Management of Refractory Constipation

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OBJECTIVES

- Case of Constipation
- Epidemiology
- Pathophysiology
- Clinical/Pathophysiological subtypes
- New modalities of Investigations
- Therapies - One size does not fit all!
40 yr old Nurse, Severe Constipation-2 yrs

**Constipation:**
- B.M once/week, Type 1-2, Straining ++++, FICE ++, No blood
- Laxatives give diarrhea then no BM 1-2 wks, Tried Bisacodyl, PEG, Ex-lax, Senna, Lubiprostone- ? Colectomy

**Pain:** RLQ, sharp, radiates RUQ, every other day, worse p.prandial and with BM, lasts few hours, uses lortabs 1-2/day

**Bloating/gas:** worse p.prandial, avoids eating, wt loss

Significantly affects QOL, missed several wks work

**Past Hx:** Cholecystectomy, Benign breast tumor

**Investigations:**
- Labs, Colonoscopy, CAT scans, EGD & MRI Spine-Normal

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40 yr old Nurse, Severe Constipation, pain, gas & bloating- worse 2 yrs

**O/E:** General Exam normal, tender RUQ, stool ++ in LLQ

**DRE:**
- Anocutaneous reflex intact
- Adequate Resting/squeeze tone, No stool, Guaiac - ve
- Good perineal descent, incomplete relaxation

**Anoscopy - Normal**
Does she have Colonic Inertia or severe Slow transit Constipation?
Does she have dyssynergic defecation + STC?
Does she have pseudoobstruction/generalized dysmotility?
Does she have CHO malabsorption
Is her constipation secondary to opioids?

Constipation is Common in the General Population

Prevalence of constipation (%)

Sex

Study 1
N = 890,394
Hammond
18.8
33.7

Study 2
N = 15,014
Sandler
7
18.2

Study 3
N = 11,024
Everhart
8
20.8

Study 4
N = 42,375
Harari D, et al
Population: NHIS 1987
Criteria: self-report

Age group (years)

Healthcare Burden: Costs - Constipation

Population Assessed = 76,854 patients without supplementary insurance and enrolled in MEDI-CAL
Average cost/patient = $246

Resources = $18,891,008

- Procedues and Tests ($14,052,503)
- Physician Visits ($3,016,017)
- Hospitalizations ($1,433,708)
- All Medications ($388,780)


Functional Subtypes: Primary Constipation

- Slow-transit Constipation 47%
- Irritable Bowel Syndrome 58%
- Evacuation Disorders 59%

• Dyssynergic Defecation
- Outlet Obstr.
  • Rectocele
  • Descending perineum syndrome
  • Rectal prolapse

Slow transit and IBS-C overlap in half of each group

Secondary Causes of Constipation

- Pregnancy
- Collagen vascular and muscle disorders
- Metabolic disorders
- Neurological disorders
- Malignancy (Colorectal cancer, Ovarian cancer)
- Mechanical obstruction
- Endocrine disorders

Complications and co-morbidities

- Fecal impaction
- Anal fissure
- Diverticulitis
- Hemorrhoids
- Volvulus
- Intestinal obstruction
- Ulcers (stercoral or rectal)
- Rectal Bleeding/anemia
- Fecal Incontinence
- Urinary Problems (UTI, Incontinence, Frequency)


Singh et al, Gastroenterology 2005; 128(4 Suppl. 2): S960
40 yr old Nurse, Severe Constipation, pain, gas & bloating - worse 2 yrs

- **Investigations:**
  - Breath Tests - Glucose/ fructose/ lactose
  - Anorectal Manometry
  - Defecography
  - Colonic Transit – Wireless motility Capsule (SmartPill)
  - Colonic Manometry

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**Lactose Breath Test**

- [Graph showing breath test results]
### 40 yr old Nurse, Severe Constipation, pain, gas & bloating- worse 2 yrs

#### Anorectal Manometry

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Normal Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrarectal Pressure</td>
<td>46 mm Hg</td>
<td>52 (45-61)</td>
</tr>
<tr>
<td>Anal residual Pr</td>
<td>20 mm Hg</td>
<td>30(20-40)</td>
</tr>
<tr>
<td>Defecation index</td>
<td>2.0</td>
<td>1.9(1.5-2.8)</td>
</tr>
<tr>
<td>Desire to defecate cc</td>
<td>120 cc</td>
<td>130 (105-170)</td>
</tr>
<tr>
<td>Balloon expulsion time</td>
<td>26 s</td>
<td>&lt; 60 s</td>
</tr>
</tbody>
</table>

#### SmartPill:

**Whole Gut Transit and Motility**

**Gastric emptying**

**Small Bowel Transit**

**Colonic Transit**

- [Graph showing pH and motility data]
40 yr old Nurse, Severe Constipation, pain, gas & bloating - worse 2 yrs

WMC (SmartPill®) Test

<table>
<thead>
<tr>
<th>Subject</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Emptying Time</td>
<td>6 hrs 32 mins</td>
</tr>
<tr>
<td>Small Bowel Transit Time</td>
<td>5 hrs 23 mins</td>
</tr>
<tr>
<td>Colonic Transit Time</td>
<td>&gt;111 hours</td>
</tr>
<tr>
<td>Whole Gut Transit Time</td>
<td>&gt;122 hours</td>
</tr>
</tbody>
</table>
40 yr old Nurse, Severe Constipation

INVESTIGATIONS

- Breath Tests –
  - Glucose/ fructose - Normal excluding SIBO/DFI
  - Lactose Intolerance
- Anorectal Manometry- Normal
- Defecography –Normal
- SmartPill- Delayed GET, CTT & WGTT
- Colonic Manometry-Myopathy, no neuropathy

40 yr old Nurse, Severe Constipation

MANAGEMENT

- Lactose exclusion diet
- Reassure - evidence of colonic myopathy but no neuropathy, mild generalized dysmotility
- Explain Slow Transit Constipation
- Lifestyle + Behavioral + Diet
- D/C opioids & Depo Provera
- Colchicine 0.6 mg bid + Magnesium gluconate
Case Study
29-yr-old Sales Assistant

- Bothersome bowel symptoms - 9 years
  - Began during college days with a bout of constipation and rectal bleeding
  - Now, BM once every 2 weeks, hard, pellet-like stool only after Fleet's enema + Suppository and laxatives
  - Occasional use of digital disimpaction
  - Also describes excessive straining, incomplete evacuation and occasional bleeding
  - Tried OTC laxatives, MOM, PEG-no relief

Rome III Working Group Criteria for Chronic Constipation

- At least 12 weeks (not necessarily consecutive) in preceding 6 months with 2 or more of:
  - ✔ Straining
  - ✔ Sensation of incomplete evacuation
  - Sensation of anorectal obstruction/blockage
  - ✔ Manual maneuvers to facilitate defecation
  - ✔ < 3 BMs/week

- ✔ Loose stools are not present
- ✔ Insufficient criteria for IBS

Evaluation of Colonic and Anorectal Function

Balloon Expulsion Test

FECOM

Anorectal manometry

Colonic Transit Study with Sitzmarks

Day 1 - Bisects
Day 2 - Rings
Day 3 - Trisects
Day 6 (120 hrs)
- Plain abdomen x-ray

Colonic Transit Study- 3 Sitzmarkers
Abdomen x-ray at 120 hrs

68/72 markers retained
Baseline-ARM-Attempted Defecation

Baseline Manometry - Objective Changes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrarectal Pressure</td>
<td>40 mm Hg</td>
</tr>
<tr>
<td>Anal residual Pr</td>
<td>76 mm Hg</td>
</tr>
<tr>
<td>Defecation index</td>
<td>0.46</td>
</tr>
<tr>
<td>Desire to defecate cc</td>
<td>170 cc</td>
</tr>
<tr>
<td>Balloon expulsion time</td>
<td>260 s</td>
</tr>
</tbody>
</table>
Diagnostic Criteria - Dyssynergic Defecation

1. The patient must satisfy diagnostic criteria for functional constipation-Rome III (Longstreth et al Gastroenterology 2006)

2. During repeated attempts to defecate must demonstrate Dyssynergic pattern of defecation
   - Manometry
   - EMG

3. Patient must demonstrate one other abnormal test:
   a. Abnormal balloon expulsion Test (> 1 minute)
   b. Prolonged Colonic Transit Time (radioopaque markers or SmartPill or Scintigraphy)
   c. Abnormal Defecography (≥50% barium retention)

Bharucha et al. Gastroenterology 2006; 130: 1514
Biofeedback - Dyssynergia

Goals of Therapy:

- A) Teach Diaphragmatic breathing exercise
- B) Teach anal sphincter & pelvic floor relaxation
- C) Improve Rectal Sensation
- D) Eliminate Sensory Delay
- E) Improve Recto-anal Coordination

Post-Biofeedback - Attempted Defecation
Case study
Effects of Biofeedback - Objective Changes

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-Biofeedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrarectal Pressure</td>
<td>40 mm Hg</td>
<td>73 mm Hg</td>
</tr>
<tr>
<td>Anal residual Pressure Pr</td>
<td>76 mm Hg</td>
<td>32 mm Hg</td>
</tr>
<tr>
<td>Defecation index</td>
<td>0.46</td>
<td>2.3</td>
</tr>
<tr>
<td>Desire to defecate cc</td>
<td>170 cc</td>
<td>50 cc</td>
</tr>
<tr>
<td>Balloon expulsion time</td>
<td>260 s</td>
<td>10 s</td>
</tr>
</tbody>
</table>

Biofeedback Therapy for Dyssynergia - RCTs
- Biofeedback vs PEG 14.6 g
  - Chiarioni et al, Gastroenterology 2006;130:657-64
- Biofeedback vs Diazepam vs placebo
  - Heymen et al, Dis Col Rectum 2007
- Biofeedback vs Sham Therapy vs Standard Therapy
  - Rao et al, CGH 2007
- Biofeedback vs Standard-Long Term Outcome
  - Rao et al, Am J Gastro 2010
RCT-Biofeedback Therapy for Dyssynergia

n=77

- Standard Treatment
  n=24

- Biofeedback Therapy
  n=28

- Sham Feedback
  n=25

Symptom questionnaire, Stool diary, VAS, Colonic Transit, ARM, Balloon Expulsion test - Baseline and at 3 months

Rao et al CGH 2007

Effects of Biofeedback Therapy on CSBM & Dyssynergia - ITT Analysis

- CSBMs per Week (Mean ± S.E.M.)

- % of Patients with Dyssynergia after Treatment

- p < 0.0001 vs Sham, Standard, & Baseline

CONCLUSIONS

• Biofeedback Therapy
  ➢ Effectively improves symptoms and anorectal function
  ➢ This effect is mediated by modifying their physiologic behavior
  ➢ Biofeedback therapy provides sustained improvement in bowel function
  ➢ Should be the preferred treatment for patients with dyssynergia, especially when patients fail Standard Therapy

Rao et al Am J Gastro 2010
**Constipation In Hospitalized Patient**

- Acute Constipation
  - Hospitalized patient

- Fecal Impaction
  - Disimpaction
  - Sedation
  - Enemas
  - PEG, Laxatives

- Opioid-induced constipation
  - Methyl naltrexone, D/c opioids
  - Lubiprostone
  - SSRI, PEG

- Post-Op Ileus
  - Alvimopan

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**Effect of M-Naltrexone on Laxation**

*Dose= 0.15mg/kg, S.C, Injection/ alternate day*  
*Who: opioids>2 wks + laxatives>3 days*

![Graph showing the effect of M-Naltrexone on laxation response](Thomas et al, NEJM 2008;358;2332-43)
Management of Post-Op Ileus

- Correct Fluid & Electrolyte balance
- NPO/ IV Nutrition
- Withdrawal of opioid and alternative analgesia
- Discontinue drugs that affect motility
- Enemas, Suppositories
- Alvimopan- peripheral mu opioid antagonists

Alvimopan - Post-Op recovery
n=1212

Sacral Nerve Stimulation—Constipation
Prospective, multicenter, n=65 (58 f), age=40 yrs

- 43/65 (66%) had permanent SNS
- S.Frequency $\uparrow = 3.4$/wk to $6.1$/wk (p<0.001)—Primary
- Toileting time decreased $\downarrow = 17.6$ to $9.3$ min (p<0.001)
- Abdominal pain $\downarrow = 4.4$ to $2$ days/wk (p<0.001)
- CCCS (0-30) decreased $\downarrow = 18$ to $10.2$ (p<0.001)
- VAS (0-100) improved $\uparrow = 18$ to $66$ (p<0.001)

SNS is effective therapy for refractory Constipation
- Uncontrolled Study

Role of Chloride Channels in Intestinal Transport

Chloride channels located on the apical surface of the epithelial cells are a driving force for small intestinal fluid secretion.

1. As negatively charged chloride ions actively enter the lumen via chloride channels,
2. Positively charged sodium ions passively diffuse through the intracellular spaces to balance chloride,
3. Allowing water to follow passively into the lumen.

**Effects of Lubiprostone on Number of Spontaneous Bowel Movements**

- Onset of action was within 24 hours in the majority of subjects
- Most common adverse events were nausea, diarrhea, and headache

**Linaclotide—Guanylate cyclase agonist**

- Minimally absorbed, 14-amino acid peptide
- Guanylate cyclase-C (GC-C) agonist, results in generation of cyclic guanosine monophosphate (cGMP)
- cGMP has two activities:
  - activation of CFTR leads to increased luminal fluid secretion and intestinal transit
  - modulation of activity at afferent nerves believed to mediate visceral analgesia
Efficacy of Linaclotide in Chronic Constipation

Responder: ≥3 CSBM/wk & Increase of ≥1 CSBM/wk for ≥9/12 wks

Most common AE: diarrhea (14%-16% vs 4.7%);
Discontinuation (4% vs 0.5%).

Linaclotide: Phase 3 Trial in IBS-C

Primary Responder Endpoints

- ≥3 CSBM/week; and
- Increase of ≥1 CSBM/week
- Both for at least 9 of 12 weeks

- ≥30% reduction in abdominal pain; and
- ≥3 CSBM/week; and
- Increase of ≥1 CSBM/week
- All 3 for at least 9 of 12 weeks

* p<0.05; *** p<0.001; **** p<0.0001 (vs. placebo)

Rao S et al, Am J Gastroenterol 2012
Prucalopride - Severe Chronic Constipation

Entrance criteria: ≤ 2 CSBM / wk

Pathophysiological based Treatment Approach

- Chronic Constipation
  - Slow Transit/Functional Constipation: Tegaserod, Lubiprostone, PEG, Laxatives
  - IBS-C/Normal Transit: Tegaserod, Lubiprostone, SSRI, PEG
  - Dyssynergic Defecation: Biofeedback Therapy

Camilleri et al. NEJM 2008;358:2344-54