**The stomach that refuses to empty**

Michael Camilleri

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- **Funding:** NIH DK92179, DK 67071

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**The stomach that refuses to empty**

- Mechanical obstruction:
  - Pyloric stenosis e.g. peptic stricture
- Iatrogenic
- Neuromuscular dysfunction:
  - antral hypomotility,
  - pylorospasm,
  - chronic Intestinal dysmotility
- Cyclical vomiting
- Rumination syndrome

*Figure from Nature Reviews Gastroenterology & Hepatology 10, 125 (2013)*
**Learning Objectives:** Participants in this session will be able to

- Identify nuances in the history and examination to increase their diagnostic capabilities in the management of patients presenting with chronic nausea and/or vomiting
- Identify the main causes and clinical associations of gastroparesis
- Recognize, through case studies, conditions that are to be considered in the differential diagnosis of gastroparesis including lower GI causes of nausea, cyclical vomiting syndrome, cannabinoid hyperemesis, rumination and RED-RUM syndrome

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**Clinical Guideline: Management of Gastroparesis**

Michael Camilleri, MD; Henry P. Parkman, MD; Mehmaz A. Shafi, MD; Thomas L. Abell, MD and Lauren Gerson, MD, MSc

**Definition of gastroparesis syndrome and gastroparesis symptoms**

**Recommendations**

1. The diagnosis of gastroparesis is based on the combination of symptoms of gastroparesis, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying.
   (Strong recommendation, high level of evidence)
2. Accelerated gastric emptying and functional dyspepsia can present with symptoms similar to those of gastroparesis; therefore, documentation of delayed gastric emptying is recommended before selecting therapy with prokinetics agents or gastric electrical stimulation (GES).
   (Strong recommendation, moderate level of evidence)

Diabetic Gastroparesis: no outlet obstruction

Gastric retention in scleroderma
Small bowel anastomotic staple line in the left lower quadrant and another in the right lower quadrant that appears to be in the distal ileum. There is marked dilatation of the small bowel, with small bowel feces in the segment proximal to the ileal staple line.

Gastroparesis

- Idiopathic
- Post-viral
- Iatrogenic
- Post-surgical
- Diabetic
- Neurological disease

- Others

Soykan, McCallum et al
Dig Dis Sci. 1998; 43:2398-404

- DIABETIC GASTROPARESIS: T1 or T2DM with upper gastrointestinal symptoms
- Classical picture (-triopathy, T1DM>10y may be absent)
- Accelerated GE produces same picture: THEREFORE, MEASURE GE
Iatrogenic gastroparesis

• Post-Surgical: vagotomy or vagal injury
  • Fundoplication
  • Bariatric surgery
  • Peptic ulcer surgery: worse with vagotomy and antrectomy than PGV or vagotomy plus drainage

• Other curve balls related to Diabetes
  Type II DM Rx: Amylin analog (Pramlintide) and GLP-1 agonists (Exenatide), NOT with DPP IV inhibitors (Vildagliptin, Sitagliptin)
  In pancreas/kidney transplanted Calcineurin inhibitors: Cyclosporine A, not tacrolimus (macrolide chemistry)
  • Others e.g. opiates (including tramadol and tapentadol at high doses), cannabinoid hyperemesis
Antroduodenal motility in Disease: Fed pattern

Camilleri, Dig Dis Sci, Vol 38, 1993

Relationship of Gastric Motility to Emptying

Antral pressure activity in trituration of solids and in emptying of solids and liquids from stomach in humans

Michael Camilleri, MD, FACG

Postprandial pylorospasm ? Narcotic-induced

Distal antrum 1

Distal antrum 2

Pylorus

7-358-338

Pylorospasm usually with antral hypomotility


An accurate gastric emptying test is required to exclude gastroparesis

- Society (ANMS, SNM) recommended scintigraphic gastric emptying test 300kcal, 2% fat: >10% retained at 4h
- Well validated Mayo Clinic gastric emptying test: 320kcal, 32% fat, scintigraphy: >23% retained at 4h
- Wireless motility capsule: retention at 5h
- Future in some countries, already available in Europe: stable isotope gastric emptying test
Treatment algorithm for gastroparesis

- Suspected Gastroparesis
- Confirm Diagnosis, Testing for Cause
- Restoration of Fluids and Electrolytes
- Dietary Modifications
- Glucose Control
- Prokinetic Therapy qac
- Anti-emetics pm
- Consider Feeding Jejunostomy
- Decompressive Gastrotomy
- Gastric Electrical Stimulation OR Surgical Therapy

- "Gastroparesis" diet
- Metoclopramide 5-10 mg ac b.i.d.-t.i.d.

- Clinical Response
  - Maintain at Lowest Effective Dose

- Side effects
  - Start Domperidone 10 mg ac t.i.d.
  - Dose Titration

- Incomplete Response
  - Increase to 10-20 mg t.i.d.-q.i.d. as tolerated

- Persistent Symptoms
  - Re-evaluation of Diet
  - Nutritional Support
  - Consider Short-Course Erythromycin 250-500 mg ac t.i.d.

CASE #1  72 year old man with weight loss food intolerance, stool incontinence, never smoker

- Back DJD and pain, unable to walk, peripheral weakness
- Macrocytic anemia, normal B12, ferritin
- Albumen 3.1g/dL, Creatinine 1.8mg/dL, sTSH 6.5u/L, glucose 118mg/dL, urine 236 protein mg/24h
- SPEP, immunofixation –ve
- Sed Rate 23 mm 1st h
- Paraneoplastic screen serology, syphilis, urine heavy metals –ve
- CXR, bone survey for myeloma -ve
### Delayed gastric emptying, other transit normal

<table>
<thead>
<tr>
<th>Gastric Emptying:</th>
<th>0</th>
<th>24%</th>
<th>33%</th>
<th>76%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-SC:0</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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<tr>
<td>C-SC:1</td>
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<td><img src="image7.png" alt="Image" /></td>
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<tr>
<td>C-SC:2</td>
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<tr>
<td>C-SC:4</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colonic filling At 6 h:</th>
<th>94%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic transit At 24 h:</td>
<td>GC 2.0</td>
</tr>
</tbody>
</table>

### Thermoregulatory Sweat Test

**Indication:** GI MOTILITY DISORDER; PERIPHERAL & TRUNCAL NEUROPATHY

**RESULTS:**
- Oral temperature before: **36.7°C** after: **38.0°C**
- Body surface anhidrosis: **91%**
- Distribution: **GLOBAL**

**IMPRESSION:**
- The patient was essentially anhidrotic, with relative sparing of the hands, thighs and distal feet. Such pattern can be seen in widespread autonomic neuropathies or central autonomic disorder.
HEART RATE RESPONSES

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameter</th>
<th>Result</th>
<th>[Normal Range for age, gender]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva Maneuver</td>
<td>Valsalva Ratio</td>
<td>1.14</td>
<td>&gt; 1.29</td>
</tr>
<tr>
<td>Deep Breathing</td>
<td>Heart Rate Range (bpm)</td>
<td>1.3</td>
<td>&gt; 7</td>
</tr>
</tbody>
</table>

BLOOD PRESSURE & HEART RATE RESPONSES TO TILT

Values with subject to 70 degree tilt up

<table>
<thead>
<tr>
<th>Supine</th>
<th>1 min</th>
<th>5 min</th>
<th>7 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mmHg)</td>
<td>134/78</td>
<td>108/64</td>
<td>80/54</td>
</tr>
<tr>
<td>Pulse</td>
<td>74</td>
<td>78</td>
<td>83</td>
</tr>
</tbody>
</table>

QUANTITATIVE SUDOMOTOR AXON REFLEX TEST (QSART)

<table>
<thead>
<tr>
<th>Site</th>
<th>Test</th>
<th>Current (mA)</th>
<th>Duration (min)</th>
<th>Output (uL/cm²)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Forearm</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>4.76</td>
<td>[M 0.84-5.42; F 0.12-4.39]</td>
</tr>
<tr>
<td>L Proximal Leg</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>2.11</td>
<td>[M 0.76-3.91; F 0.20-2.36]</td>
</tr>
<tr>
<td>L Distal Leg</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>0.19</td>
<td>[M 0.93-4.98; F 0.20-2.98]</td>
</tr>
<tr>
<td>L Foot</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>0.50</td>
<td>[M 0.70-5.39; F 0.16-3.03]</td>
</tr>
</tbody>
</table>

Widespread autonomic and peripheral neuropathy

- **Autonomic**: Cardiovagal, cardiovascular adrenergic, and postganglionic sympathetic sudomotor dysfunction

- **EMG, Nerve conduction**: a length-dependent axonal sensorimotor neuropathy

- **Anal sphincter pressure**: rest 54mmHg; squeeze 83 mmHg (pudendal nerve dysfunction)
Neuro and other consults

- Macroglossia; dysgeusia
- Special urine studies: small monoclonal κ light chain
- Fat aspirate +ve for amyloid protein
- NOTE SPEP does not exclude monoclonal gammopathy and AMYLOIDOSIS
- Cardiac Echo: left ventricular wall thickness, diastolic dysfunction, bi-atrial enlargement
- Bone marrow: Systemic amyloidosis, AL type, comprised of κ Ig light chains
- NOTE GI diagnosis aided by autonomic tests
- Unfortunately, patient died 4 months later

CASE #2 42 year old male diabetic patient diagnosed with cyclical vomiting syndrome

- Transit, accommodation and MRI brain: all normal 5 yr previously at Mayo Clinic (another GI staff).
- 7 year history of morning sickness,
- Acute attacks occurring approximately once every month for past 6 years, requiring multiple admissions to hospital for 24 to 48 hours after presentation to the emergency room.
- Experiences excessive heat and sweating during acute emesis.
- In the past year, i.m. Compazine and Versed to abort the episodes of severe nausea and vomiting.
- Denies history of retinopathy, neuropathy, or nephropathy in association with diabetes,
- Onset of nausea/vomiting very soon after onset of diabetes.
- Rx: Metformin 500mg b.i.d. and Exenatide 5μg b.i.d.
CASE #2 42 year old male diabetic patient diagnosed with cyclical vomiting syndrome

- The patient acknowledges that he may use marijuana in order to control the nausea, and that if available, he would use daily.
- He acknowledges exposure to marijuana in his late teens.
- Scintigraphic gastric emptying:
  - 1 hr 22% (normal 11-39%)
  - 2hr 56% (normal 40-76%)
  - 4 hr 87% (normal 84-98%)
- Gastric accommodation test 432 mL (normal >428 mL).
- **Diagnosis:** Probably cannabinoid hyperemesis
- Refer: Psychiatry for withdrawal of cannabinoids.

CASE #3: 43 year old female with recent history of breast cancer (will require chemo and radiotherapy) referred for chronic vomiting

- Extensively evaluated elsewhere, including negative upper GI endoscopy, gastroduodenal manometry, esophageal manometry and impedance, Bravo pH testing, etc…
- Cholecystectomy for a small stone in the gallbladder
- **What is the appropriate NEXT STEP?**
  - CT/MRI of brainstem
  - Other?
CASE #3: 43 year old female with recent history of breast cancer (will require chemo and radiotherapy) referred for chronic vomiting

• TAKE A HISTORY

• Past three years:
  • daily, effortless vomiting occurring after every meal starting within one hour of eating, typically immediately after breakfast.
  • The food tastes just like the food she has just eaten as it regurgitates back in the throat.
  • Sometimes she does have acid or burning food coming back into her throat.
  • She does not swallow food back down but expels it from the throat and mouth.

Rumination Syndrome

• Repetitive regurgitation of gastric contents occurring within minutes after a meal
• Episodes often persist for 1 to 2 hours.
• Regurgitant: partially recognizable food
• Regurgitation is effortless or preceded by a sensation of belching immediately before the regurgitation or arrival of food in the pharynx
• No retching or nausea precedes regurgitation.
• Conscious decision: swallow or spit
• A "meal in, meal out, day in, day out" behavior

O'Brien MD, Bruce BK, Camilleri M. Gastroenterology 1995;108:1024-1029
“You cannot be serious, doc! You have got to do more tests”

GE may be modestly delayed in Rumination syndrome as food moves back and forth, up and down in the stomach.
SPECT Method to Measure Gastric Volumes

Transaxial images reconstruction with ANALYZE

Abdo perimeter

REGION OF INTEREST AROUND STOMACH

Gastric Volume, mL

SPECT camera to measure gastric volume

Fasting

Postprandial

Normal Gastric Accommodation

Normal >428mL

Rx: Behavioral therapy with diaphragmatic breathing
Normal Fasting and Postprandial Upper GI Motility

Antroduodenal 1
Antroduodenal 2
Antroduodenal 3
Antroduodenal 4
Antroduodenal 5
Desc. duodenum
Distal duodenum
Proximal Jejunum

50 mmHg
5 min
Meal-related "reflux" with no supine pH drops = Rumination

Meal-related and supine pH drops = TRUE GE reflux

Rumination syndrome with complications

- Iatrogenic
- RED-RUM syndrome
CASE #4:
F, 21y “Past 5 y, my stomach does not allow food to digest”

- **Effortless regurgitation**
  - Daily, immediately after every meal
  - Several hours
  - Solids and liquids
  - Non-acid → acid and bitter
  - Re-swallowing

- **Other symptoms**
  - Abdominal bloating
  - Nausea, no vomiting
  - Weight fluctuation
  - Burning retrosternal sensation
  - Constipation

Past Medical History

- Anorexia nervosa – bulimia
- Bipolar disorder
- ADHD (attention deficit, hyperactivity disorder)
- **EGD**: grade C esophagitis (Los Angeles)
- **Esophageal manometry**
  - abnormal GE junction + hypotensive LES
- Laparoscopic Nissen fundoplication (01-2008);
  “leak” leading to localized gastric resection;
  G tube feeding for 3 months
Physical examination
- BMI 18.3 kg/m²
- Abdomen
  multiple scars, nl bowel sounds,
  no succussion splash/organomegaly/mass
- Rectum
  no signs of evacuation disorder

Gastric Emptying of Solids: Markedly delayed:
Note the esophagus
Gastric Accommodation: Markedly reduced 290mL

Plasma pancreatic polypeptide response to modified sham feeding: test of abdominal vagus

\[ \Delta <25\text{pg/mL}, \text{ Flat response} \]
Treatment strategy

- Rumination syndrome
  - Diaphragmatic breathing
- Severe gastroparesis
  - Homogenized solids
  - Liquid formula metoclopramide 5mg 4x/d
  - Buspirone 5mg 2x1/d
- Bile acid reflux
  - Al-Mg 30ml 3x/d

CASE #5: 18y, F with 10 year history of

- Abdominal pain: sharp, epigastric, without radiation, relieved by lying down, curling up in bed, or stooping forward.
- Vomiting worse with fast foods and red sauces: worse with anxiety, and associated with nausea, loss of appetite
- Food would regurgitate easily in an effortless manner, almost on its own without any straining, retching, or contraction of the abdominal muscles. The effortless regurgitation of food consisted of material that was containing unchanged food, but subsequently it also occurred repeatedly and the subsequent regurgitant was bitter or acid to taste.
- Started on domperidone 10 mg tablets on awakening.
- 3 EGDs and colonoscopy elsewhere: essentially negative.
CASE #5: 18y, F with 10 y vomiting and abdo pain

• EXAMINATION

• Abdomen: palpable stool in RLQ and LLQ.

• Rectum: 2/4 maneuvers to evacuate the examining finger paradoxical contraction of the puborectalis and anal sphincter.
Michael Camilleri, MD, FACG

Anorectal Manometry

Resting Anal Pressure 160mmHg
Squeeze Anal Pressure 289mmHg
R-A pressure differential -30.6mmHg
Balloon expulsion 94g

Results in 57 patients with this syndrome

<table>
<thead>
<tr>
<th>Physiological measurement</th>
<th>Patients (n=57)</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average resting anal sphincter pressure (mmHg)</td>
<td>91.5±5.2</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Balloon expulsion test (g)</td>
<td>435±28</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>

**Diagnosis:** Rumination syndrome, Rectal Evacuation Disorder (Anismus), RED-RUM syndrome

Reduced gastric accommodation

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**Diagnosis: RED-RUM syndrome**

- Rumination syndrome + Rectal Evacuation Disorder
- Of 438 patients evaluated for RED over the 19 years, 57 (13%) had concomitant rumination syndrome:
  - 95% F, 89% Caucasian
  - Mean 30.3 ± 1.6 y (8 being <18 years)
  - BMI 20.8 ± 0.5 kg/m² (15 BMI <18.5 kg/m²)

Vijayvargiya, Iturrino, Camilleri et al
UEG Journal 2014:2:38-46
Take Home: Chronic Nausea and Vomiting

- Inquire about constipation and rumination
- Examine the whole patient (especially rectum)
- Consider iatrogenic disease
- Measure whole GI and colonic transit
- Have a low threshold to evaluate rectal emptying
- Ockham’s razor or law of parsimony (used in logic and problem-solving: “among competing hypotheses, the hypothesis with the fewest assumptions should be selected”) does not work
Limiting the urgency for patients with IBS-D

Paul Moayyedi
Co-Editor in Chief of American Journal of Gastroenterology
Director, Division of Gastroenterology
McMaster University, Hamilton Ontario, Canada

Overview

• Definition of IBS
• Epidemiology
• Key diagnostic tests
• Efficacy of therapy
Rome III definition of IBS

- Recurrent abdominal pain or discomfort at least three days a month in the last three months with two or more of the following:
  - i) improvement with defecation
  - ii) onset associated with a change in frequency of stool
  - iii) onset associated with a change in form (appearance) of stool

http://www.romecriteria.org

World wide prevalence of Rome II IBS

7% (95% CI = 6-7%)

36 populations, 128,893 subjects

Lovell RM et al. CGH 2012; 10: 712-21
Epidemiology of IBS

- Female > male (OR = 1.67; 95% CI = 1.53-1.82)
- No clear racial differences
- No differences between socioeconomic groups
- Younger > older

Lovell RM et al. CGH 2012; 10: 712-21

Age and IBS

<table>
<thead>
<tr>
<th>Age band</th>
<th>% with IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>11</td>
</tr>
<tr>
<td>30-39</td>
<td>11</td>
</tr>
<tr>
<td>40-49</td>
<td>9.6</td>
</tr>
<tr>
<td>50-59</td>
<td>7.8</td>
</tr>
<tr>
<td>≥ 60</td>
<td>7.3</td>
</tr>
</tbody>
</table>

P<0.001
IBS subtypes

- IBS-C
- IBS-D
- IBS-M
- IBS-U

Lovell RM et al. CGH 2012; 10: 712-21
Lewis SJ et al. SIG 199
Rome III IBS subtypes

Investigations

- Celiac antibodies
- Colonoscopy
Celiac disease in IBS

- 14 studies
- 2278 IBS patients
- 4% had celiac disease
- OR 3.4 (1.6 to 7.1) compared to normal

Yield of colonoscopy in non-constipated IBS

- 466 IBS patients and 451 controls
- No significant increase in pathology in IBS
- 7/466 (1.5%) had microscopic colitis
- 4/171 (2.3%) in those ≥ 45 years
Therapy for IBS-D

Systematic Review on the Management of Irritable Bowel Syndrome in North America

Lawrence J. Brandt, M.D., Chairman,1 David Bjorland, M.D., T M. Brian Fennerty, M.D. 2
G. Richard Locke, M.D., 3 Kevin O'Mor, M.B., 4 Walter Peterson, M.D., 5 Graham Quigley, M.D., 6
Philip Schoenfeld, M.D., M.S.Ed., M.Sc., (Epi), 7 Marvin Schuster, M.D., 7 and Nicholas Talley, M.D., Ph.D. 8

1Albert Einstein College of Medicine, Bronx, NY; 2University of Utah School of Medicine, Salt Lake City,
3Mayo Clinic, Rochester, MN; 4Mayo Clinic, Scottsdale, AZ; 5University of Texas Southwestern Medical School, Dallas, TX; 6National University of Ireland, Cork, Ireland; 7University of Michigan School of Medicine, Ann Arbor, MI; 8Johns Hopkins Bayview Medical Center, Baltimore, MD, and 9Nepean Hospital, Penrith, New South Wales, Australia

2.9 EFFECTIVENESS OF ANTIDEPRESSANTS IN THE MANAGEMENT OF IRritable BOWEL SYNDROME

Tricyclic antidepressants (TCAs) are not more effective than placebo at relieving global IBS symptoms. TCAs improve
### IBS and antidepressants

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antidepressant</th>
<th>placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H Random, 95% CI</td>
</tr>
<tr>
<td>Heffer 1978</td>
<td>9 14</td>
<td>8 17</td>
<td>1.37 [0.72, 2.58]</td>
</tr>
<tr>
<td>Vj 1991</td>
<td>10 23</td>
<td>19 25</td>
<td>0.53 [0.31, 0.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>19 39</td>
<td>27 42</td>
<td>0.83 [0.33, 2.12]</td>
</tr>
</tbody>
</table>

Test for overall effect: z = 2.45 (P = 0.01)

Quartero AO et al. CDSR 2009; issue 1

### IBS and antidepressants revisited

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>antidepressant</th>
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<th>Risk Ratio</th>
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<tr>
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<td>9 14</td>
<td>0.73 [0.39, 1.39]</td>
</tr>
<tr>
<td>Vj 1991</td>
<td>10 23</td>
<td>19 25</td>
<td>0.53 [0.31, 0.89]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>18 28</td>
<td>28 39</td>
<td>0.60 [0.40, 0.90]</td>
</tr>
</tbody>
</table>

Test for overall effect: z = 2.45 (P = 0.01)
First line therapy

- Fibre
- Probiotics
- (loperamide)
- Restriction diets (e.g. low FODMAPS)
Fibre and IBS

- Bran
  - 6 trials
  - 441 patients
  - Not effective
- Soluble fibre (psyllium)
  - 7 trials
  - 499 patients
  - Effective
  - NNT = 7 (95% CI = 4 to 25)

Probiotic therapy in IBS

- 34 trials involving 3205 patients
- 13 trials of low risk of bias
- NNT = 5 (95% CI = 4 to 10)
### Type of probiotic in IBS symptoms

<table>
<thead>
<tr>
<th>Probiotic (Combination)</th>
<th>Number of Patients</th>
<th>Number of Patients Treated</th>
<th>bowel symptom improvement</th>
<th>No. of Studies</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>42</td>
<td>42</td>
<td>42</td>
<td>2 RCTs</td>
<td>No statistically significant effect</td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2 RCTs</td>
<td>No statistically significant effect</td>
</tr>
<tr>
<td>Loperamide</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2 RCTs</td>
<td>No statistically significant effect</td>
</tr>
</tbody>
</table>

**Combination**
- Lactobacillus
- Bifidobacterium

**Loperamide**
- 2 RCTs
- 42 IBS patients
- No statistically significant effect
Restriction diets in IBS

• Serum IgG guided food sensitivity
• Gluten sensitivity
• Low FODMAPs diet

Potentially eligible studies

• 17 RCTs
• 1,568 patients
Eligibility

17 trials
- 9 cross-over trials data not extractable

8 trials
- 1 not an RCT, 4 no symptom data or continuous data only

3 eligible trials

Diet RCTs

- 150 patients food exclusion according to IgG antibody test – real versus sham
  - 18/65 (28%) real vs. 11/66 (17%) sham (p=0.14)

- 41 patients FODMAPs versus habitual diet
  - 13/19 (68%) low FODMAP improved vs. 5/22 (23%) usual diet (p=0.005)

- 39 patients gluten challenge vs. GFD
  - 13/19 (68%) gluten group had symptoms vs. 6/15 (40%) placebo group (p=0.16)
Second line therapy

- Rifaximin
- Antidepressants
- (Cholestyramine)
Rifamixin in IBS

- 5 RCTs
- 1803 patients
- 550mg t.i.d for 2 weeks
- Follow up 10-12 weeks
- NNT = 10

Menees SB et al. AJG 2012; 107: 28-35

Antidepressants

- Tricyclic antidepressants
  - 11 RCTs
  - 744 patients
  - NNT = 4 (95% CI 3 to 6)
  - Constipation a side effect
- SSRI
  - 7 RCTs
  - 356 patients
  - NNT = 4 (95% CI 2 to 20)

Cholestyramine

- 23 case series
- 801 BAM patients
- 70% responded to therapy

Third line therapy

- Alosetron
Alosetron

- 8 RCTs
- 4,987 IBS patients
- NNT = 8
(95% CI = 5 to 17)

Ford AC et al. AJG 2009; 104: 1831-40

Risk management plan

- Clinical trials and post-marketing surveillance
- 29,072 patients received alosetron
- 16,762 patient years
- 39 potential cases of ischemic colitis
- 15 probable IC cases (5 possible)
- Risk = 0.95 per 1000 patient years
- No deaths, megacolon, surgeries, perforations

Chang L et al. AJG 2010; 105: 866-75
Conclusions

• IBS-D impacts 2% US population
• Exclude organic pathology
• Effective first and second line therapies
  – Fiber
  – Probiotics
  – TCA
  – Rifaximin
Advice to Alex Ford

- Reviews been done already
- Won’t be much work
- Won’t be that interesting
- Won’t be cited much
- This is an important and influential monograph

Citations for 2009 IBS ACG monograph

<table>
<thead>
<tr>
<th>Paper</th>
<th>Journal</th>
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<tbody>
<tr>
<td>Antidepressants and psychological therapies</td>
<td>Gut</td>
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<tr>
<td>Monograph on IBS</td>
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<td>Probiotic therapy</td>
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<tr>
<td>Fibre, antispasmodic therapy, peppermint oil</td>
<td>BMJ</td>
<td>121</td>
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<td>SIBO in IBS</td>
<td>CGH</td>
<td>92</td>
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<td>5-HT3 Antagonists and 5-HT4 Agonists</td>
<td>AJG</td>
<td>86</td>
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<td>Celiac disease in IBS</td>
<td>Archives Int Med</td>
<td>80</td>
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<td>Symptom diagnosis</td>
<td>JAMA + Gut</td>
<td>40 + 34</td>
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<tr>
<td>Errors in systematic reviews + placebo effect</td>
<td>AJG + APT</td>
<td>18 + 30</td>
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<td><strong>Total</strong></td>
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</table>
Clearing Out the Pipes in IBS-C

Adil E. Bharucha, MBBS, M.D.
Professor of Medicine,
Division of Gastroenterology and Hepatology,
Mayo Clinic College of Medicine,
Rochester, MN

Outline

- Case report
- Classification of chronic constipation
- Diagnosis and management of defecatory disorders
- Management of chronic constipation and C-IBS
### A Patient with Constipation

- 19 yo lady with constipation for 2 years
- Infrequent bowel movements; hard stools (Bristol 1)
- No urge to defecate
- Abdominal discomfort and bloating; not related to eating
- Pain → hard stool and relieved by defecation
- Normal colonoscopy
- Exam – lower abdominal tenderness
- What is your diagnosis?

**Constipation-predominant IBS**

### A Patient with Constipation

- 19 yo lady with constipation for 2 years
- Infrequent bowel movements; hard stools (Bristol 1)
- No urge to defecate
- **Excessive straining, sense of anal blockage during defecation**
- **Sense of incomplete evacuation after defecation**
- Right lower abdominal discomfort and bloating; not related to eating
- Pain associated with hard stool and relieved by defecation
- Normal colonoscopy
- Exam – lower abdominal tenderness
  - Rectal – stool, high anal resting tone, reduced perineal descent during evacuation
Tests and Outcome

Stool
Anal manometry + rectal balloon test → defecatory disorder
Pelvic floor retraining

Air

Take Home Messages

- Chronic constipation → distention of right colon → abdominal bloating and pain
- Defecatory disorders → chronic constipation
  - Diagnosed by anal manometry and rectal balloon expulsion tests
  - Amenable to pelvic floor retraining, and
  - Not managed by colectomy
Population-Based Incidence of Common GI Disorders in Olmsted County

Outline

• Classification of chronic constipation

Prevalence of Crohn's disease and IBS-C from previous studies:

Noelting J, Eaton J, Gastroenterology 2013 abstract
### Classification of Chronic Constipation

<table>
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<tr>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Anorectal tests</td>
<td>+</td>
</tr>
<tr>
<td>Colonic transit</td>
<td>-</td>
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</table>

- Normal transit constipation
- Isolated slow transit constipation
- Defecatory disorders

### What is the difference between Chronic Constipation and C-IBS?

- **C-IBS is defined by abdominal discomfort**, which is associated with ≥ 2 of the following criteria:
  - Relieved by passing a bowel movement
  - Associated with harder stools or
  - Less frequent stools
- **Chronic constipation is only defined by bowel symptoms** (infrequent stools, hard stools, straining, anorectal blockage, anal digitation, and sense of incomplete evacuation)
  - Patients may also have abdominal discomfort

---

1 Camilleri M. Neurogastroenterol Motil (2010) 22, 293–e82
Outline

- Diagnosis and management of defecatory disorders

Assessment of Anorectal Functions

Suspected defecation disorder

Anorectal manometry and balloon expulsion

Both Normal

No defecation disorder

Both abnormal

Functional defecation disorder

Assessment of Anorectal Functions

Suspected defecation disorder

Anorectal manometry and balloon expulsion

Both Normal

One test abnormal

No defecation disorder

Defecography

Both abnormal

Functional defecation disorder

False positive and negative tests occur

Normal versus Disordered Defecation

Normal

Defecatory disorder
Rectal Balloon Expulsion Test and Anorectal Manometry

• Measure time required to expel a balloon filled with 50 mL of water while seated on a commode
  - Normal – technique dependent - typically 1 minute\(^1\), sometimes 2 minutes\(^2\)
  - Very (> 85%) sensitive and specific for identifying defecatory disorders\(^3\)
  - Simple test – no independent billing code
  - An abnormal balloon expulsion test predicts the response to biofeedback therapy\(^4\)

• Anorectal manometry
  - High anal resting pressure
  - Impaired rectoanal coordination during evacuation


Anorectal Pressure Profiles

Propulsion + relaxation = Fecal expulsion

• Dyssynergia is not “abnormal”
  - 16% of asymptomatic women - conventional manometry \(^1\)
  - 37% by high resolution manometry \(^2\)
• Dyssynergia by conventional ARM did not predict abnormal balloon expulsion in healthy subjects \(^3\)

Asymptomatic women can have a
Anal > rectal pressure and
negative rectoanal gradient
(Rectal – anal pressure)
during simulated evacuation

Biofeedback Therapy for Disordered Defecation

- Anorectal functions recorded by surface EMG (perianal or anal sensors), manometry, or a rectal balloon
- Patient visualizes (hears) activity and thereby
- Learn to correct abnormal muscle motion
  – i.e., to coordinate abdominal motion and pelvic floor relaxation
- Several sessions daily over 10 days or less frequent sessions (e.g., weekly)
- Three studies (216 patients) vs sham therapy/PEG\(^1-3\)
  – NNT 2 (95% CI 1.6-4)\(^4\)
- Not widely available, variable insurance coverage

Outline

- Classification of chronic constipation
- Diagnosis and management of defecatory disorders
- Management of chronic constipation and C-IBS

Pharmacotherapy for Constipation

- Available/approved in the US
  - Fiber supplements
  - Osmotic laxatives
  - Stimulant laxatives
  - Secretagogues
    - Chloride channel-2 stimulant – lubiprostone
    - Guanylate cyclase C (GCC) agonist - linaclotide
- Approved in Mexico, Canada, Europe
  - Serotonin 5-HT₄ agonists – prucalopride
- Undergoing phase 3 trials
  - Ileal bile acid transporter (IBAT) inhibitor A3309
  - GCC agonist - Plecanatide
Comparison of Intestinal Secretagogues

<table>
<thead>
<tr>
<th></th>
<th>Lubiprostone</th>
<th>Linaclootide</th>
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<tr>
<td>Chemistry</td>
<td>Prostone</td>
<td>Peptide</td>
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<tr>
<td>Target receptor</td>
<td>Chloride channel (CIC2); ? CFTR</td>
<td>Guanylate cyclase C CFTR-mediated</td>
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<tr>
<td>Pharmacodynamics</td>
<td>↑ small bowel + colonic transit in health</td>
<td>↑ colonic transit in IBS</td>
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<tr>
<td>Clinical trial efficacy</td>
<td>Phase II and III - CC, C-IBS</td>
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<tr>
<td>Commonest AEs</td>
<td>Diarrhea, nausea</td>
<td>Diarrhea</td>
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<tr>
<td>Potential other actions</td>
<td>Mucosal protection</td>
<td>Anti-nociceptive</td>
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Therapeutic Efficacy for Chronic Constipation and C-IBS

Lower NNT is better

Caveats
• Trials are not head-to-head comparisons
• Endpoints differed across studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chronic Constipation</th>
<th>C-IBS</th>
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<tr>
<td></td>
<td>NNT (95% CI)</td>
<td>Patients</td>
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<tr>
<td>Soluble fiber</td>
<td>2 (1.6-3)</td>
<td>293</td>
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<tr>
<td>PEG</td>
<td>3 (2-4)</td>
<td>573</td>
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<tr>
<td>Lactulose</td>
<td>4 (2-7)</td>
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<tr>
<td>Bisacodyl</td>
<td>3 (2-3.5)</td>
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<tr>
<td>Bisacodyl</td>
<td>3 (2-3.5)</td>
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<tr>
<td>Lubiprostone</td>
<td>4 (3-6)</td>
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<tr>
<td>Linaclootide</td>
<td>6 (5-8)</td>
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<tr>
<td>Prucalopride</td>
<td>5 (4-8)</td>
<td>3140</td>
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</table>

**Initial Therapy**

**Practical Suggestions**

- Fiber supplementation – Start with 10g daily in divided doses, increase if required. Manage expectations.
- Osmotic laxatives
- Use rescue measures (eg, bisacodyl or glycerine suppository or sodium phosphate enema) 30 minutes after breakfast for patients who have no stool for 2 days.
- For patients with anxiety or depression
  - Consider behavioral therapy (also for abdominal bloating) and/or
  - SSRIs (eg, paroxetine) – which reduce pain, improve well being and anxiety.

---

**Putting it Together**

- Fiber +/- osmotic +/- stimulant laxatives
- Poor response → Yes → Biofeedback therapy
- ? Pelvic floor dysfunction → No
  - Linaclotide or lubiprostone
    - Poor response → Assess colonic transit
      - Slow transit → Consider prucalopride
        - Poor response → Consider subtotal colectomy
      - Fast transit → Continue
    - Efficacy of linaclotide and lubiprostone in patients who have failed “simple” laxatives is unknown.
    - Is the response to treatment influenced by pathophysiology of constipation?
Occasionally, consider removing the pipe…
Surgery for Slow Transit Constipation

- When – Refractory slow transit constipation without pelvic floor dysfunction
- Subtotal colectomy with ileorectostomy – NOT partial resection
- In 1 series of 74 patients
  - No mortality, early complications (~ 20%), delayed small bowel obstruction (7 patients)
  - Spontaneous defecation - 100% at 5 years; quality of life improved in 87%
- Laparoscopic procedure possible


Summary

- Assess symptoms + exam + tests (colonic transit and anorectal functions) in chronic constipation
- Normal transit, isolated slow transit constipation or defecatory disorders
- Anorectal tests are necessary to diagnose defecatory disorders
- Management
  - Defecatory disorders- biofeedback therapy
  - The rest - Fiber supplements, laxatives, secretagogues
  - Refractory slow transit – subtotal colectomy