Evaluation and Management of Chronic Constipation

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Burden

- Most common digestive complaint in general population
 - Pooled global prevalence 14%
 - Higher in women (OR 2.22), older adults (OR 1.41), lower socioeconomic class (OR 1.32), and IBS (OR 7.98)
 - Substantial overlap with other GI diseases and mood disorders
 - Power et al: No association between chronic constipation and CRC
 - Prevalence US 2-30% (12-19%)
 - Higgins et al: 63 million fulfilled Rome II criteria
 - Age and sex adjusted prevalence normal transit constipation 19%, rectal evacuation disorders 11%
 - Substantial economic cost
 - In US, 4 million ambulatory case visits 1990s inc to 8 million 2000s
 - Singh et al 2007: 78,854 Medi-Cal patients, 15 month period
 - Direct cost per patient per
 - Visit \$39
 - Procedures and laboratory \$183
 - Medications (OTC and prescription) \$5
 - Admission to hospital \$2993
 - Total cost \$246







Definition

- Acute <1 week; Chronic >4 weeks (>3 months)
- Rome IV criteria (for at least 3 months, with symptom onset at least 6 months prior to diagnosis)
 - 1. Must include <u>two or more</u> of the following >25% of defecations:
 - Straining
 - Lumpy or hard stools (Bristol Stool Scale Form 1-2)
 - Sensation of incomplete evacuation
 - Sensation of anorectal obstruction/blockage
 - Manual maneuvers to facilitate defecation (digital evacuation, support of the pelvic floor)
 - Fewer than three spontaneous bowel movements per week
 - 2. Loose stools are rarely present without the use of laxatives
 - 3. There are insufficient criteria for IBS





Main causes – Primary Chronic Constipation

- Normal transit constipation (functional constipation)
- Rectal evacuation disorders (outlet delay disorders)
- Slow transit constipation (colonic inertia, chronic colonic pseuoobstruction)



Normal transit constipation (NTC)

- Normal transit about 20-72 hours
- Normal ano-rectal function
- Most common type
- <u>Considerable overlap with IBS</u>
- Significantly higher scores for psychological distress



Rectal evacuation disorders

- Characterized by impaired rectal evacuation from inadequate rectal propulsive forces and/or increased resistance to evacuation
- Lack of coordination between straining and relaxation pelvic floor/anal sphincter
- 2nd most common type of chronic constipation
- Normal passage of radio-opaque markers in the proximal colon but stagnate in the rectum
- DDx:
 - Dyssynergic defecation or pelvic floor dyssynergia**
 - Anismus (high anal resting pressure)
 - Anatomic abnormalities (rectocele, descending perineum syndrome, rectal prolapse, etc.)
 - Hirschprung disease
 - Fecal impaction
 - Megarectum



Dyssynergic defecation (pelvic floor dyssynergia)

Acquired, behavioural disorder of defecation



- Results from faulty toilet habits, painful defecation, obstetric or back injury, dysfunction of the gut–brain axis, pshycosocial issues
- Unable to coordinate abdominal, rectal, anal and pelvic floor muscles during attempted defecation
- Manifests as paradoxical anal contraction, inadequate anal relaxation or impaired rectal or abdominal propulsive force
 - 60% patients have rectal hyposensitivity
 - 60% patients have slow transit constipation



Slow transit constipation (STC)

- Resting colonic motility similar to normal controls
- Little to no high-amplitude propagating contractions after meals or with bisadocyl challenge
 - Reduced colonoic propulsive activity
 - Uncoordinated motor activity in the distal colon
- Appears to be dysfunction in the extrinsic parasympathetic or enteric neural control
- Often afflicts young women
- Colonic inertia
 - Delayed passage of radio-opaque markers through the proximal colon
 - No evidence of defecatory disorder
- Chronic megacolon
 - Chronically dilated colon
 - Reduced colonic compliance
 - Can be seen in genglioneuromatosis of the colon (MEN 2B)



Secondary causes

Neurologic and motility disorders

Amyloidosis Diabetes Hirschsprung disease Hypothyroidism Multiple sclerosis Parkinson disease Spinal cord injury Spinal or ganglionic tumors Stroke

Diseases in which treatment can cause constipation

Bipolar disorder Chronic pain Depression Parkinson disease Schizophrenia

Medications Anticholinergics Anticonvulsants Antidepressants Antipsychotics Antispasmodics Calcium channel blockers Opioids

Other causes

Chagas disease Conversion disorder Decreased fluid intake Hypercalcemia Hyperparathyroidism Low-fiber diet Mechanical obstruction



Initial evaluation

<u>History</u>

- Pattern constipation, onset, comorbidities, associated symptoms, medications (opiates, CCB, anti-cholinergic)
- Psychosocial
- Alarm features
- Tenesmus, sensation of incomplete evacuation, urgency
- Digital maneuvers (splinting), prolonged and excessive straining
- Other motility issues (dysphagia, early satiety)

- <u>Rectal exam</u>
- Sn 75-93%, Sp 59-87% for dyssynergia
- Key findings
 - With straining paradoxic contraction of external anal sphincter, lack of perineal descent (puborectalis contraction)
 - Abnormal abdominal push effort
 - Pain to palpation posterior rectal wall (puborectalis muscle tenderness)
 - Rectal prolapse



Ano-rectal angle in Dyssynergic defecation





Management algorithm





Lifestyle Modifications

- Increase dietary fiber (NTC), liquid consumption, physical activity
- Recommendation based on epidemiological studies
- Inconsistent results
 - Fluid intake:
 - no high-quality evidence or randomized controlled trials
 - No apparent benefit to ingest dietary fiber supplements with extra water
 - Dietary fiber
 - Based on systematic reviews
 - At least 25-30g/day
 - Soluble fiber (pectins, gums, mucilages and storage polysaccharides present in oat bran, barley, nuts, seeds, beans, lentils, peas, some fruits and vegetables and psyllium fiber supplements)
 - Avoid <u>in</u>soluble fiber (cellulose, hemicelluloses and lignin present in wheat bran, vegetables and whole grains), specially in IBS-C

Nonpharmacologic management of chronic constipation

Increase physical activity (most beneficial in early morning)

Toilet training. Instruct patients to: Not ignore urges to defecate Use correct posture, ie, "brace-pump" technique: sit on the toilet and lean forward, with knees higher than hips and with feet supported on a step to straighten the anorectal angle Do deep-relaxation techniques while defecating Avoid straining when passing stool Not stay on the toilet for more than 5–10 minutes

Dietary changes

Drink a hot caffeinated beverage after waking up Eat breakfast within 1 hour of waking up Increase fluid intake to 1.5–2 L daily Increase dietary fiber to 25–30 g daily; do this slowly to avoid abdominal cramps and bloating



Pharmacological management of chronic constipation Effectiveness Mechanism of action/dosing Adverse events Drug **Bulk laxatives** Increases stool water content to soften Soluble fiber is more effective than Soluble fiber (psyllium, Bloating, abdominal distention • ٠ insoluble fiber in NTC methylcellulose, calcium Early satiety, might worsen stool polycarbophil, partially Decrease transit time colon Good effect in mild to moderate ٠ dyspepsia hydrolyzed guar gum, wheat Avoid when dyssynergia present Increased stool mass might stimulate constipation ٠ dextrin) and insoluble fiber Psyllium and ispaghula husk most * less bloating with Citrucel peristalsis (bran, flaxseed, rye) 1 tsp up to 3 times a day studied (strong rec, very low qual) Don't use insoluble fiber • • **Osmotic laxatives** Macrogols (Polyethylene glycol Generation of an osmotic gradient in Effective for intermittent and chronic Abdominal distention, incontin. • constipation (Stool Fz + consistency and Safe chronic use, well tolerated 3350) gut lumen • Promotes movement of water into straining -strong rec; high qual); NNT 5 Pregnancy C ٠ lumen, speed transit Non-absorb carbs (Lactulose) Less effective; safe in pregnancy Gas, bloating, cramping; DD Luminal water softens stool and stimulates secondary peristalsis Poor evidence Magnesium salts Electrolyte disturbances in CKD PEG: 8-32oz daily or twice a day • Sorbitol Onset 24-48h Abdominal cramps, flatulence Lactulose: 15-30mL daily or bid **Stimulant laxatives** Effective for mild intermittent Anthraquinones (cascara Stimulation of intestinal motility Diarrhea and abdominal pain • • common; incontinence sagrada and senna) Colonic wall irritant constipation; no large, RCT performed; Stimulation sensory nerves colon onset 8-12h Bisacodyl: hyperkalemia ٠ Inhibition water absorption Lack long data Diphenylmethanes (bisacodyl, Effective for chronic constipation Prostaglandin release by acting on Senna: (unproven) degeneration sodium picosulfate) (strong rec, mod qual); onset 8-12h of Meissner's and Auerbach's the enteric nervous system plexus; melanosis coli Misoprostol, castor oil

Pharmacological management of chronic constipation								
Drug	Mechanism of action	Effectiveness	Adverse events					
Surfactant laxatives (stool softeners)								
ducosate sodium, ducosate calcium	 Anionic detergents (dioctyl sodium sulphosuccinate) lower the surface tension of stool and allows water to penetrate stool 100mg twice daily 	 Docusate is less effective than soluble fiber; mild, transient constipation Use in combination with stimulant laxative 12-72 onset action 	SafePregnancy category A					
Enemas								
Soapsuds, Tap water enema, phosphate enema, Mineral oil retention enema, glycerin	 Evacuation induced by distended colon; mechanical lavage Stool softened and lubricated 	 Time to onset 5-15 minutes Stimulant laxatives: use 30 minutes after meals 	 Accumulated damage to rectal mucosa Mechanical trauma Fleets: hyperphosphatemia, hypocalcemia, acute phosphate nephropathy 					
Other								
Prunes	• 50g (around 6 prunes BID)							

Prunes• 50g (around 6 prunes BID)
• Better than psyllium in
• Improve spontaneous bowel movements
• Improve stool consistencyHemp seed extract• 7.5 g twice a day better than placebo at increasing weekly spontaneous bowel movements, improving straining and
decrease need for rescue therapy; more side effects than placebo (13% bloating, gas, diarrhea)

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Management algorithm





Evaluation after failure of empiric therapy

- Up to 50% of patients with dyssynergic defecation have STC
- Coexistent slow colonic transit does not alter the management of defecatory disorders
- Many will normalize after successful treatment of the dyssynergic defecation
- Pelvic floor retraining is superior to laxatives for defecatory disorders
- Assessment of colonic transit is recommended only after excluding a defecatory disorder
- Labs: CBC; AGA 2013 metabolic work up not recommended (TSH, Calcium)



Anorectal structure and function tests

Anorectal manometry

- physiological tests that assesses:
 - Sphincter tone in the resting and contracted state ٠
 - **Recto-anal reflexes** •
 - **Rectal sensation** •
 - Pressure changes during attempted defecation •

a Typel



Anal

c Type III











d Type IV





Anorectal structure and function tests

Balloon expulsion test

- Screening method for rectal evacuation disorders
- expulsion time of >1 minute is abnormal
- does not distinguish between functional and mechanical or anatomical causes
- Normal test does not exclude defecatory disorder



• Defecography

- Perform is ARM and BET are inconclusive
- Contrast (barium) vs functional (MRI)
- Provide information about
 - Function (dyssynergic defecation)
 - Anatomy (anal stenosis, enterocele, rectal intussusception, rectal prolapse and rectocele)





Management algorithm





At the conclusion of the initial clinical evaluation of patients with constipation, it should be possible to tentatively classify patients into one of

Defecatory disorders (anismus/dyssynergia [failure of relaxation] or descending perineal syndrome and other flaccid disorders) NTC with normal colonic transit and defecation; some patients in this group have symptoms of IBS (eg, abdominal pain, bloating, and incomplete defecation)

STC when pelvic floor function is normal and there is evidence of slow transit

Combination of defecatory disorders and STC;



Management defecatory disorders

- Managed by biofeedback-aided pelvic floor retraining to improve abdominal/pelvic floor coordination
- Use visual or auditory feedback of anorectal and pelvic floor muscle activity; sensory retraining
- Patients learn to appropriately increase intraabdominal pressure and relax the pelvic floor muscles during defecation



- 70% improvement compared to 8% STC
- 65% normalized colonic transit
- More effective than laxatives





Rao et al. Nature Reviews Gastroenterol and Hepatol. 2016

San Antonio
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Tests of colonic transit

- Radiopaque marker test
 - 95% of normal subjects pass more than 80% of markers within 120 hours
 - Hinton method:
 - One capsule containing 20–24 radiopaque markers given on day 1
 - Abdominal radiograph on day 5
 - Slow colonic transit is identified if >5 (20%) ingested markers are retained on day 5
 - Simple, low cost, reproducible, widespread availability (?)
 - Radiation exposure, additional hospital visit





Tests of colonic transit

- Wireless motility capsule test
 - enables the detection of
 - Segmental and whole-gut transit time
 - By detecting changes in intraluminal pH
 - Good correlation with radiopaque marker tests
 - Helpful in patients with overlapping symptoms in the UGI tract

- Intraluminal pH increases
 - Increases ~3 units from the stomach to the duodenum
 - Decreases ~1 unit from the ileum to the caecum
 - Delayed GTT: > 5 hours
 - Delayed SBTT: > 6 hours
 - Delayed CTT: > 59 hours



Pharmacological management of chronic constipation

Drug	Mechanism of action	Indications	Effectiveness	Adverse events					
Intestinal Secretagogues									
Chloride channel activators									
PgE derivative Lubiprostone (\$180/m)	 Stimulate intestinal CI and fluid secretion by activating CIC-2 channels (also CFTR) Increases intestinal Na and H20 and promotes intestinal transit Accelerated small bowel and colonic transit and facilitate ease of defecation 	CICIBS-COIC	 CIC: 24 µg twice daily IBS-C: 8 µg twice daily Take with food Strong recommendation, high qual; NNT 4 	 Pregnancy class C; avoid during breast feeding Dose-dependent nausea (8- 30%) Diarrhea, headaches Can start once daily 					
Guanylate cyclase-c agonist									
Linaclotide (\$518)	Activation of guanylate cyclase c receptor (STA) generating cGMP Increases intestinal secretion of CI and HCO3 by activating CFTR Increases intestinal Na and H20 and promotes intestinal transit Accelerated small bowel and colonic transit and	CICIBS-C	 CIC: 145 μg/day IBS-C: 290 μg/day Take 30 to 60 minutes before breakfast Strong rec, high qual' NNT 6 	 Diarrhea (leads to discontinuation in 4% pts with Linaclotide) Minimal oral bioavail and extra-intestinal SE No arrhythmic effects 					
Plecanatide (\$500)	 facilitate ease of defecation Decreases the firing rate of the visceral afferent pain fibers decreasing visceral pain 	CICIBS-C	• NNT 6						
Serotonin 5	-HT4 receptor agonists								
Prucalopride (benzofuran carboxamide)	 High selectivity and affinity for 5-HT4 receptors Accelerated GI and colonic transit 	• CIC	1-2mg dailyComparative effect to PEG	 Diarrhea, headache no clinically relevant adverse cardiac effects 					

Other pharmacological management of chronic constipation

- Serotonin 5-HT4 receptor agonists
 - Naronapride, Velusetrag
- Bile Acid Transporter Inhibitors
 - Elboxibat
- Bile-acid analogues
 - chenodeoxycholic acid
- NHE3 sodium transporter inhibitors
 - Tenapanor

Surgical management of slow transit constipation

- Functional/anatomic tests and psychosocial analysis to be done prior to surgery
 - Avoid surgery in
 - Dyssynergic defectation*
 - IBS-C
- Rule out upper GI motility disorders
- Most recommendations weak , based low quality evidence
- Failure rates as high as 100% in segmental colon resection

- Options
 - Repair rectocele/intussusception (avoid transrectal stapled repair STARR)
 - Sacral nerve stimulation
 - Intractable constipation
 - Low quality studies, experimental
 - Ileostomy
 - Uncorrectable pelvic floor dysfunction
 - Cecostomy with anterograde enemas
 - Total colectomy with ileo-rectal anastomosis
 - 50-100% improvement
 - Strong recommendation, weak evidence
 - Surgical complications as high as

Opioid induced constipation

- 40%-90% of patients who use opioids have constipation and other GI adverse effects
- Opioid receptors μ , κ , and δ
 - delay gastrointestinal transit
 - stimulate non-propulsive motor activity, intestinal segmentation, and increased sphincter tone
 - increase fluid absorption by prolonging contract time for absorption to occur
 - decrease secretion of electrolytes and water into the intestinal lumen

Table 3. Available Opioid Antagonists

	Receptor Antagonism ^a			
Drug	μ	К	δ	Permeable to Blood-Brain Barrier
Naloxone	+++	++	++	Yes
Naltrexone	+++	++	++	Yes
Methylnaltrexone	+++	++	++	No
Alvimopan	+++	None	None	No
Naloxegol	+++	None	None	No

Naloxone

- Luthra et al: Naloxone ranked best drug and safest
- Combination opiate/naloxone
- PAMORAs:
 - Naldemedine: Approved for OIC in adult patients with chronic noncancer pain
 - Methylnaltrexone bromide (8-12 mg sc or 450mg oral): Approved for OIC in patients taking opioids for chronic noncancer pain
 - Naloxegol (25mg, oral): approved for use in patients with OIC with chronic noncancer pain
 - Alvimopan is indicated only to shorten the duration of postoperative ileus; not FDA approved

Recommendations of the AGA Clinical Guidelines for the Medical Management of Opioid-Induced Constipation

Recommendations	Strength of recommendation	Quality of evidence
1. Traditional laxatives		
a. In patients with OIC, the AGA recommends use of laxatives as first-line agents	Strong	Moderate
2. PAMORAs		
a. In patients with laxative refractory OIC, the AGA recommends naldemedine over no treatment	Strong	High
b. In patients with laxative refractory OIC, the AGA recommends naloxegol over no treatment	Strong	Moderate
c. In patients with laxative refractory OIC, the AGA suggests methylnatrexone over no treatment	Conditional	Low
3. Intestinal secretagogues		
a. In patients with OIC, the AGA makes no recommendation for the use of lubiprostone	No recommendation	Evidence gap
4. Selective 5-HT agonists		
a. In patients with OIC, the AGA makes no recommendation for the use of prucalopride	No recommendation	Evidence gap

Take home points

- Initial limited evaluation, mostly based on history and exam findings
- 1st line therapy includes fiber, osmotic laxatives (PEG), stimulant laxatives (Bisadocyl)
- Poor evidence senna, MOM, docusate
- Limit metabolic work up
- 1st step after failure empiric treatment is ARM + BET, followed by colonic transit studies
- All secretagogues have good evidence, limitations price
- Biofeedback best treatment for pelvic floor dysfunction
- Surgery reserved for refractory STC with no rectal evacuation disorders

