Colonic Motility and Constipation

Hammad Liaquat
The Colon

- Colonic innervation emanates from two sources: the extrinsic (parasympathetic/sympathetic) and the intrinsic (ENS) nerves.

- Storage of stool in AC and TV.

- Mixing of contents through phasic contractions, long. muscle contractions – formation of haustra

- Mass movements – via HAPCs over 15 cm each. Circular muscle contraction. 5-6 times/day btw 6 am to 2 pm
Interstitial cells of Cajal (ICC)

- ICC play role of pacemaker

- Facilitate electric current conduction and neural signalling to muscles

- Ach, 5HT, Substance P (excitatory) vs VIP, NO (inhibitory)
Physiology

- Colon gets 1.5 l fluid daily, most of it absorbed, 100-200 ml expelled with stool.
- Na/Cl exchange and short chain fatty acid transport stimulate water absorption.
- Mean colonic transit time in 36 hours (max 74 hours)
Defecation

• Distension of rectum and relaxation of int. anal sphincter

• Coordinated relaxation of the puborectalis and external anal sphincter muscles

• Increased intra-abdominal pressure

• Inhibition of colonic segmenting activity
Constipation
Definition

- Variable amongst patients and physicians!

- Patients: Stools may be too hard or too small, too difficult or infrequent.

- Physicians: Reduced stool frequency, straining to defecate, hard stools, or inability to defecate.

- Normal bowel habits vary widely:
  - 2/day to 2/week
  - 20-250g/day
  - Formed to semi-formed
Rome III criteria for functional constipation

- Presence of two or more of the following for at least three months (with symptom onset at least six months prior to diagnosis):
  - Straining during at least 25% of defecations
  - Lumpy or hard stools in at least 25% of defecations
  - Sensation of incomplete evacuation for at least 25% of defecations
  - Sensation of anorectal obstruction/blockage for at least 25% of defecations
  - Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  - Fewer than 3 stools/week

- Loose stools are rarely present w/o use of laxatives
- Criteria for IBS not fulfilled

Epidemiology

<table>
<thead>
<tr>
<th>LOCATION OF STUDY (REFERENCE)</th>
<th>SURVEY METHOD</th>
<th>SAMPLE SIZE</th>
<th>DEFINITION OF CONSTIPATION</th>
<th>AGE RANGE (YR)</th>
<th>PREVALENCE (%)</th>
<th>PREVALENCE BY GENDER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States^7</td>
<td>Face-to-face interview, Questionnaire administered in person</td>
<td>15,014, 563</td>
<td>SR</td>
<td>12-74 Mean, 24 (65% students)</td>
<td>12.8</td>
<td>M: 7.0; F: 18.2</td>
</tr>
<tr>
<td>United States^8</td>
<td>Face-to-face interview</td>
<td>14,407</td>
<td>SR</td>
<td>&lt;40 to &gt;80</td>
<td>3.5</td>
<td>M: 8.06; F: 20.8</td>
</tr>
<tr>
<td>Olmsted County, Minn^12</td>
<td>Face-to-face interview with questionnaire</td>
<td>42,375</td>
<td>Straining and hard stools or frequency &lt; three/wk</td>
<td>30-64</td>
<td>17.4</td>
<td>—</td>
</tr>
<tr>
<td>East Bristol, UK^14</td>
<td>Mailed questionnaire</td>
<td>835</td>
<td>Stool type and frequency</td>
<td>25-69</td>
<td>—</td>
<td>M: 0.6; F: 3.5</td>
</tr>
<tr>
<td>Olmsted County, Minn^15</td>
<td>Face-to-face interview</td>
<td>1,897</td>
<td>SR; RI, FC; RI, OD</td>
<td>65-93</td>
<td>24.1</td>
<td>—</td>
</tr>
<tr>
<td>Olmsted County, Minn^16</td>
<td>Mailed questionnaire</td>
<td>328</td>
<td>Straining and hard stools or frequency &lt; three/wk SR; RI, FC; RI, OD</td>
<td>30-64</td>
<td>12.5, SR; 18.3, FC; 11.0, OD</td>
<td>—</td>
</tr>
<tr>
<td>United States^27</td>
<td>Mailed questionnaire</td>
<td>690</td>
<td>SR, RI, FC; RI, D</td>
<td>15 to &gt;45 (mean, 49)</td>
<td>3.6, FC; 13.8, D</td>
<td>—</td>
</tr>
<tr>
<td>United States^8</td>
<td>Telephone interview</td>
<td>5,430</td>
<td>RI, FC; RI, OD</td>
<td>18-70</td>
<td>4.6, FC; 4.6, OD</td>
<td>—</td>
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<tr>
<td>Canada^8</td>
<td>Mailed questionnaire</td>
<td>1,149</td>
<td>SR</td>
<td>18-65</td>
<td>27.2, SR; 16.7, RI; 14.9, RI</td>
<td>—</td>
</tr>
<tr>
<td>Spain^9</td>
<td>Mailed questionnaire</td>
<td>349</td>
<td>SR, RI, RII</td>
<td>18-65</td>
<td>29.5, SR; 19.2, RI; 14.0, RII</td>
<td>—</td>
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</tbody>
</table>

Epidemiology

- MEDLINE literature review, 68 studies included
- Subjects: children and adults
- Median prevalence of constipation was 16% (range, 0.7%–79%) in adults overall; 33.5% in adults aged 60 to 101 years.
- More in the nonwhite population
- Median female-to-male ratio of 1.5:1
- Higher in institutionalized than community-living elderly residents
- Individuals of lower social, economic and educational level seem to have a tendency towards higher constipation rates.

- Lack of uniform definitions used to classify constipation, variable age groups studied, and different methods of data collection.
- Average prevalence of constipation was found to be 20.6%.
- In studies using the Rome I, II, and III criteria the prevalence rates were respectively 18%, 12.7% and 11%, respectively.

Worldwide distribution

- Worldwide variation in prevalence rates may arise from diverse cultural, dietary, genetic, environmental and socioeconomic conditions and different health care systems.

- Lack of data in the literature about the prevalence of constipation in developing countries
Epidemiology

- 2.5 million physician visits, 92,000 hospitalizations, and several hundred million dollars of laxative sales/year.

- The annual direct medical costs for constipation were recently estimated to exceed $230 million.

- At tertiary referral centers, the average cost of a medical evaluation was $2,252, with the greatest cost attributed to colonoscopy.

- Patients followed by adult primary care providers (33.4%), pediatricians (20.9%), and gastroenterologists (14.1%).
Risk Factors

- Advanced age
- Female gender
- Low level of education
- Low level of physical activity
- Low socioeconomic status
- Nonwhite ethnicity
- Use of certain medications
### Causes of chronic constipation

<table>
<thead>
<tr>
<th>Neurogenic disorders</th>
<th>Non-neurogenic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>Intestinal pseudoobstruction</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Central</td>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td><strong>Idiopathic constipation</strong></td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Normal colonic transit</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Slow transit constipation</td>
</tr>
<tr>
<td><strong>Irritable bowel syndrome</strong></td>
<td>Dyssynergic defecation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
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<tbody>
<tr>
<td>See separate table</td>
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</table>

### Drugs associated with constipation

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Anticholinergics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antihistamines</td>
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<tr>
<td></td>
<td>Antispasmodics</td>
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<tr>
<td></td>
<td>Antidepressants</td>
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<tr>
<td></td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Cation-containing agents</td>
<td>Iron supplements</td>
</tr>
<tr>
<td></td>
<td>Aluminum (antacids, sucralfate)</td>
</tr>
<tr>
<td>Neurally active agents</td>
<td>Opiates</td>
</tr>
<tr>
<td></td>
<td>Antihypertensives</td>
</tr>
<tr>
<td></td>
<td>Ganglionic blockers</td>
</tr>
<tr>
<td></td>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>5HT3 antagonists</td>
</tr>
</tbody>
</table>
Constipation and Parkinsonism

- Abnormally low GI motility is the most common autonomic symptom in patients with PD.
- Constipation reported by 80% of PD patients
- Autopsy findings in PD patients showed LB pathology in enteric neurons along the entire gastrointestinal tract.
- Constipation is recognized as the most reliable autonomic disturbance in premotor PD.

- The strongest evidence that constipation can precede PD comes from the Honolulu Heart Program.
- 6790 men aged 51 to 75 years without PD
- 24 yr follow up
- 2.7-fold risk of PD among men with < 1 BM/day vs. men having 1 or more bowel movements/day
- 4.5-fold risk of PD when compared with men with more than 2 bowel movements/day.

Classification

- Idiopathic/Primary: disordered function of colon and rectum
  - Normal transit constipation (NTC) – 59%
  - Slow transit constipation (STC) – 13%
  - Defecatory disorders – 25 %
  - Mixed – 3%

- Secondary
Normal transit constipation (NTC)

- Pathogenesis not well understood.

- Stool travels along the colon at a normal rate.

- Barostat measurements revealed reduced fasting, postprandial colonic tone and/or compliance in 40% of patients.

- Some patients have abnormalities of anorectal sensory and motor function indistinguishable from those in patients with STC.

- Unclear if increased rectal compliance and/or reduced rectal sensation are effects of chronic constipation or contribute to the failure of the patients to experience an urge to defecate.
Slow transit constipation (STC)

- Most common in young women

- Infrequent bowel movements (less than one bowel movement/week)

- Arises from disordered colonic motor function – marked reduction in colonic intrinsic nerves and interstitial cells of Cajal

- Resting colonic motility that is similar to normal controls.

- Fewer high-amplitude propagated contractions & reduced phasic contractile responses to a meal and/or to pharmacologic stimuli (eg, bisacodyl or neostigmine)
Onset of symptoms is gradual and usually occurs around the time of puberty.

Conservative measures are usually ineffective.

Colonic inertia
- symptoms at the severe end of the spectrum.
- colonic motor activity absent or fails to increase after any stimulus
Defecatory Disorders

- Also known as anismus, dyssynergia, pelvic floor dyssynergia, spastic pelvic floor syndrome, obstructive defecation, or outlet obstruction.
- Acquired and may start in childhood
- Can be learned behavior to avoid discomfort or pain during defecation
- The pathogenesis is not completely understood.
  - Inappropriate contraction of the ext. anal sphincter.
  - Failure of the pelvic floor to descend on straining.
  - Can also be associated with rectal hyposensitivity, delayed colonic transit, structural disturbances
Rome III Criteria for Functional Defecation Disorders

- Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

- During repeated attempts to defecate must have at least two of the following:
  - Evidence of impaired evacuation, based on balloon expulsion test or imaging
  - Inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) or less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
  - Inadequate propulsive forces assessed by manometry or imaging
Evaluation

- History
- Physical Exam
- Diagnostic tests
History

- Duration, frequency, stool consistency, stool size, and degree of straining during defecation.
- Red flags: unintentional weight loss, rectal bleeding, change in the caliber of the stool, severe abdominal pain and family history of colon cancer.
- Dietary history including amount of daily fiber and fluid consumed
- Co-morbidities, Obstetric and surgical histories, drug history.
- History of sexual/physical abuse
Bristol stool form scale

- 66 volunteers
- Whole-gut transit time (WGTT) measured with radiopaque marker pellets and stools weighed.
- Kept a diary of stool form on a 7-point scale and of their defecatory frequency.
- WGTT measurements correlated with defecatory frequency ($r = 0.35, P = 0.005$) and with stool output ($r = -0.41, P = 0.001$) but best with stool form ($r = -0.54, P < 0.001$).

The rectal exam

Rectal Examination (with patient in left lateral position)

*Inspection*
Anus “pulled” forward during attempts to simulate strain during defecation
Anal verge descends <1 cm or >4 cm (or beyond ischial tuberosities) during attempts to simulate straining at defecation
Perineum balloons down during straining; rectal mucosa partially prolapses through anal canal

*Palpation*
High anal sphincter tone at rest precludes easy entry of examining finger (in absence of a painful perianal condition such as an anal fissure)
Anal sphincter pressure during voluntary squeeze only minimally higher than anal tone at rest
Perineum and examining finger descend <1 cm or >4 cm during simulated straining at defecation
Puborectalis muscle tender to palpation through rectal wall posteriorly, or palpation reproduces pain
Palpable mucosal prolapse during straining
“Defect” in anterior wall of the rectum, suggestive of rectocele
Diagnostic tests

- Labs and Imaging to exclude secondary causes
- Colonic transit study
  - Radiopaque markers
  - Wireless motility capsule
  - Colonic monometry/barostat-manometric testing
- Defecation disorder study
  - Defecography
  - Balloon expulsion test
  - Anorectal manometry
  - Electromyographic Testing of Striated Muscle Activity
  - Rectal Sensitivity and Sensation Testing
Radiopaque markers test (ROM)

- The patient ingests a high fiber diet (20 to 30 g per day)

- Abstain from laxatives, enemas, and medications that may affect bowel function for 2-3 days prior to the test.

- A single capsule with 24 markers is administered on day 1 and followed by single x-ray on day 5 (after 120 hours).

- Retention of more than five markers on day 5 is considered abnormal

- Retention of all or most of the markers in distal sigmoid/rectum (defecation disorder)

Wireless Motility Capsule (WMC)

- Approved by the FDA for the eval of patients with suspected delayed gastric emptying and colonic transit time in patients with chronic idiopathic constipation

- Continuously measures the temperature, pH, and pressure of its surrounding environment

- Any meds that disturb GI physiology should be discontinued prior to test

- Gives segmental transit times

- Abnormal gastric or small bowel motility can influence treatment of constipation.
158 eligible patients underwent simultaneous measurement of colonic transit time (CT) 

ROM (Metcalf method, cut-off for delay >67 h), and WMC (cutoff for delay >59 h).

Substantial equivalence defined as diagnostic agreement > 65% for patients.

59/157 patients had delayed CT.

Positive percent agreement between WMC and ROM for delayed transit was approximately 80%; agreement vs null hypothesis (65%) \( P = 0.01 \).

Negative percent agreement (normal transit) was approximately 91%; agreement vs null hypothesis (65%), \( P = 0.00001 \).

Overall device agreement was 87%. This validates WMC relative to ROM in differentiating slow vs normal CT.

Defecation Proctography

- Thickened 150 mL of barium instilled into rectum
- Patient sits on a radiolucent commode.
- Films or videos are taken during fluoroscopy with the patient resting, deferring defecation, and straining to defecate.

Limitations
- Variability in interpretation among radiologists
- Inhibition of normal rectal emptying
- Differences in texture between barium paste and stool.
Balloon Expulsion Test

- The methodology has not been standardized.
- Requires expulsion of a 50 mL water-filled balloon in rectum with 200g weight attached at the end of balloon within 2 minutes.
- Failure to evacuate balloon in time indicated defecation disorder.
- An effective and useful screening tool for identifying patients with a defecatory disorder who do not have pelvic floor dyssynergia.
- Diagnosis in 21/24 patients with DD and 12/106 w/o dyssynergia.
- Findings confirmed with manometry and defecography.

Anorectal Manometry

- Measures rectal sensation and compliance, reflexive relaxation of the IAS, and manometric patterns produced upon attempted expulsion of the apparatus.

- Pressure recordings of the anal sphincter transducers indicate relaxation or inappropriate contraction.

- No evidence that HRM is inferior to regular procedure

Anorectal Manometry

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Disease states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting pressure (50-100 mmHg)</td>
<td>• 70-85% internal anal sphincter</td>
</tr>
<tr>
<td></td>
<td>• parasympathetic motor (S2-S4)</td>
</tr>
<tr>
<td></td>
<td>Diabetes, autonomic neuropathy, incontinence (low),</td>
</tr>
<tr>
<td></td>
<td>fissure (high)</td>
</tr>
<tr>
<td>Squeeze pressure (50-100mmHg above</td>
<td>• 70-85% external anal sphincter</td>
</tr>
<tr>
<td>resting pressure)</td>
<td>• pudendal motor (S2-S4)</td>
</tr>
<tr>
<td></td>
<td>OB trauma, excessive straining, perineal descent,</td>
</tr>
<tr>
<td></td>
<td>incontinence (low)</td>
</tr>
<tr>
<td>Rectal sensation</td>
<td>• central &amp; spinal sensory</td>
</tr>
<tr>
<td></td>
<td>• parasympathetic sensory (S2-S4)</td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury, multiple sclerosis, cauda</td>
</tr>
<tr>
<td></td>
<td>equina</td>
</tr>
<tr>
<td>Anorectal inhibitory reflex</td>
<td>• sphincter relaxation reflex with</td>
</tr>
<tr>
<td></td>
<td>balloon distension (&gt;20 ml)</td>
</tr>
<tr>
<td></td>
<td>• myenteric plexus</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung, Chagas, dermatomyositis, scleroderma</td>
</tr>
</tbody>
</table>
EMG

- Small electrical sensors are placed in the anal canal to record the electrical activity of sphincter muscles when they squeeze and relax.

- Can be very useful in biofeedback therapy.

- Useful in suspected spinal cord or cauda equina lesions, in whom bilateral or unilateral dysfunction of the external anal sphincter can be demonstrated.

Rectal Sensitivity and Sensation Testing

- Successive volumes of air is introduced into a rectal balloon

- Volume is recorded when:
  - the stimulus is first perceived
  - an urge to defecate develops
  - further addition of air is uncomfortable

- Can be useful with biofeedback therapy.

Medical Management

- Lifestyle Changes
- Fiber Supplementation
- Bulk forming laxatives
- Osmotic agents
- Stimulant laxative
- Emollients/Stool softeners
- Enemas/Suppositories
- Newer therapies
Fiber and Fluid

- Supplementation of 20 to 35 g/day of fiber in diet
- Low cost, are easy to use and safe
- Multiple food sources
- For some patients (eg STC) fiber increases bloating and distention leading to poor compliance


- NO evidence that increasing fluid intake increases colonic transit time
- Maintaining adequate intake of fluids prevents dehydration and slowing down colon transit beyond baseline.
- AI for men 13 cups (3 liters), for women is about 9 cups (2.2 liters) per day.

## Medications

### Table 18-8 Commercial Fiber Products

<table>
<thead>
<tr>
<th>AGENT</th>
<th>STARTING DAILY DOSE (G)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylcellulose</td>
<td>4-6</td>
<td>Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation and tends to cause less bloating and flatus than psyllium</td>
</tr>
<tr>
<td>Psyllium</td>
<td>4-6</td>
<td>Made from ground seed husk of the ispaghula plant; forms a gel when mixed with water, so an ample amount of water should be taken with psyllium to avoid intestinal obstruction; undergoes bacterial degradation, which may contribute to side effects of bloating and flatus; allergic reactions such as anaphylaxis and asthma have been reported but are rare</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>4-6</td>
<td>Synthetic fiber made of polymer of acrylic acid, which is resistant to bacterial degradation</td>
</tr>
<tr>
<td>Guar gum</td>
<td>3-6</td>
<td>Soluble fiber extracted from seeds of the leguminous shrub <em>Cyamopsis tetragonoloba</em></td>
</tr>
</tbody>
</table>
## Medications

### Table 18.9 Laxatives Commonly Used for Constipation

<table>
<thead>
<tr>
<th>TYPE OF LAXATIVE</th>
<th>GENERIC NAME(S)</th>
<th>DOSE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic Laxatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly Absorbed Ions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium hydroxide</td>
<td>15-30 mL once or twice daily</td>
<td>Hypermagnesemia can occur in patients with renal failure and in children.</td>
</tr>
<tr>
<td></td>
<td>Magnesium citrate</td>
<td>150-300 mL every day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate</td>
<td>15 g every day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium sulfate</td>
<td>5-10 g every day</td>
<td></td>
</tr>
<tr>
<td>Sulfate</td>
<td>Sodium phosphate</td>
<td>0.5-10 mL with 12 oz of water</td>
<td>Sulfate is generally not used by itself as a laxative agent.</td>
</tr>
<tr>
<td>Phosphate</td>
<td></td>
<td></td>
<td>Hyperphosphatemia can occur, especially in patients with renal failure.</td>
</tr>
<tr>
<td>Poorly Absorbed Sugars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Lactulose</td>
<td>15-30 mL once or twice daily</td>
<td>Gas and bloating are common side effects.</td>
</tr>
<tr>
<td>Sugar alcohols</td>
<td>Sorbitol</td>
<td>15-30 mL once or twice daily</td>
<td>Sorbitol is commonly used as a sweetener in sugar-free products. In older adults, sorbitol has an effect similar to that of lactulose but has a lower cost.</td>
</tr>
<tr>
<td></td>
<td>Mannitol</td>
<td>15-30 mL once or twice daily</td>
<td></td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Polyethylene glycol electrolyte</td>
<td>17-34 g once or twice daily</td>
<td>Tends to cause less bloating and cramps than other agents; tasteless and odorless, can be mixed with noncarbonated beverages. Typically used to prepare colon for diagnostic examinations and surgery; also available as powder without electrolytes for regular use (MiraLax)</td>
</tr>
</tbody>
</table>
# Medications

## Stimulant Laxatives

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Dose</th>
<th>Notable Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinones</td>
<td>Cascara sagrada</td>
<td>325 mg (or 5 mL) at bedtime</td>
<td>Cause apoptosis of colonic epithelial cells phagocytosed by macrophages; result in lipofuscin-like pigmented condition known as pseudomelanosis coli; no definitive association established between anthraquinones and colon cancer or myenteric nerve damage (cathartic colon)</td>
</tr>
<tr>
<td></td>
<td>Senna</td>
<td>1-2 7.5-mg tablets daily</td>
<td></td>
</tr>
<tr>
<td>Ricinoleic acid</td>
<td>Castor oil</td>
<td>15-30 mL at bedtime</td>
<td>Cramping is common.</td>
</tr>
<tr>
<td>Diphenylmethane Derivatives</td>
<td>Bisacodyl</td>
<td>5-10 mg at bedtime</td>
<td>Has effects in small intestine and colon</td>
</tr>
<tr>
<td></td>
<td>Phenolphthalein</td>
<td>30-200 mg at bedtime</td>
<td>Removed from U.S. market because of teratogenicity in animals</td>
</tr>
<tr>
<td>Sodium picosulfate</td>
<td></td>
<td>5-15 mg at bedtime</td>
<td>Likely has effects only on colon</td>
</tr>
<tr>
<td>Stool Softeners</td>
<td>Docusate sodium</td>
<td>100 mg twice daily</td>
<td>Efficacy in constipation not well established.</td>
</tr>
<tr>
<td>Emollients</td>
<td>Mineral oil</td>
<td>5-15 mL at bedtime</td>
<td>Long-term use can cause malabsorption of fat-soluble vitamins, anal seepage, and lipid pneumonia in patients predisposed to aspiration of liquids.</td>
</tr>
<tr>
<td>Enemas, Suppositories</td>
<td>Phosphate enema</td>
<td>120 mL</td>
<td>Serious damage to rectal mucosa can result from extravasation of enema solution into the submucosa; hypertonic phosphate enemas and large-volume water or soapsuds enemas can lead to hyperphosphatemia and other electrolyte abnormalities if enema is retained; soapsuds enemas can cause colitis.</td>
</tr>
<tr>
<td></td>
<td>Mineral oil retention enema</td>
<td>100 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tap water enema</td>
<td>500 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soapsuds enema</td>
<td>1500 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycerin suppository</td>
<td>60 g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bisacodyl suppository</td>
<td>10 mg</td>
<td></td>
</tr>
</tbody>
</table>
## Newer therapies

<table>
<thead>
<tr>
<th>Generic name (chemistry)</th>
<th>Mechanism of action</th>
<th>Metabolism, bioavailability</th>
<th>Pharmacodynamic effects</th>
<th>Clinical trials</th>
<th>Common side effects</th>
<th>Cardiovascular safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretagogues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lutropine (prostogene)</td>
<td>Stimulate intestinal chloride and fluid secretion by activating chloride channels</td>
<td>Intestinal degradation, minimal oral bioavailability</td>
<td>Accelerated small bowel and colonic transit in health</td>
<td>Phases 2 and 3 in CC, IBS-C</td>
<td>Diarrhea, nausea</td>
<td>No arrhythmic effects</td>
</tr>
<tr>
<td>Linaclootide</td>
<td>Stimulate intestinal chloride and fluid secretion by activating CFTR</td>
<td>Intestinal degradation, minimal oral bioavailability</td>
<td>Dose-related acceleration of colonic transit in IBS-C</td>
<td>Phases 2 and 3 in CC, IBS-C</td>
<td>Diarrhea</td>
<td>No arrhythmic effects</td>
</tr>
<tr>
<td>Serotonin 5-HT&lt;sub&gt;4&lt;/sub&gt; receptor agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prucalopride&lt;sup&gt;2&lt;/sup&gt; (benzofuran carboxamide)</td>
<td>High selectivity and affinity for 5-HT&lt;sub&gt;4&lt;/sub&gt; receptors; much weaker affinity for human D4 and s1 and mouse 5-HT&lt;sub&gt;3&lt;/sub&gt; receptors</td>
<td>Limited hepatic, not CYP3A4</td>
<td>Accelerated colonic transit in health and CC</td>
<td>Phases 2 and 3 in CC</td>
<td>Diarrhea, headache</td>
<td>No arrhythmic activity in atrial cells; inhibits hERG at very high µmol/L concentration; no clinically relevant adverse cardiac effects in large trials (&gt;4000 subjects)</td>
</tr>
</tbody>
</table>

- Prucalopride not available in US.
- Tegaserod no longer available d/t cardiovascular side effects.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Number needed to treat</th>
<th>Number of patients</th>
<th>Quality of evidence</th>
<th>Number needed to treat</th>
<th>Number of patients</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble fiber</td>
<td>a</td>
<td>368\textsuperscript{111}</td>
<td>Very low</td>
<td>4.5\textsuperscript{114}</td>
<td>275</td>
<td>Moderate</td>
</tr>
<tr>
<td>Osmotic and stimulant laxatives</td>
<td>3 (2–4)</td>
<td>1411</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
<td>Moderate\textsuperscript{b}</td>
</tr>
<tr>
<td>PEG</td>
<td>2.4\textsuperscript{117}</td>
<td>573</td>
<td>High</td>
<td>NA</td>
<td>NA</td>
<td>Moderate\textsuperscript{b}</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>4 (3–7)</td>
<td>610</td>
<td>Moderate</td>
<td>13\textsuperscript{206}</td>
<td>1171</td>
<td>Moderate</td>
</tr>
<tr>
<td>Linaclotide</td>
<td>6 (5–8)</td>
<td>2858\textsuperscript{207}</td>
<td>Moderate</td>
<td>10\textsuperscript{208}</td>
<td>420</td>
<td>Moderate</td>
</tr>
<tr>
<td>Prucalopride</td>
<td>6 (5–9)</td>
<td>2639</td>
<td>Moderate</td>
<td>NA</td>
<td>NA</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Management of defecatory disorders

- **Defecation training**
  - 3 to 5 treatment sessions, each lasting at least 30 minutes.
  - Discussion about normal defecation process, life style changes to improve defecation.
  - Reduce dependence on laxatives.

- **Anorectal biofeedback**
  - Follows defecation training.
  - Patients receive visual and/or auditory feedback, on the functioning of their anal sphincter and pelvic floor muscles.
  - Assisted with EMG or anorectal manometry catheter.
  - Simulated evacuation with a balloon or silicone-filled artificial stool is commonly taught.
  - Therapy can range from 6 sessions in 6 weeks to 3 sessions/day for 10 successive days.
Success of Anorectal feedback

- Systemic review found 67% success rate in 1996 but no controlled studies available then.

- More recently some RCT have supported efficacy of biofeedback

- Recent study, 109 patients, 54 got biofeedback training, 55 got PEG with 5 counseling sessions

- At 6 months, greater reductions in straining, sensations of incomplete evacuation and anorectal blockage, use of enemas and suppositories, and abdominal pain was reported by 80% of patients who underwent biofeedback compared with 22% of the laxative-treated patients (P < 0.001).

- The benefits of biofeedback were sustained at 12 and 24 months.

- Most other trials also have small sample sizes and favorable results.

Sacral Nerve Stimulation

- Most common lower GI indication for SNS is constipation.

- 10 studies, 225 temporary neuromodulations and 125 permanent implants performed.

- Bowel diaries showed improvement more than 50% of patients on temporary neuromodulation.

- Results were maintained in approximately 90% of patients who underwent permanent implantation over medium to long-term follow-up.

- Longest follow up was 42 months in a study of 13 patients

- Largest study (N=60) with medium follow up found high rates of adverse effects related to electrode displacement

- Currently SNS is not approved for treatment of constipation in the US.

Surgery

- Subtotal colectomy with ileorectal anastomosis can dramatically ameliorate incapacitating constipation in carefully selected patients
  - The patient has chronic, severe, and disabling symptoms from constipation that are unresponsive to medical therapy.
  - The patient has slow colonic transit of the inertia pattern.
  - The patient does not have intestinal pseudoobstruction, as demonstrated by radiologic or manometric studies.
  - The patient does not have pelvic floor dysfunction based on anorectal manometry.
  - The patient does not have abdominal pain as a prominent symptom.
Treat secondary causes of constipation (see Table 18-4) → History and physical examination

- Stop/change medication(s)
- Medication history

Supplement diet with 20 g fiber/d → No response

Colonic transit study

- Normal transit
  - Fiber (>20 g/d), osmotic laxative, stimulant laxative
    - No response
      - Assess for defecatory disorder (e.g., anorectal manometry, balloon expulsion test)
        - Abnormal
          - Defecography
            - Evacuation disorder
              - Biofeedback, physical therapy, consultation with psychologist and/or dietitian
            - Rectal anatomic defect
              - Repair of prolapse or rectocele
          - Normal
          - Slow-transit constipation
            - Osmotic laxative, stimulant laxative, prokinetic agent; rarely colectomy
        - Normal
          - Treat as for irritable bowel syndrome
Fecal Incontinence (FI)

- Risk factors include diarrhea, advanced age, female gender, disease burden, obesity, decreased physical activity and smoking.

- Prior childbirth, pelvic floor anatomical disturbances are also associated.

- Pathogenesis: dysfunction of the anal sphincters, abnormal rectal compliance, decreased rectal sensation, altered stool consistency, or a combination of any of these abnormalities. **Usually multifactorial.**

**Evaluation**
- Anorectal manometry
- Anal rectal sensation testing
- Defecography
- Endorectal ultrasound/magnetic resonance imaging
- Balloon expulsion test

**Causes of fecal incontinence**

<table>
<thead>
<tr>
<th>Structural abnormalities</th>
<th>Functional abnormalities</th>
<th>Stool characteristics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal sphincter muscles</td>
<td>Obstetric injury, hemorrhoidectomy, anal dilation, radiation, inflammatory bowel disease</td>
<td>Volume and consistency</td>
<td>Physical mobility and cognitive function</td>
</tr>
<tr>
<td>Rectum</td>
<td>Rectal prolapse, hypersensitivity/hypersensitivity, neoplasms, congenital abnormalities, excessive perineal descent</td>
<td>Irritants</td>
<td>Psychosis</td>
</tr>
<tr>
<td>Puborectalis muscle</td>
<td>Trauma, obstetrical injury</td>
<td>Hard stools and retention</td>
<td>Medications</td>
</tr>
<tr>
<td>Pudendal nerve</td>
<td>Surgical injury, excessive perineal descent</td>
<td>Dyssynergic defecation</td>
<td>Lactose, fructose, sorbitol</td>
</tr>
<tr>
<td>Central nervous system,</td>
<td>Spinal cord injury, head injury, stroke, back surgery, diabetes mellitus, multiple sclerosis, tabes dorsalis, cauda equina injury or tumor</td>
<td>Inflammatory bowel disease, irritable bowel syndrome, medications, infections</td>
<td>Aging, disability, dementia, sedation</td>
</tr>
<tr>
<td>autonomic nervous system</td>
<td></td>
<td>Bile salt malabsorption, laxatives</td>
<td>Willful soiling</td>
</tr>
</tbody>
</table>

**Causes of fecal incontinence**
Fecal Incontinence - Management

- **Conservative measures** (effective in 25%)
  - Fiber
  - Antidiarrheals
  - Scheduled toileting
  - Pelvic floor exercises

- **Biofeedback**
  - Improved quality of life in 75%
  - Improved continence in 55%

- **Injectable anal bulking agents**
  - 4 Inj, 5 ml each, 5 mm above the dentate line
  - Increased resting anal pressures
  - Proctalgia, rectal hemorrhage, abscess

- **Tibial nerve electric stimulation**
  - Promising but evidence is weak at this point
  - Needs long term studies

- **Sacral nerve stimulation**
  - Improved resting and squeeze pressures, rectal sensation
  - 120 patients, 86% achieved > 50% reduction in FI, and 40% had no fecal incontinence at 3 year follow-up
  - Implant-site pain, paresthesia, change in the sensation of stimulation, and infection


- **Anal sphincteroplasty**
  - Long term (5 year) outcomes poor

- **Dynamic graciloplasty**
  - Electrical stimulation of the gracilis muscle
  - Implantable pulse generator
  - Not available in the US
Acute colonic pseudo-obstruction (Ogilvie's syndrome)

- Gross dilatation of the cecum and usually right hemicolon
- Absence of obstruction the flow of intestinal contents.
- Pathogenesis unclear; increased sympathetic and/or decreased parasympathetic innervation of distal colon incriminated
- Inflammation may also derange neuromuscular function
- Patients present with nausea, vomiting, abdominal pain, constipation.

<table>
<thead>
<tr>
<th>Common clinical conditions associated with Ogilvie’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma, especially fractures</td>
</tr>
<tr>
<td>Obstetrical surgery, especially involving spinal anesthesia</td>
</tr>
<tr>
<td>Pelvic, abdominal, or cardiothoracic surgery</td>
</tr>
<tr>
<td>Major orthopedic surgery</td>
</tr>
<tr>
<td>Severe medical illness, such as pneumonia, myocardial infarction, or heart failure</td>
</tr>
<tr>
<td>Neurologic conditions</td>
</tr>
<tr>
<td>Retroperitoneal pathology, such as malignancy or hemorrhage</td>
</tr>
<tr>
<td>One of the above plus metabolic imbalance or medication administration (eg, narcotics, phenothiazines, calcium channel blockers, alpha-2-adrenergic agonists, epidural analgesics)</td>
</tr>
</tbody>
</table>
Acute colonic pseudo-obstruction (Ogilvie's syndrome)

- If peritoneal signs present ~ impending perforation

- Hypokalemia, hypocalcemia, and hypomagnesemia in > 50% patients

- Conservative management for 1-2 days if colonic diameter < 12cm

- Correction of fluids, electrolytes, NG suction, rectal tube, gentle enemas, treat reversible causes, discontinue meds that can cause/worsen disease

- Serial abd exam and imaging (q12-24) hours

- Neostigmine 2.0 mg IV with cardiovascular monitoring

- Relistor – opioid induced disease
Acute colonic pseudo-obstruction (Ogilvie's syndrome)

- Role of endoscopic decompression in patient remains controversial.

- Success rates for endoscopic decompression in uncontrolled series vary from 69 to 90 percent.

- In a retrospective study of 25 patients with cancer, pseudo-obstruction, and a cecal diameter ranging from 9 to 18 cm, 23 resolved without colonoscopy, usually within 48 hours.

- Complication and death rates associated with colonoscopy for treatment of Ogilvie's syndrome are 3 and 1 percent in two recent studies.

- An attempt at colonoscopic decompression is indicated when supportive measures have failed with increasing colonic diameter (11 to 13 cm).

- Recurrence requiring repeated colonoscopic decompression occurs in approximately 40%.

- Percutaneous endoscopic colostomy can be attempted.

- Percutaneous tube cecostomy reserved for patients requiring repeat c-scope.

- Surgery for perotinitis/perforation.
Irritable Bowel syndrome

- Pathophysiology is evolving.
- Altered intestinal motility/secretion in response to various stimuli
- Enhanced pain perception and dysregulation of brain-gut axis.
- Diagnosis via Rome III criteria can help avoid costly and invasive testing to rule other diseases

- Treatment is sx based:
  - Pain: TCA, SSRI, antispasmodics
  - Bloating: antibiotics, probiotics
  - Diarrhea: imodium, lomotil, alosetron, enteragam
  - Constipation: High fiber, laxatives, lubiprostone
Serum-derived bovine immunoglobulin (Enteragam)

- Randomized, double-blind, placebo-controlled study

- Evaluate impact on gastrointestinal symptom scores and quality of life (QoL)

- 66 subjects diagnosed with IBS-D were enrolled: 25 in the 10 g/day SBI group, 19 in the 5 g/day SBI group, and 22 in the placebo group

- SBI at 10 g/day (N = 15) had statistically significant within-group reductions in abdominal pain (p < 0.01), loose stools (p < 0.01), bloating (p < 0.05), flatulence (p < 0.01), urgency (p < 0.05) and any symptom (p < 0.01) at EOT vs. baseline

- Subjects receiving 5 g/day of SBI (N = 15) realized statistically significant within-group reductions in days with flatulence (p < 0.035), incomplete evacuation (p < 0.05), and any symptom (p < 0.01).

- No significant changes in QoL scores.

- Additional studies are underway with larger numbers of subjects to validate these findings.

Hirschsprung disease (HD)

- Failure of neural crest cells (precursors of enteric ganglion cells) to migrate completely during intestinal development.
- 1 in 5000 live births with male predominence 5:1
- Mutations in RET protooncogene
- Variable length of distal colon can be involved
- Aganglionic segment fails to relax -> dilation of proximal colon
- Usually presents in neonatal period with failure to pass meconium or stool with bilious emesis, abdominal distension
- Can present in adults with chronic constipation and recurrent fecal impaction
- Eval includes barium enema, anorectal manometry and rectal biopsy
Hirschsprung disease (HD)

- Barium enema can miss very short segment disease

- Anorectal manometry: failure of int. anal sphincter relaxation with rectal distension

- False positives on manometry when capacious rectum with chronic constipation -> ballon distension may not result in IAS relaxation

- Rectal biopsy: absence of ganglion cells and hypertrophy of nerve fibres

- Treatment: Resection of involved segment, bring the normal ganglionic bowel down close to the anus, and preserve sphincter function
THE END