org/ http://www.medgadget.com/2015/02/pelvalons-eclipse-vaginal-insert-for-fecal-incontinence-fda-approved.html; Cottenden et al., ICI6-ICS 2017)

Pros and Cons of Devices

Pros

- 40%-80% effective
- ↑ QoL

Cons

- Uncomfortable. soreness
  - VBD – higher comfort
- Unwanted expulsion
- Feel need to defecate/ urgency, vaginal irritation, UI/frequency/urgency, cramping
- VBD needs to be sized
- Need to insert and remove, temporary

(Cottenden et al; ICI6-ICS 2017; Norton & Kamm, *Colorectal Dis* 2001; Deutekom & Dobbin CD005086, 2015; Lukacz et al., *Dis Colon Rec* 2015; Richter et al., *Obstetrics & Gynecology*. 2015)

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Fecal Incontinence
Behavioral therapy for faecal incontinence

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- Affiliations to disclose:

- Clinical Director Femeda Ltd.
- Consultant to deSmit Medical Ltd.
- Consultant to Lucid innovations Ltd.
- Honorarium Astellas

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Aims of this presentation

- Define behavioural therapy
- Review types of therapy appropriate for Faecal / Anal incontinence
- Review the evidence to support therapy

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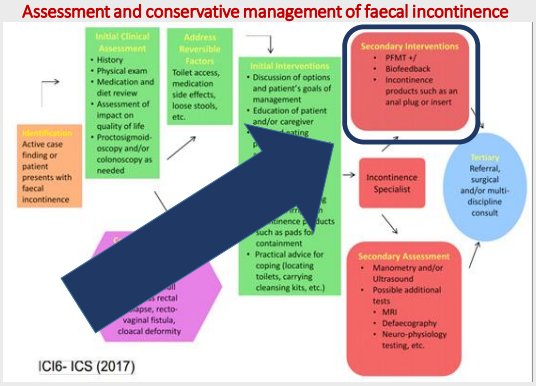
Assessment and conservative management of faecal incontinence



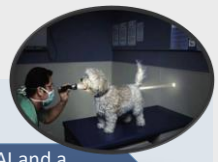
ICS

Behavioural therapy: Definitions

- The process of learning new motor patterns through movement patterns in contrast to the old.
- Aims to teach the individual to differentiate between old patterns/habits and the new , thus correcting poor habit
- Phases: cognitive, associative & automatized (Haugstad, 2008)

ICS

Education



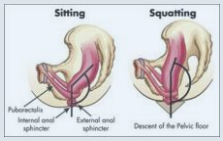
Education about the causes of FI/AI and a systematic effort to remove barriers to effective toileting is an intervention likely to be beneficial based on the consensus of experts.

Norton et al. 2003
Bliss et al. 2013

ICS

Defaecation dynamics

X



ICS

Behavioural therapy: Types

Pelvic Floor Muscle Training (PFMT)

Biofeedback (BF)

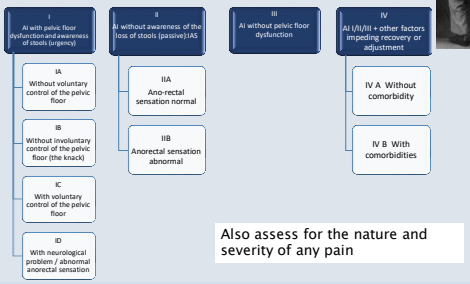
- addition of electronic or mechanical devices to aid PFMT (strength training)
- sensory training (rectal balloon training)
- Urge resistance training – used in addition to strength and sensory training

Electrical stimulation of the anal mucosa (ES)

(Bliss et al 2017)

ICS

Assessing the problem



Also assess for the nature and severity of any pain

(Dutch evidence statement for pelvic physical therapy in patients with anal incontinence. 2014)

ICS

Pelvic floor muscle training (PFMT)

Summary of current evidence / Recommendations

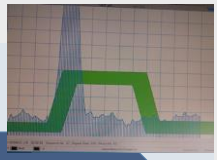
PFMT is possibly effective for the treatment of faecal incontinence. Studies comparing PFMT alone to BF augmented by PFMT and ES have shown mixed results and the optimal protocol for teaching PFMT has not been standardised, limiting the generalisability of findings (Level of evidence 2)

PFM exercises are recommended as an early intervention in the treatment of faecal incontinence as part of a conservative management bundle of interventions (Recommendation Grade B)

(ICI6 - ICS 2017)

ICS

Biofeedback (BF)



Definition:
Biofeedback therapy is a technique in which physiological activity (neuromuscular and autonomic) is monitored, amplified and conveyed to the patient via visual or acoustic signals

(Newman and Wein 2009)

ICS

Biofeedback (BF)

Anal probe better than vaginal (Fynnes 1999)

Manometry more specific to anal sphincter function?
– Expert opinion

MAPLe EMG – Able to isolate external anal sphincter
(Voorham-van de Zalm 2013)

ICS

Biofeedback (BF)

There are numerous uncontrolled trials

There is a low morbidity associated with Biofeedback

Those most likely to benefit from Biofeedback for AI are:
- Motivated
- Have intact cognitive skills
- Some rectal sensation
- Nearly intact sphincters and innervation

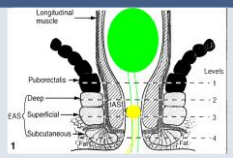
Bo et al. 2014

ICS

Rectal sensation training

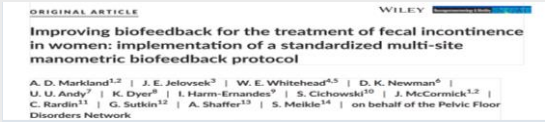
Single / Double balloon catheter
Air filled syringe
3-way tap

Bols et al 2012
Markland et al 2017



ICS

Biofeedback (BF)



ORIGINAL ARTICLE WILEY

Improving biofeedback for the treatment of fecal incontinence in women: implementation of a standardized multi-site manometric biofeedback protocol

A. D. Markland[1,2] | J. E. Jelovsek[3] | W. E. Whitehead[4,5] | D. K. Newman[6] | U. U. Andy[7] | K. Dyer[8] | I. Harm-Ernandes[9] | S. Cichowski[10] | J. McCormick[1,2] | C. Rardin[11] | G. Sutkin[12] | A. Shaffer[13] | S. Meikle[14] | on behalf of the Pelvic Floor Disorders Network

Treatment:
Strength training
- Improve external anal sphincter (EAS) squeeze pressure
- Improve endurance EAS (50% of maximum squeeze)
- Improve co-ordination of EAS

Sensory training
- Uptrain / downtrain rectal sensation threshold

Urge resistance training

ICS

Biofeedback (BF)

Recommendations

Biofeedback +/- PFMT and sensory training with a rectal balloon, is recommended as second line treatment for faecal incontinence after other behavioural and conservative / medical management have been tried and failed to provide adequate symptom relief
(ICI6 - ICS 2017 Recommendation Grade A)

Home Biofeedback using a portable battery-operated device is recommended as an adjunct to biofeedback training in the clinic, especially for younger patients
(ICI6 - ICS 2017 Recommendation Grade B)

ICS

Electrical stimulation of the anal mucosa (ES)

Recommendations

Based on current evidence it is not possible to recommend low frequency (100Hz) for FI
Percutaneous tibial nerve stimulation remains an investigational treatment protocol cannot currently be recommended for FI
(ICI6 - ICS 2017 Recommendation Grade B)

Triple therapy (combined biofeedback and 3000Hz stim) appears to be effective but requires further evidence

ICS

Electrical stimulation of the anal mucosa (ES)

Further recommendations

ES is useful in a specific group of patients; to improve the voluntary control of the pelvic floor in patients who lack this voluntary control

(Dutch evidence statement for pelvic physical therapy in patients with anal incontinence. 2014)

ICS

Thank you

ICS

Evolving Surgical Treatment Approaches for Fecal Incontinence in Women: An Evidence and Case-Based Approach

Holly E Richter, PhD, MD, FACOG, FACS
J Marion Sims Endowed Professor Obstetrics and Gynecology
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Director, Division of Urogynecology and Pelvic Reconstructive Surgery
University of Alabama at Birmingham

ICS

Holly E. Richter

Affiliations to disclose†:

Pelvalon-research funding; consulting	
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NIAID-research funding	

Funding for speaker to attend:

- [X] Self-funded
- [ ] Institution (non-industry) funded
- [ ] Sponsored by:

ICS

Evolving Surgical Treatment Approaches for Fecal Incontinence in Women: An Evidence and Case-Based Approach

WS22

September 12, 2017

Florence, Italy

Learning Objectives

- To appreciate that the optimal treatment regimen for fecal incontinence (FI) may be a complex combination of various non-surgical and surgical approaches
- Surgery is a credible option for the treatment of FI
- Present evidence and case-based surgical treatment approaches for FI

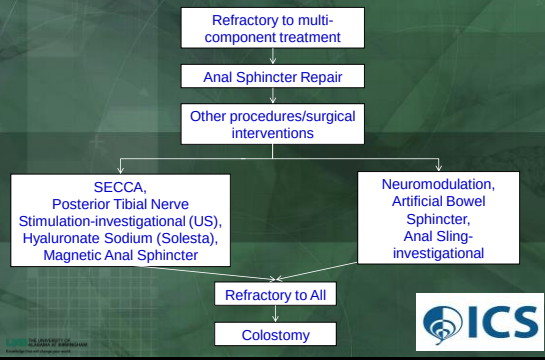
Cochrane Review 2013 Surgery for Fecal Incontinence

The review is striking for the lack of high quality randomized controlled trials with any fecal incontinence surgeries that have been carried out in the last 10 years…..

*Larger rigorous RCTs (including the use of sham treatments) are needed, however, it should be recognized that the optimal treatment regime may be a complex combination of various surgical and non-surgical therapies"

Brown et al 2013

Surgical/Other Procedural Treatments for Fecal Incontinence

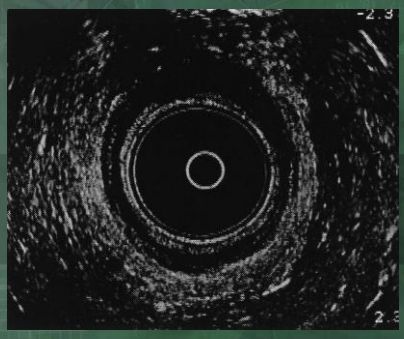


Case 1

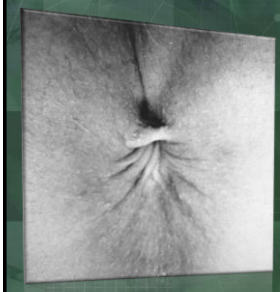
- 55 yo female P3013 with 5 year history of FI and ano-rectal urgency
- FI of liquid/solid stool and gas despite a credible attempt at management with behavioral therapy
- Spontaneous vaginal delivery (SVD) X 3 with largest infant weighing 3700 g
- Forceps delivery and a lot of "stitches" with first SVD
- Alternating constipation & diarrhea
- PMH: obesity
- PSH: cholecystectomy

Physical Examination and Diagnostic Testing

- Examination: decreased anal tone, intact reflexes, dove tail appearance, 1.5 cm thickness
- Surface Electrode EMG: reasonable isolation with decreased squeeze pressure activity, good relaxation, no evidence of dysynergia
- Anal Manometry: anal resting tone of 25 mm Hg, squeeze to 55 mmHg, normal sensation, compliance 200 cc, normal RAIR
- Endoanal Ultrasound:



Fecal Incontinence with Abnormal Sphincter

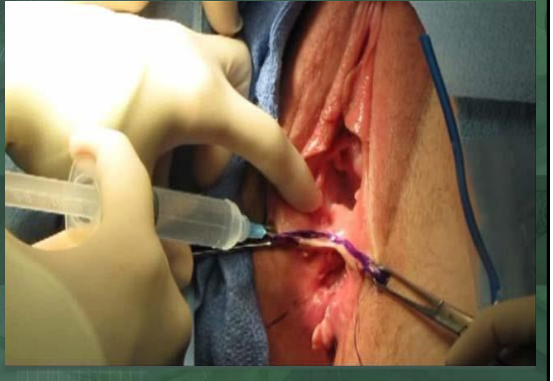


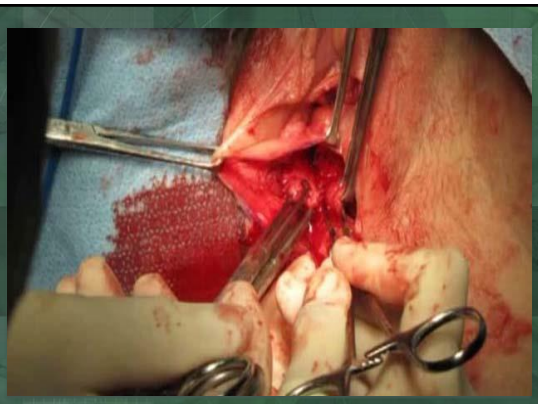
- Direct sphincter injury
  - Obstetric (majority)
  - Surgical (anal or rectal)
  - Trauma
- Congenital anomalies

Sphincteroplasty

- The term sphincteroplasty is used to describe secondary or delayed reconstruction of the anal sphincter musculature, injury to which has either not been recognized or the outcome of the repair unsatisfactory
- Among women who had a sphincter tear repaired at the time of delivery, 35% continued to have IAS gaps and of those women, the majority had concomitant EAS disruptions at 6 and 12-months*

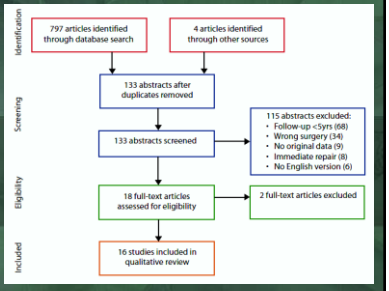
*Bradley, Richter, Gutman et al. Am J Obstet Gynecol, 2007





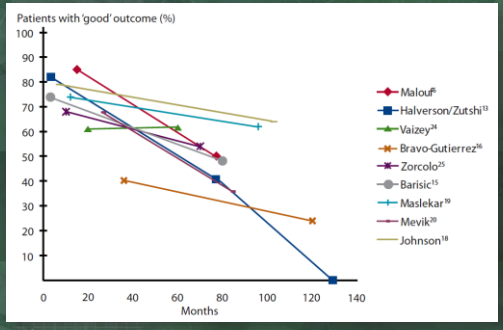
Evidence for efficacy?

- Systematic Review of FI studies 1991-2010
- 16 studies selected with 900 patients



Glasgow, Lowry DCR 2012

Long Term Data



Glasgow, Lowry DCR 2012

Outcome Data

- Data reflects effectiveness in the short-term where 70-80% of patients report symptom improvement
- Long-term success deteriorates over time: 20-67% by 5 years, 0-40% at 10 years

Anandam 2014; Sung et al 2007; Tjandra et al 2003; Garcia et al 2005

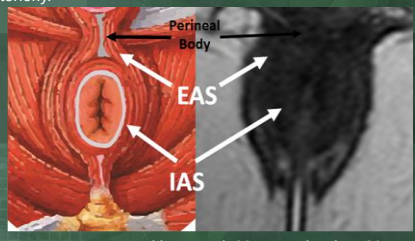
Sphincteroplasty-Summary

- Approximately 2/3 of patients report improvement
  - Based on patient recall, little prospective data
  - Defined by "good", no standardized outcomes used until recently
  - No factor significantly associated with a worse outcome (age, severity, duration, previous repair and pudendal nerve delay implicated)
- Still an appropriate first line therapy for women with major sphincter defects
  - Restore sphincter to circumferential configuration- although MRI data may dispute this
  - Build up perineal body

Most common complication: wound infection (2.2-35%)

Potential Reason for Lack of Efficacy:

Example of distal MRI sphincter pre-pregnancy and corresponding diagram displaying how external sphincter (EAS, white arrows) is not anatomically contiguous across the midline at 12 o'clock or 6 o'clock, but sends fibers to other structures in the perineal body (black arrows) by turning anterio-lateral. In contrast, the internal anal sphincter (IAS) is a cylindrical structure that is continuous across the midline posteriorly and anteriorly.



Lockhart, et al, 2017; Meriwether, 2017, submitted

Case 2

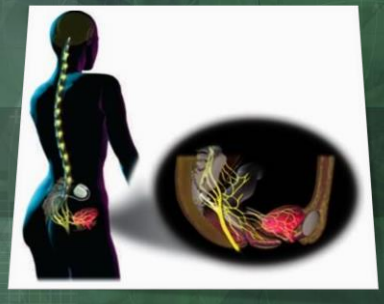
- 67 yo female with a 7-year history of FI
- FI of liquid/solid stool, 3-times per week necessitating constant pad use and scared to leave her home
- Has had a sphincter repair, tried behavioral therapy including pelvic muscle exercises, other PT strategies, attention to diet, and use of medications with some improvement, but still room for improvement
- Recent 2 week diary revealed nearly daily bowel movements with leakage 2 times the first week and 3 times week 2
- PMH: hypertension
- PSH: hysterectomy

Physical Examination & Diagnostic Testing

- Examination: decreased rectal tone, intact reflexes
- Surface Electrode EMG: reasonable isolation with good subjective squeeze pressure activity, good relaxation, no evidence of dysynergia
- Anal Manometry: anal resting tone of 40 mm Hg, squeeze to 70 mmHg, normal sensation, compliance 100 cc, normal RAIR
- Endoanal Ultrasound: intact external and internal anal sphincters

She is considering colostomy-
what surgical options are available?

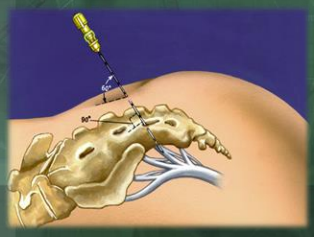
Sacral Nerve Stimulation



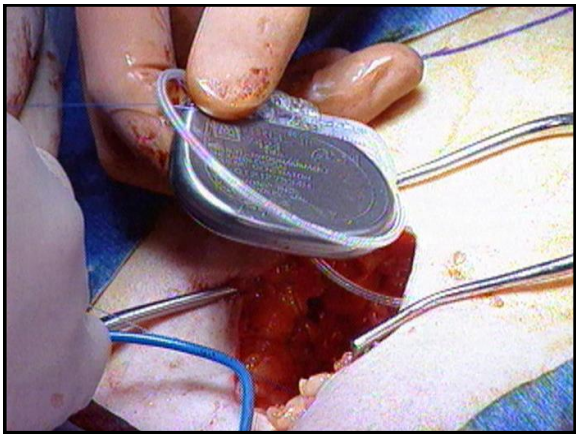
How Does It Work?

- Many potential neurologic targets
  - Voluntary somatic
  - Afferent sensory
  - Efferent autonomic
- Rectal blood flow increased with stimulation as measured by doppler flowmetry-effect was reversible[1]
- Decreased episodes of spontaneous sphincter relaxation[2]
- Electrical stimulation of the sacral nerves causes:
  - Modulation of neural reflexes
  - Interrupts constant sensory input from rectum

[1]Kenefick, Br J Surg 2003; [2]Vaizey, Gut 1999



- Staged testing
- Simple outpatient procedure done under local anesthesia with IV sedation
- 2-4 week bowel diary prior to placement, then 2-4 week stimulation trial with diary



Show Me the Data!

SNS Data Summary Short, Medium, Long-term

- When reviewing short (<12 months), medium (12-36 months) and long-term (>36 months) success (success defined as a 50% reduction in FI episodes):

  -ITT median (range) rates of 63% (33-66%), 58% (52-81%), 54% (50-58%), respectively

  -Per protocol median (range) rates of 79% (69-83%), 80% (65-88%) and 84% (75-100%), respectively

Matzel et al, 2009

SNS Adverse Events

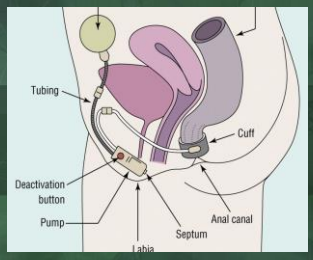
- Most AEs occur within 1st year of implantation
- Common events include: device pain (28%) and paresthesia (15%)
- Meta-analysis reported lower rate of implant site pain (6%)*
- With advancements in lead design and techniques, explantation rarely necessary (3-4%)*
- Infection rate 3-11%**

*Tan et al 2011; **Wexner et al,2010; Mellgren et al, 2011

Other Procedural/Surgical Treatment Approaches for Treatment of Fecal Incontinence

Artificial Bowel Sphincter (ABS)

- Severe, refractory FI
  - Efficacious
  - High morbidity



ABS Results

Success Rates 50-77%

Results of Artificial Bowel Sphincter

Study	No. of Patients	Follow-Up (mo)	Preoperative Score	Postoperative Score	*P* Value
Cleveland Clinic Score*					
Altomare *et al.*[120]	28	19	14.9	2.6	<0.001
Devesa *et al.*[121]	53	26.5	17	4	0.001
Lehur *et al.*[122]	13	30	17	4.5	<0.001
O'Brien *et al.*[123]	14	6	19	4.8	0.002
Ortiz *et al.*[124]	22	28	18	4	<0.001
Vaizey *et al.*[125]	6	10	19.5	4.5	0.001
American Medical Systems Score†					
Altomare *et al.*[120]	28	19	98.5	5.5	<0.001
Casal *et al.*[126]	10	29	99.9	28.4	<0.001
Dodi *et al.*[127]	8	10.5	95	19.4	<0.004
Lehur *et al.*[128]	24	20	106	25	<0.001
Lehur *et al.*[129]	16	25	105	23	<0.05
Wong *et al.*[130]	112	12	106	48	<0.001
Williams Score‡					
Christiansen *et al.*[131]	17	60	5	2.5	<0.001
Fecal Incontinence Scoring System§					
Parker *et al.*[132]	35	24	103	24	<0.001

* Cleveland Clinic Score – scale of 0 to 20: 0 = complete continence and 20 = complete incontinence.[119]
† American Medical Systems Score – scale of 0 to 120: 0 = complete continence and 120 = complete incontinence.[119]
‡ Williams Score – scale of 1 to 5: 1 = complete continence and 5 = complete incontinence.[119]
§ Fecal Incontinence Scoring System – score of 0 to 120: 0 = complete continence and 120 = complete incontinence.[132]

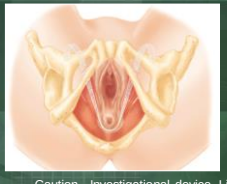
ABS Complications

Complications of Artificial Bowel Sphincter

Study	Explants (%)	Revision (%)	Erosion (%)	Infection (%)
Altomare *et al.*[120]	18	25	11	18
Casal *et al.*[126]	30	10	10	60
Christiansen *et al.*[131]	41	35	6	18
Devesa *et al.*[121]	23	30	21	21
Dodi *et al.*[127]	25	Not stated	25	25
Lehur *et al.*[122]	31	62	8	7
Lehur *et al.*[28]	33	38	13	4
Lehur *et al.*[129]	31	13	6	Not stated
O'Brien *et al.*[123]	23	31	8	23
Ortiz *et al.*[124]	41	27	23	9
Parker *et al.*[132]	40	64	11	31
Vaizey *et al.*[125]	17	17	17	33
Wong *et al.*[130]	37	65	25	38

Anal Slings-investigational, TOPAS® System

- Self-affixing Type-I Polypropylene Sling
- Minimally invasive trans-obturator post-anal sling



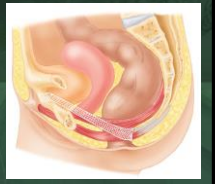
Caution - Investigational device. Limited by Federal (United States) law to investigational use

TRANSFORM Study

ClinicalTrials.gov Identifier: NCT01090739

- TOPAS (AMS) sling for FI
  - Prospective, multi-center(12 sites)
  - Single-arm, open-label, two-stage, adaptive study with one planned interim analysis
  - N=152
  - The mesh sling placed via the transobturator approach

Mellgren A et al, Am J Obstet Gynecol 2015



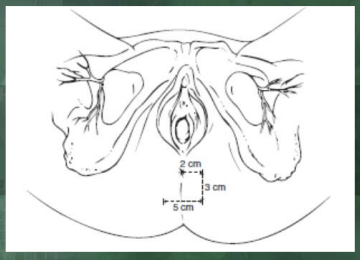
Primary Outcome

- 50% reduction in the number of FI episodes from baseline to 12 months post-operatively on a 14 day bowel diary.

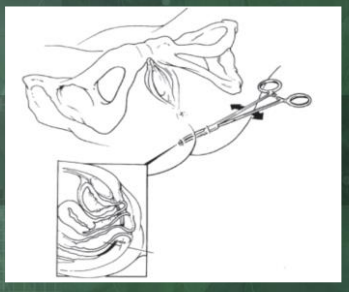
Secondary Outcomes

- Decrease in Fecal Incontinent Days and Urgency Episodes
- Symptom Severity: Cleveland Clinic Incontinence Scores
- Quality of Life: Fecal Incontinence Quality of Life (FIQOL)
- Safety

Surgery



Surgery

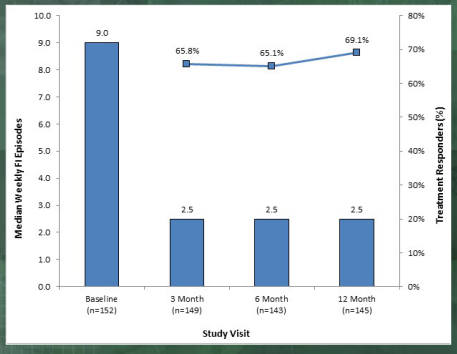


Surgery

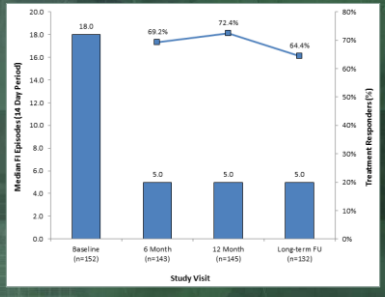
Surgery

- Mean surgical time = 33 minutes (range 11-71)
- Mean EBL = 13 cc (range 0-50)
- Mean hospital stay = 11 hours (2-57)
- NO visceral injuries or perforations

Primary Outcome-12 months (ITT)



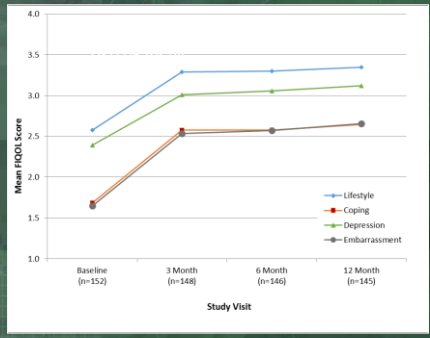
Sustained Outcomes-34 months per protocol



Secondary Outcomes

	Baseline Median (range)	12 mos. Median (range)	P value
CCIS (Wexner)	13.9 (mean)	9.6 (mean)	< 0.001
FI Episodes per week	9.0 (2-40.5)	2.0 (0-40)	< 0.001
FI Incontinent Days	5.0 (1.5-7)	2.0 (0-7)	< 0.001
FI with Urgency	2.0 (0-7)	0 (0-26)	< 0.001

Improvement in FIQOL



Treatment Related Adverse Events

Adverse Event Category	Number of Events	Number of Patients (% Patients)
Pelvic pain	47	41 (27.0%)
Infection	26	22 (14.5%)
Incision site infection	9	9 (5.9%)

17 no treatment
29 treated with medical therapy
1 sciatica surgery
10 persistent at 1 year
None classified as SAEs by FDA standards

NO mesh erosions or extrusions

Radiofrequency Therapy: SECCA®

SECCA® Efficacy Data

- Long-term* (5 year) study, mean Wexner incontinence score improved from 14 to 8, p<0.0003
- 80% subjects had 50% improvement
- N=19
- Other studies limited by short-term follow-up and small sample sizes (N=8-50)
- No comparative data
- Main AEs rectal bleeding and pain

*Takahashi-Monroy et al 2008

PTNS-targets sacral plexus

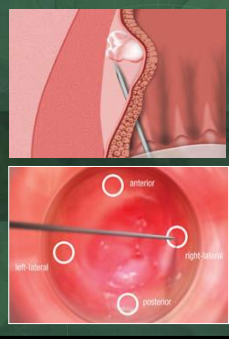
PTNS

- The largest prospective study including 115 patients with a median follow-up of 26 months (range, 12 – 42) reported 52% of patients achieving a ≥ 50% reduction in FI episodes as well as improving QOL*
- First multi-center RCT (the CONtrol of Faecal Incontinence using Distal NeuromoulaTion [CONFIDeNT]) in the United Kingdom was recently published
- This trial included 227 patients to evaluate the efficacy and cost-effectiveness of PTNS (n=115) comparing to sham electrical stimulation (n=112)
- Interestingly, the study reported no difference between the PTNS and sham groups in efficacy at 12 weeks: 38% in PTNS versus 31% in sham achieving a ≥50% reduction in the number of FI episodes per week, adjusted ratio 1.28 (95%CI 0.72-2.28; p=0.40) **

*Hoturas et al 2014; **Knowles 2015

Non-Animal Sodium Hyaluronate-NASHA Dx

- Dextranomer microspheres and sodium hyaluronic acid
  - Identical to Deflux
- Administered via anoscope to the proximal anal canal
  - Out-patient setting
  - No anesthesia
  - Four 1ml blebs of Solesta



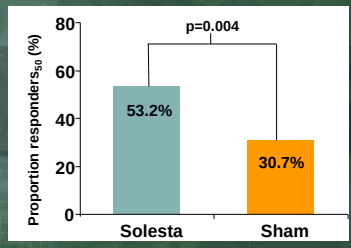
Pivotal Trial

- Only large scale trial in the literature – injectable bulking agent vs. sham
- 206 patients
  - 13 sites in U.S. and EU
  - 80% female
- Three part primary endpoint
  - Superiority over sham at 6 months
  - Threshold responder rate at 6 months
  - Durability of effect to 12 months

Graf et al, Lancet 2011

Pivotal Trial: Results

- All 3 success criteria were met
  - Responder rates superior to sham at 6 months
    - Above the predetermined threshold
  - Durability of effect out to 12 months: 57.4% Responder$_{50}$



Most Common Related AEs - Solesta Patients Pivotal Study Through 18 Months

Preferred term	Events	% patients
Proctalgia	41	17.3
Injection site hemorrhage	18	8.1
Rectal hemorrhage	15	7.6
Pyrexia	14	6.6
Injection site pain	10	5.1
Diarrhea	10	4.1
Anal hemorrhage	9	4.1
Anorectal discomfort	8	4.1
Rectal discharge	7	3.6
Proctitis	5	2.5

Majority of AE's were mild and self limited

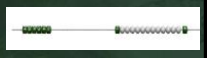
Magnetic Anal Sphincter

- Fenix™, Torax Medical; sold to J&J
- Series of titanium beads with magnetic cores linked together with independent titanium wires
- To defecate, the force generated by straining separates the beads to open up the anal canal
- The technique of implantation is simple with no requirement of adjustments

FENIX® Continence Restoration System

FENIX Device
- Titanium beads with magnetic cores
- Range of Sizes: 14-20 beads
- Double suture joining mechanism

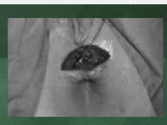
FENIX Sizing Tool
- Assists in selection of proper FENIX device
- Single use



FENIX Introducer Tool
- Assists in placing the sizing tool and device
- Reusable

FENIX Implant Procedure

Pre Op Testing	Patient Procedure	Supplies/Equipment
Endoanal Ultrasound	~60 minutes	Standard colorectal surgical tray
Manometry	Perineal incision	Electro-cautery & Suction
Defecography	Peri-anal tunnel	Portable fluoroscopy
	Sizing / device placement	
	X-Ray confirmation (Optional)	
	Close the wound	



FENIX® Feasibility Study Study Design

- Prospective, observational, open label
- Non-randomized, single-arm, multi-center
- First-in-man use, safety and efficacy
- 35 patients from sites in Europe and the US
- Followed for five years

Sugrue J, et al. Dis Colon Rectum, 2017; 60:87-95

FENIX Feasibility Study 2 Primary Endpoints

Safety Endpoint

Descriptive analysis of device or procedure-related adverse events, summarized by incidence and severity

Efficacy Endpoint

Proportion of patients achieving a 50% or greater reduction in FI episodes per week as compared to baseline:
- Tool: 20-day bowel diary completed by the patient
- Timeline: Baseline, 6, 12, 24, 36, 48 and 60 months after surgery

Primary Efficacy Endpoints

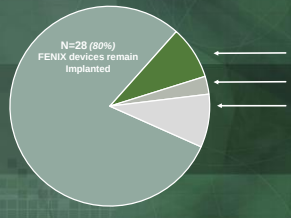
Improved Continence Post-Implant Reported by Patients on Bowel Diaries

Reduction in FI Episodes, FI Days, and Urgency Episodes From Baseline at 1 – 5 Years of Follow-up					
Outcome (per week)	12 Months % (n/N)	24 Months % (n/N)	36 Months % (n/N)	48 Months % (n/N)	60 Months % (n/N)
≥50% reduction in FI episodes	78.6% (22/28)	70.4% (19/27)	90.9% (20/22)	81.8% (18/22)	72.7% (16/22)
≥50% reduction in FI days	67.9% (19/28)	59.3% (16/27)	77.3% (17/22)	68.2% (15/22)	72.7% (16/22)
≥50% reduction in urgent episodes	50.0% (13/26)	48.0% (12/25)	65.0% (13/20)	75.0% (15/20)	60.0% (12/20)

FENIX Feasibility Study Safe Surgical Option

No long-term sequelae associated with device explants

7 Explants Due To



Final Consideration

- Fecal Diversion

Fecal Diversion

- Considered “last resort”
- One case-control and two cohort studies
- Results in improved QOL
- More cost effective at 5 years than artificial AS and dynamic graciloplasty
- Usually an end sigmoid colostomy without proctectomy (rectal stump)
- Laparoscopic approach, safe and effective

Colquhoun et al 2006; Norton et al 2005; Ludwig et al 1996

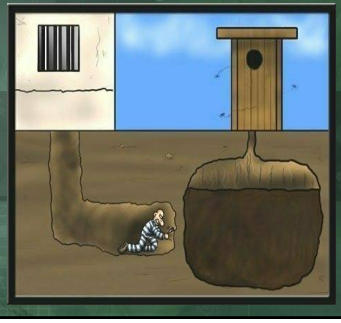
Conclusions

- Cause of fecal incontinence (a lecture unto itself) is often multi-factorial
- 1st line treatment is…
  - Education
  - Pelvic Floor Muscle Exercises
  - Medications
  - Normalization Of Stool Consistency
  - Bowel Habits
  - Devices*
- Surgery helpful for many women
- Need to be able to discuss all options with patients and individualize care

Conclusions

- Sphincteroplasty has reasonable short-term but reduced long-term results
- Neuromodulation therapy helps those with refractory FI
- Other therapies needed-recent data on devices; need RCTs!
- Individualization of treatment

Things could always be worse…….



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W22: Management of Fecal Incontinence from Bench to Bedside

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Professor, Nursing, USA
Julia H Herbert, Grad Dip Phys. MSc. MCSP, MPOGP
Consultant Physiotherapist, UK
Holly E. Richter PhD, MD, FACOG, FACS
J Marion Sims Professor Obstetrics and Gynecology and Director, Division Urogynecology and Pelvic Reconstructive Surgery, USA
Massarat Zutshi, MD
Colorectal Surgeon and Associate Professor of Surgery, USA

ICS

Massarat Zutshi

- Affiliations to disclose:

- Speaker : Laborie
- Travel for conference presentation from Laborie/AMI

Funding for speaker to attend:

x	Self-Funded
	Institution (non-industry) funded
X	Sponsored by: Laborie/AMI

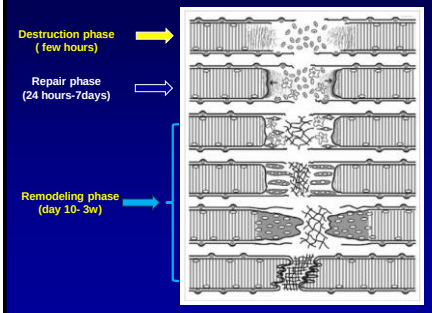
ICS

Fecal Incontinence: Bench to Bedside

Massarat Zutshi

Digestive Disease Surgery Institute
Department of Colorectal Surgery
Cleveland Clinic Foundation
Cleveland, Ohio, USA

The stages of remodeling of skeletal muscle



Muscles, Ligaments and Tendons Journal 2013; 3 (4): 337-345

Why do tissues not regenerate completely at the time of injury?

- Cytokine expression in the tissues that are injured is often short-lived; expression levels are not elevated enough to sustain effective cellular migration.
- The acute injury in the anal sphincter is recognized infrequently and patients become symptomatic many years after initial injury.
- Age-related factors may worsen this problem.
- We have evolved to scar and not regenerate.

What can we do about it?

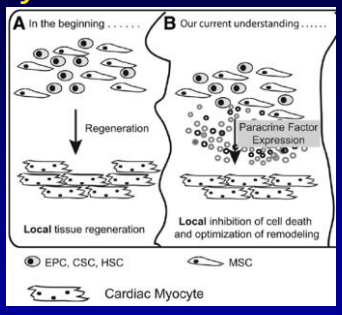
- Cytokine expression increased to reestablishing homing by exogenous introduction of chemokines in the area of injury or using a conditioning injury.

Adult stem cells

- Mesenchymal stromal cells (MSCs) cells isolated from various tissue sources, with multipotent differentiation capacity in vitro.
- Bone marrow
- Adipose
- Muscle derived
- Wharton's jelly
- Dental bud

Mode of action:
Regeneration
Paracrine effect

Why do stem cells work?



Penn MS. Circ Res. 2012; 111:12-13; 2.
Orlic D et al. Nature. 2001;410: 701–705.

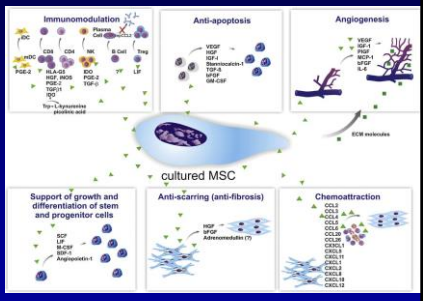
Mesenchymal Stem Cells (MSC)

- Differentiation
- New spotlight: Paracrine & autocrine effects

Singer et al., Annu Rev Pathol Mech Dis , 2011

Autocrine : Hormone binds to receptors on and affects the function of the cell type that produced it.

Paracrine : Hormone has effect only in the vicinity of the cell secreting it.



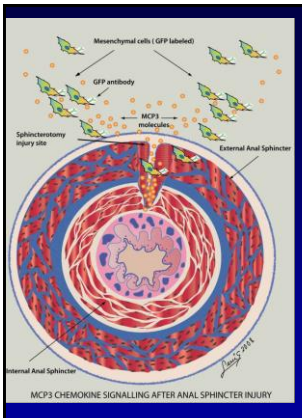
Mesenchymal Stem Cells (MSC)

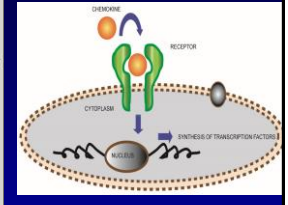
- Bone marrow, skeletal or adipose derived
- Give rise to cells of mesodermal origin
- Commonly used in models of injury
- Immune privileged
  - Low rejection potential
  - Allogeneic sources

Now termed medicinal signaling cells (Caplan) who says MSC's are pericytes that reside in the vasculature and are the first line of defense.

When do stem cells work?

1. Signals at site of repair should last.
2. Stem cells should reach the site of intended repair.
3. Cells should be in sufficient numbers to initiate and sustain repair.





Chemokine expression causes intra-cellular signaling and transcription of factors and protein synthesis

SDF-1

Stromal-cell-derived factor 1 (CXCL12) + CXCR4

- MSC showed significant chemotaxis to CXCL12, chemokines preferentially expressed in the area of inflammatory bone destruction.

- Cardiogenesis, primordial germ cell migration, and the recruitment of endothelial-cell progenitor cells to ischemic tissue.

Systemic overexpression of CXCL12 can lead to stem-cell mobilization.

Takano T, et al. Lab Invest., 2014 Jan 6. doi: 10.1038/labinvest.2013.152
Levesque JP, et al. J Clin Invest 2003; 111:187-96;
Yamaguchi J, et al. Circulation 2003; 107: 1322-28.
Heissig B, et al. Cell 2002; 109: 625-37

MCP-3

- Monocyte chemoattractant proteins, now known as CC chemokine ligands (CCL)
- Regulates the recruitment of monocytes to sites of inflammation
- Critical for host defense by attracting cells through activation of their cognate receptor CCR2.
- CCL7 (MCP-3) /CCR2 is critical for monocyte mobilization from bone marrow.
- Over-expression of CCL7 in urethral sphincter and serum in a mouse model of simulated birth trauma-induced urinary incontinence.

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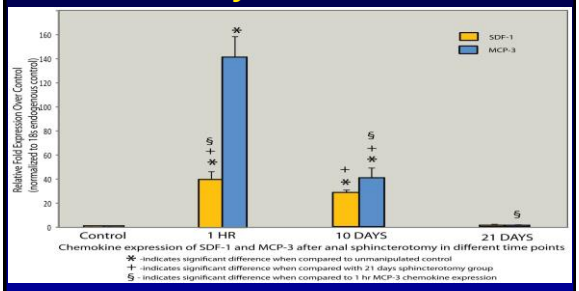
Cytokines



Expression of SDF-1 and MCP-3 after anal sphincterotomy

Bone marrow derived MSC: Acute injury models

Treatment of Experimental Injury of Anal Sphincters with Primary Surgical Repair and Injection of Bone Marrow Derived Mesenchymal Stem Cells.
Bruno Lorenzi, Federica Pessina, Paola Lorenzoni, et al. 2008 Dis Colon Rectum 51: 411–42

Potential of human umbilical cord matrix and rabbit bone marrow-derived mesenchymal stem cells in repair of surgically incised rabbit external anal sphincter.
Aghee-Afshar M,Rezazardehkermani M,Asadi A et al. Dis Colon Rectum 2009 Oct;52(10):1753-61.

Recovery of the Injured External Anal Sphincter After Injection of Local or Intravenous Mesenchymal Stem Cells.
Sujatha D. Pathi, MD,Jesus F. Acevedo, BA., et al. 2012 Obs and Gyn 119 , 134-144

MSC–Acute injury models

Functional outcome after anal sphincter injury and treatment with mesenchymal stem cells.
Salcedo L, Penn M, Damaser M, Balog B, **Zutshi M**.
Stem Cells Transl Med. 2014 Jun;3(6):760-7.

Mesenchymal stem cells can improve anal pressures after anal sphincter injury.
Salcedo L, Mayorga M, Damaser M, Balog B, Butler R, Penn M, **Zutshi M**. Stem Cell Res. 2013 Jan;10(1):95-102

Skeletal muscle cells: Acute injury models

Sphincter contractility after musle derived stem cells autograft into the cryoinjured anal sphincter of rats
Kang SB, Lee JY et al. 2008 Dis Colon Rectum 51: 411–42

Functional external anal sphincter reconstruction for treatment of anal incontinence using muscle progenitor cell autografting.
Kajbafzadeh AM, Flmi A et al Dis Colon Rectum 2010;53, 1415-21

Effect of myogenic stem cells on contractile properties of the repaire and unrepaired transected external anal sphincter in an animal model.
White AB ,Keller P, et al Obstet Gynecol. 2010 Apr;115(4):815-23.

Recovery of the injured external anal sphincter after injection of local or intravenous mesenchymal stem cells.
Sujatha D. Pathi, MD, Jesus F.Acevedo, BA, et al. 2012 Obs and Gyn 119 ,

In vivo recovery of the injured anal sphincter after repair and injection of myogenic stem cells.
Jacob S 134-144 et al. J Korean Surg Soc 2013, 84;216-24

Skeletal Muscle cells - Safety

Safety assessment of myogenic stem cell transplantation and resulting tumor formation.
Jacobs SA Lane FL et al. Female Pelvic Med Reconstr Surg. 2013 Nov-Dec;19(6):362-8.

No evidence of cell migration to liver or lung was found.
2 transplanted rats developed abnormal foci of growth, i.e. tumors, from the external anal sphincter-raising further safety questions.

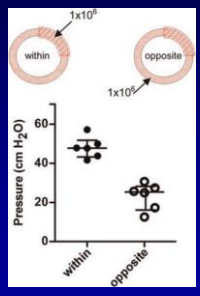
Skeletal muscle cells: Injection at a normal site

Restoration of anal sphincter function after myoblast cell therapy in incontinent rats.

Bisson A , Freret M et al. Cell transplant ;2015 24(2) 277-86

Cryoinjury 90 degrees.

Intralesional and at the borders injection was equally effective but opposite to the lesion were not.



Stem cells: MDSC Human trial

Muscle-derived cell injection to treat anal incontinence due to obstetric trauma: pilot study with 1 year follow-up.
Frudinger A, Kolle D, et al. Gut. 2010 Jan;59(1):55-61.
5 year f/u : Colorectal disease 2015

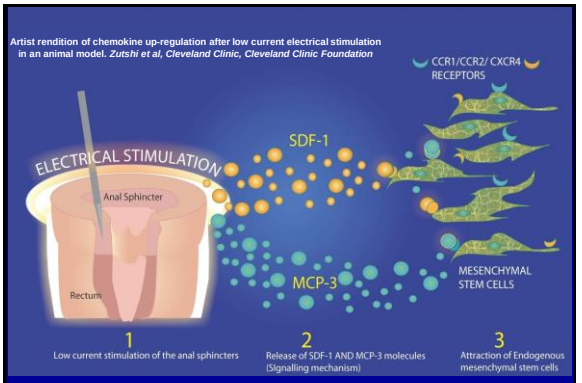
- 10 women . Electrical stimulation preop 21 days
- Autologous myoblasts were cultured from a pectoralis muscle biopsy
- Injected under ultrasound control
- At 12 months the Wexner incontinence score had decreased by a mean of 13.7 units (95% CI, -16.3 to -11.2), anal squeeze pressures were unchanged, and overall quality of life scores improved by a median of 30 points (95% CI, 25 to 42).
- At 5 years patients still did well

Zutshi lab : Ultimate goal

- Prove that the effect of cell/non cell therapy lasts over time.
- Find the right factor to allow stem cells to home to the entire anal sphincter.
- Find the right factor to correct neuropathic incontinence

Currently we are evaluating the SDF-1 plasmid with and without MSC in a chronic large injury in a pig model

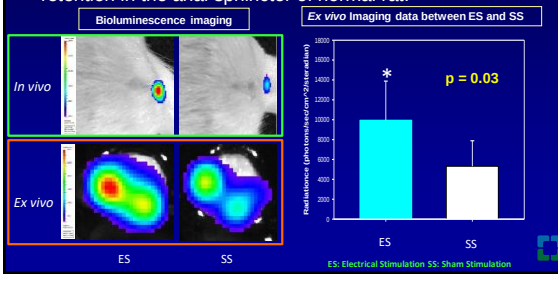
Another study is evaluating SDF-1 in anal fistula in a rat model of Crohn's disease.



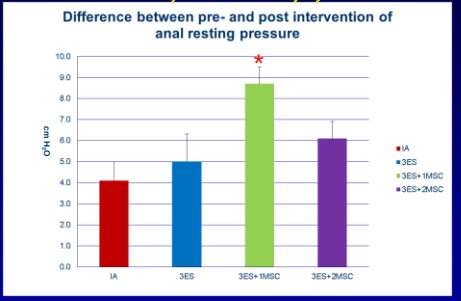
Mesenchymal stem cells following local electrical stimulation improve function in a rat anal sphincter injury model at a time remote from injury. Sun L, et al 2015 DCR

Electrical stimulation and stem cell retention

- We have reported upregulation of CXCL12 and CCL7 expression with both acute injury as well as low current ES.
- Selected ES parameters also achieved the significant MSC retention in the anal sphincter of normal rat.

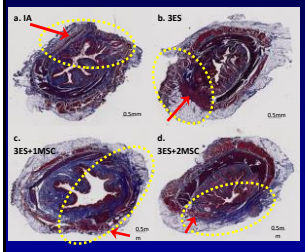


Results : Anal manometry-resting pressure after E stim and MSC injection in an injury model

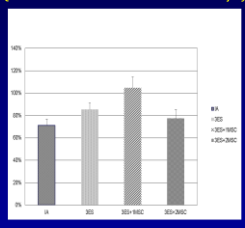


ES with single direct MSC injection significantly improved the resting pressure in a rat model of chronic anal sphincter injury (* p<0.05).

Muscle regeneration in various groups



Quantification of muscle in the area of injury



ES with single direct MSC delivery significantly increased the new muscle seen in the area of injury (*p<0.05)

Conclusion

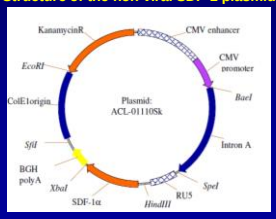
- In a rat model of chronic large anal sphincter defect, daily ES with a single local MSC delivery given 3 weeks after injury significantly improves both anal sphincter pressure and new muscle formation in the area of injury.
- The injection of MSC directly into the anal sphincter at the site of injury following ES may be an easily accessible delivery option.

Re-establishing the microenvironment using SDF-1 plasmid

Plasmid –based transient human stromal derived factor 1 gene transfer improves cardiac function in chronic heart failure. Sundaram S, Miller TJ, Pastore J,et al Gene Therapy,2011,18,867-73

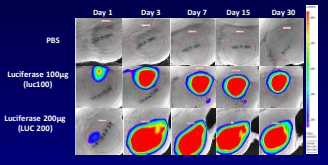
Local injection of SDF-1 plasmid improved vascular regeneration and cardiac function in a rat model of chronic heart failure.

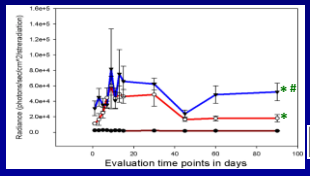
Structure of the non viral SDF-1 plasmid



SDF-1 plasmid is currently in clinical trials for heart failure, wound healing and ischemia.

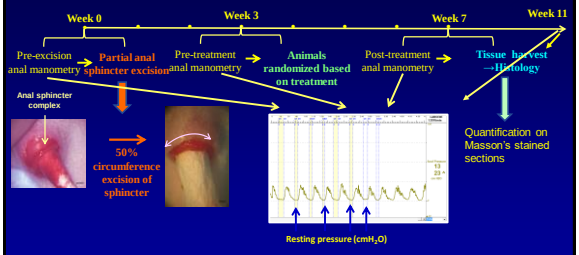
Background : Expression of luciferase encoded plasmid in local tissues after an acute injury





- Two-way ANOVA on Ranks followed by Tukey post hoc test.
- mean ± standard error of the mean (n=6).
- * p<0.05 compare to PBS; # p<0.05 compare to LUC100.

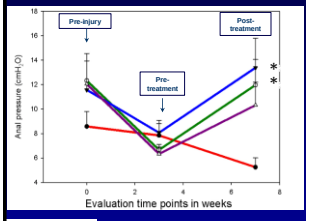
Study Design



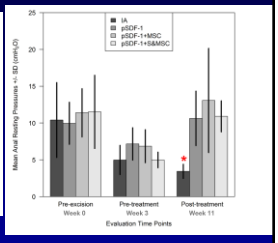
Sun L et al. Regenerating the anal sphincter : Cells cytokines or both? DCR April 2017

Anal pressure measurement over time

4 weeks

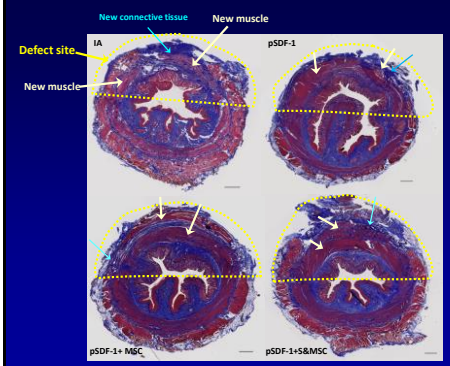


8 weeks



Significant improvement in resting pressure was found in the groups using SDF-1 plasmid alone and the group using SDF-1 &MSC, compared to the IA at 4 weeks and with SDF-1 alone at 8 weeks

Results : Histology - Masson's staining



In the area of the defect, all treatment groups showed filling of the defect with muscle.

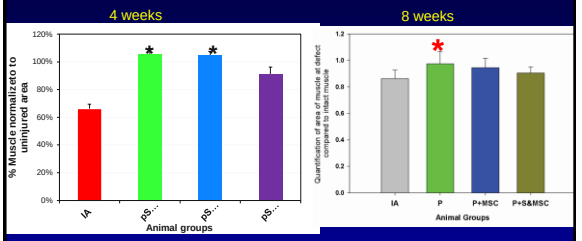
The pSDF-1+MSC group showed the most organization of fibers, the IA group however, showed patchy filling of the defect with a disorganized architecture.

This was sustained at 8 weeks

- Scale bar= 500µm

Sun L et al. Regenerating the anal sphincter : Cells cytokines or both? DCR April 2017

Quantification of muscle at the site of the defect



Compared to the IA group, all three groups receiving the plasmid had significantly greater muscle percentage at the site of the defect at 4 weeks and the SDF-1 plasmid alone had significantly more muscle at 8 weeks

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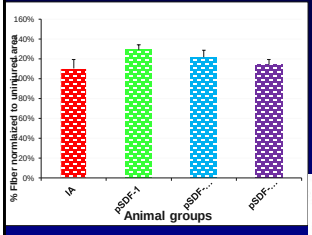
Results : Quantification of connective tissue at the site of the defect



At 4 weeks : No significant difference noted among the four groups in the connective tissue at the site of the defect.

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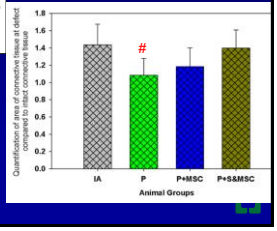
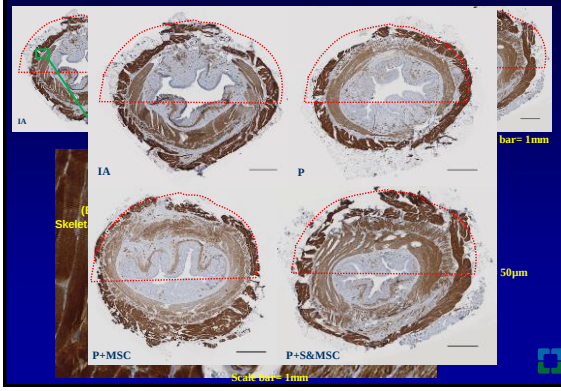
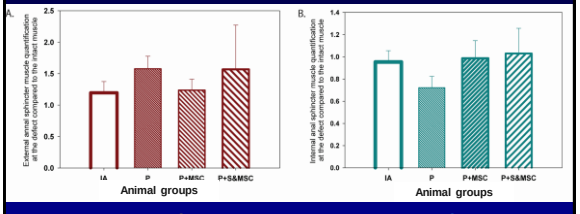


At 8 weeks Significantly less fibrosis was seen in the group receiving **SDF-1 plasmid alone** compared with the IA group and pSDF-1+(S+MSC) group.

Results : Histology – Immunohistochemistry using Desmin



Quantification of skeletal muscle (external anal sphincter) and smooth muscle (internal anal sphincter)



EAS **IAS**

No significant difference was found between groups in quantification of either skeletal or smooth muscle normalized to the uninjured area in the same animal . This signifies that the regenerated muscles were not in excess of that in the intact area.

- One way ANOVA followed by Tukey post hoc test.
- Mean ± SD (n=8).
- p>0.05

Interpretation of results

- **In a rat model of a large anal sphincter excision, local injection with SDF-1 plasmid achieved higher resting pressures, a greater percentage of muscle and less fibrosis at the site of defect 8 weeks post treatment.**
- **SDF-1 plasmid alone or in conjunction with MSC resulted in regeneration of both skeletal and smooth muscle with no change in their ratio compared to normal tissue.**
- **There was no significant difference in functional outcome or CXCR4 or Myf5 expression among the 3 groups receiving the SDF-1 plasmid.**

Conclusions

- SDF-1 alone without stem cells resulted in sustained muscle regeneration in the long term.
- The function recovered to pre-excisional (normal) levels with morphological evidence of both smooth and skeletal muscle regeneration.
- CXCR4 / Myf5 cytokines were not involved in this effect.

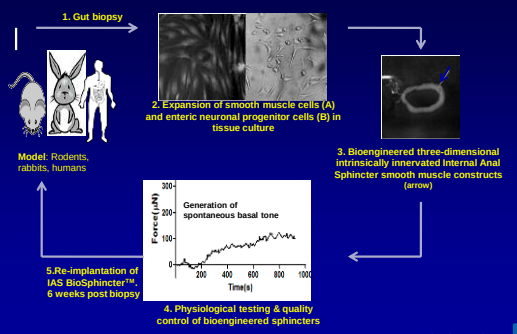
Neo-Anal sphincter ???

- Is there a role?
- Easy to create and implant : Wake Forest University.
- ? Neural control

Bioengineered Internal anal sphincter

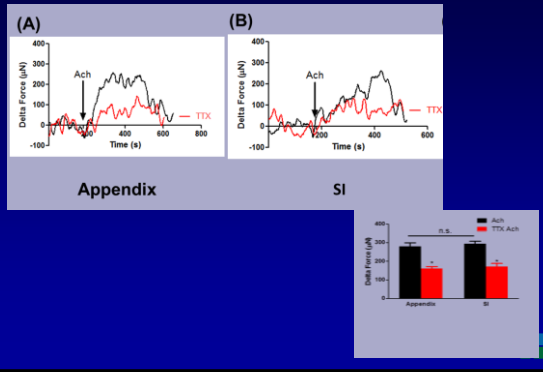
- Successful implantation of bioengineered, intrinsically innervated, human internal anal sphincter . Raghavan S, Gilmont RR, Miyasaka EA et al. Gasteroenterology 2011 Jul;141(1):310-9.
- Previously bioengineered model
- Inserted in mice in the back muscle
- Implanted, intrinsically innervated bioengineered human IAS tissue preserved the integrity and physiology of myogenic and neuronal components.

Restoration of GI motility using autologous cell sources

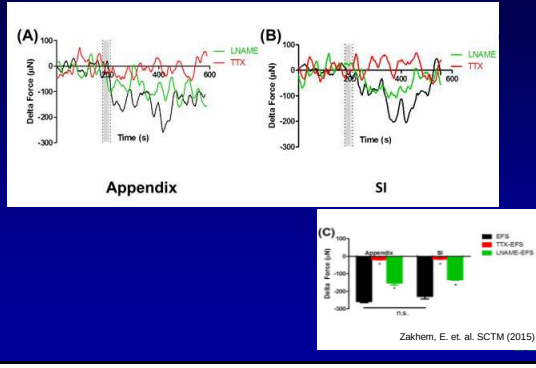


Orlando et. al. Gut 2013

Contractile response of the constructs



Relaxation of the constructs



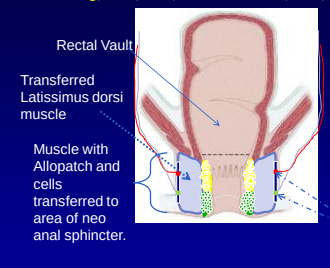
Zakhem, E. et. al. SCTM (2015)

Tissue engineered tubular neuro-muscular tissue

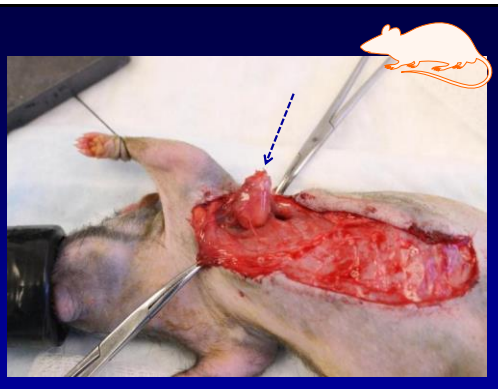
Zakhem et. al. Surgery 2015

Medically Engineered Functional Anal Sphincters Using Composite Tissue Engineering and Novel Electrode Interfaces

S E. Feinberg, DDS, PhD,M G. Urbanchek, PhD, University of Michigan

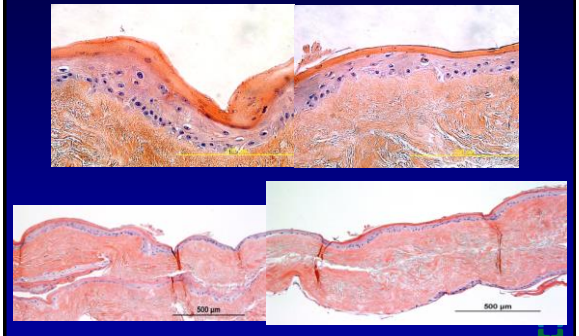


Implant bipolar electrodes on neoanal sphincter.
Implant battery and controller modulator subcutaneously.



Muco-cutaneous Construct

SKIN **ORAL MUCOSA**

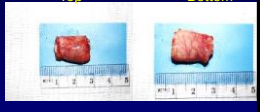


NeoAnal Sphincters of Rat Latissimus Dorsi Muscle with Cells and Alloplast in the Sphincter

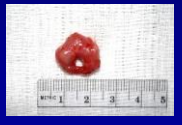
Top Bottom

Neo Spincter with cells explanted POD 0

Top Bottom



Neo Sphincter with cells explanted POD 2wk



Native sphincter

Clinical trials ongoing

A Prospective Nonrandomized Study of Autologous Muscle Derived Cell (AMDC) Transplantation for Treatment of Fecal Incontinence

- UK
- Cook Myosite
- 50 patients

Treatment of Fecal Incontinence by Injection of Autologous Muscle Fibers Into the Anal Sphincter

- **Denmark**
- **15 patients . Muscle biopsy from leg**

Study, Double Blind, Randomized, Comparing Two Groups to Evaluate the Safety and Efficacy of Autologous Mesenchymal Stem Cells From Adipose Tissue (CMMAd) in the Treatment of the Faecal Incontinence

Spain

16 patients (not enrolling)

Summary

- Many new innovations in the future
- Devices as well as cellular/ non cellular therapy will change how we treat fecal incontinence
- Stem cells will be an option only if they can be guided to the anal sphincter at a time remote from injury to heal the entire anal sphincter.
- Bioengineered anal sphincter may be an option with engineering of both IAS and EAS

So, will stem cells be available in the near future?

- That is the hope.
- If not stem cells it may be a cytokine
- Or it may be a ready to use scaffold with cells which can be implanted
- Or maybe a bioengineered anal sphincter
- The possibilities are vast

Funding is however limited

A word of caution

Clinical trials

Injecting stem cells is easy –must have a scientific basis for it.

Questions to be asked

What do stem cells do when injected in normal tissue or in scar tissue or at a time distant from injury?

What can go wrong? Tumors/ tissue in excess?

How do we gauge success?

Thank you