COPING WITH EXTREMES:
From C. difficile to Constipation

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Learning Objectives:
- Appropriately evaluate the patient with change in bowel habits, more specifically chronic constipation.
- Become aware and educated on treatment options for chronic constipation.
- Understand the pathogenesis, disease progression and treatment options available for Clostrium difficile colitis.

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Coping with GI Extremes

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Epidemiology

- Constipation is a chronic condition causing pain, reduced ability to function and poor overall general health
- Estimates of 4-56 million people in the US alone suffering leading to 2.5 million annual medical visits to primary care physician or gastroenterologist
- More common in women & elderly

- The prevalence of chronic constipation rises with age (above 65)
- In this older age group, approximately 26 percent of men and 34 percent of women complain of constipation
Definition

- Each patient has their own definition of constipation
- Hard stool, discomfort, reduced frequency of defecation, etc.
- Many patients denote a change in their frequency is termed "constipation"
- Historically constipation has been interpreted as stool frequency as little as 3 times per week.
- Constipation is a symptom complex and not a disease.

Etiology

- Causative or contributing factors are numerous
  - Neurogenic/Non-neurogenic
  - Drug Induced
  - Functional
  - Mechanical Obstruction

- Idiopathic causes as well
  - Normal colonic transit
  - Slow transit
  - Dyssynergia (PFD)
Neurogenic Causes

- DM, autonomic neuropathy
- Multiple sclerosis, Parkinson’s disease, SCI

Non-Neurogenic Causes

- Hypothyroidism
- Hypokalemia
- Hypomagnesaemia

Drugs

- Definitely a contributing factor
- Can pose a very challenging dilemma; what to stop, when to stop, etc
Drugs - Prescription

- Opiates
- Anticholinergics
- Antihistamines
- Antipsychotics
- TCA
- Calcium Channel Blockers
- Anti Parkinson Agents


Drugs – Nonprescription

- Calcium-containing antacids
- Calcium supplements
- Iron supplements
- Anti-diarrheal agents


Clinical Evaluation

- Excellent history
  - review of prescribed/non-prescribed drugs
  - frequency of defection
  - character of stool
  - physical complaints/concerns
  - level of inactivity
  - accessibility to proper facilities
  - psychosocial assessment
  - consider “bowel function diary”
Clinical Evaluation

- Degree of straining (? Incomplete evacuation; possible PF disorder)
- Assess need or requirement for manual pressure or disimpaction
- What methods of therapy have or are presently being employed
- Ignoring the urge to defecate

Physical Examination

- Assessment of rectal tone
- Quality of stool in rectal vault
- Rule out distal obstructing lesion

http://gastrolab.1g.fi/ja/a025/slides/5.jpg
Diagnostic Testing

- Electrolytes
- TSH

Colonoscopy recommended only for patients displaying evidence of mechanical obstruction.

General agreement that all constipated patients >50yrs of age should undergo CRC screening.

Each case is patient & physician dependent.

Cash BD. Fresh perspectives in chronic constipation and other functional bowel disorders. Rev Gastroenterol Disord 2007; 7(3): 116-33


“Red Flags”

- New onset constipation in the elderly
- Severe persistent constipation that is unresponsive to empiric treatment
- Hematochezia
- FOBT (+)
- Unexplained anemia
- Weight loss of 10lbs or more

Diagnostic Testing

- Colonic Transit Studies
- Balloon Expulsion
- Anorectal Manometry
- Defecography

Evacuation Disorders

- What are some other causes?
- Rectocele
- Foreign devices
- Postsurgical changes

Treatment Options

- Evaluating & treating potentially causative factors
  - excluding/treat mechanical obstruction
  - discontinuation of medications possibly precipitating constipation
  - dietary/lifestyle modification
  - addressing psychosocial issues
  - pharmacotherapy
Treatment Options

- Biofeedback therapy
- Surgical options

Mechanical Obstruction

- Colorectal Cancer
- Stricture
- Solitary Rectal Ulcer Syndrome (SRUS)
- Manual disimpaction/fragmentation if indicated

Impaction

- Can use mineral oil enema to soften stool
- Water soluble contrast enema (Gastrograffin) to exclude proximal obstruction and to eliminate more proximal impactions
- Endoscopic disimpaction
- After disimpaction continue with daily enemas or oral laxative solution to ensure colon gets completely evacuated

[Reference: Treatment of constipation in older adults, UpToDate Online 17.2]
Impaction

- Patient should then be on daily bowel regimen to try and promote daily bowel movements
- Should use restroom after meals to try and take advantage of natural gastrocolic reflex

Dietary Changes

- Dietary fiber and bulk laxatives such as psyllium or methylcellulose, together with adequate fluids, are the most physiologic and effective approach to therapy, improving bowel habits in many patients with constipation
- Wheat bran is one of the more effective fiber laxatives.

- High fiber diet increases stool weight and decreases colon transit time by stimulating intestinal muscles
- Caution patients that consuming large amounts of fiber can cause abdominal bloating, flatulence –why??
  (**from colonic bacterial fermentation**)
- Recommended daily intake ~25 grams
Bulk Forming Laxatives

- Psyllium, methylcellulose, calcium polycarbophil
- Natural or synthetic polysaccharides or cellulose derivatives that primarily exert their laxative effect by absorbing water and increasing fecal mass
- These laxatives are effective in increasing the frequency and softening the consistency of stool with a minimum of adverse effects

Ward, A. Treatment of constipation in adults. UpToDate Online 17.2

Laxatives

- Osmotic
- Stimulant
- Saline
- Stool Softeners

http://www.clinicaladvisor.com/fda-approves-linzess-for-ibs-chronic-constipation/article/256919/
Osmotic Laxatives

- Miralax (PEG 3350)
  17 grams (1 tbsps) in 8 oz water daily
- Lactulose
  15-30 ml daily up to TID
- Sorbitol 15-30 ml BID


Osmotic Laxatives

- Poorly absorbed substances draw water into the lumen of the bowel from the surrounding tissue along an osmotic gradient.
- This maintains isotonicity with serum plasma, resulting in increased bulk and a softer stool.

Brenner, DM. Chronic Constipation in 2006: Where we have been, where are we going. The Gastroenterology Report 2006;1:4-10

Osmotic Laxatives

- SE:
  - diarrhea
  - electrolyte disturbances (K, Na)

PEG does not cause bloating, gas
Saline Laxative
(also osmotic)

- Magnesium hydroxide (MOM)
  1-2 tblspn daily or BID
- Magnesium Citrate
  - onset .5-6hrs


Stimulant Laxatives

- Senna (Sennokot)
  2 tablets daily up to 4 tablets BID
  - also in Smooth Move Tea®
  - Swiss Kriss®
- Bisacodyl (Dulcolax)
  5-15mg daily (po or pr)
  stimulate sensory nerves within the colonic mucosa and result in increased motility


- Efficacy
- SE: cramping, diarrhea, hepatotoxicity, electrolyte imbalances
- Enteric nerve damage with subsequent dilation of the colon and poor motility
- Melanosis coli (senna & cascara – anthraquinone-containing compounds)


Brenner, DM. Chronic Constipation in 2006: Where we have been, where are we going. The Gastroenterology Report, 2006;1:4-10.


Stimulant Laxatives

- Some individuals can develop a psychosocial dependency on stimulant laxatives
- Myenteric nerve damage - Neurogenic colon

Stool Softeners

- Docusate sodium (Colace)
  - 100mg BID
  - Detergents that lower surface tension of the stool which causes an increase in water content of the stool & softens it
  - Minimal SE
  - Benefit
  - Effect in 1-3 days

References:
- Cash BD. Fresh perspectives in chronic constipation and other functional bowel disorders. Rev Gastroenterol Disord. 2007 Jul;7(3):116-33
- Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Eur J Gastroenterol Hepatol. 2005 Sep;17(9):969-70
Enemas, Suppositories & Lubricants

- Mineral oil, tap water, glycerin, bisacodyl

Chloride Channel Activator

- Lubiprostone (Amitiza®)
  - 24 mcg BID with food
  - Derived from a metabolite of prostaglandin E1 although it has no effects on smooth muscle contraction

Chloride Channel Activator

- Type 2 chloride channel (CIC-2) present in luminal membrane
- Potential to increase chloride and fluid secretion into lumen
- When activated, chloride and sodium get secreted into lumen with water passively following to maintain isotonicity.
- Adds fluid to stool and promotes increased transit
Linzess® (linactolide)

- Guanylate cyclase-C agonist
- 145mg/day for CIC
- 290mg/day for IBS-C
- Subsequent elevation in intracellular cGAMP stimulates secretion of chloride and bicarbonate ions into intestinal lumen

http://www.frx.com/pi/linzess_pi.pdf

Opioid Antagonists

- Methylnaltrexone

Methylnaltrexone

- Relistor®
- Functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.
- Administered subcutaneously
Biofeedback Therapy

- Used to correct inappropriate contraction of the pelvic floor muscles and EAS used during defecation
- Using anal electromyography or sphincter recording pressures
- Focuses on retraining, relaxation of sphincter and pelvic floor muscles
- May be effective in more than 70% of patients with dyssynergic defecation


Surgery

- Colectomy with IR anastomosis
  - for slow transit constipation
- Repair of rectocele?
- Bloating and abdominal pain are less likely to improve with surgery.


Complications from Constipation

- Stercoral Ulcer
- Perforation
- Fecal Impaction/Obstruction
- Hemorrhoids
- Anal Fissures
- Prolapse
**Basics**

- What is Cdiff?
- Gram +
- Anaerobe
- Spore forming bacillus (spores can live awhile outside the human body)

- Produces two exotoxins
- Responsible for up to 15-25% of all antibiotic associated diarrheas, 50% to 75% of those with antibiotic-associated colitis, and more than 90% of those with antibiotic-associated pseudomembranous colitis
- Important hospital-acquired infection associated with an increase in length of hospital stay and cost, and substantial morbidity and mortality.
Basics

- Spores survive gastric acidity
- In small intestine, spores convert into their vegetative state
- In the colon, normal flora has been disrupted by Abx and spores germinate and flourish

What can it do??

- pseudomembranous colitis (PMC)
- toxic megacolon
- perforations of the colon
- sepsis
- death (rarely)

Symptoms

- watery diarrhea
- fever
- loss of appetite
- nausea
- abdominal pain/tenderness
Risk factors

- antibiotic exposure
- proton pump inhibitors
- gastrointestinal surgery/manipulation
- long length of stay in healthcare settings
- a serious underlying illness
- immunocompromising conditions
- advanced age

Is it there?  Is active?

- *Clostridium difficile* colonization
  - patient exhibits NO clinical symptoms
  - patient tests positive for *Clostridium difficile* organism and/or its toxin
  - more common than *Clostridium difficile* infection
  - Studies show that colonization in LTCF can be up to 20%!

- *Clostridium difficile* infection
  - patient exhibits clinical symptoms
  - patient tests positive for the *Clostridium difficile* organism and/or its toxin

How did I get this???

- Shed in feces
- Any device contaminated with feces can transmit it
- *Clostridium difficile* spores are transferred to patients mainly via the hands of healthcare personnel who have touched a contaminated surface or item
- The estimated prevalence of *C. difficile* colonization may be as high as 50% in hospitalized patients where CDI is endemic, 5% to 7% in residents of long-term care facilities, and generally less than 2% in ambulatory adults.
The 1st step is alteration of the normal gut flora, usually as a result of administration of an antibiotic.

Clindamycin was the first antibiotic to be associated with pseudomembranous colitis, identified as a precipitant before the establishment of *Clostridium difficile* as the causal pathogen.

Since that initial observation, almost all antimicrobials have been associated with CDI including cephalosporins, penicillins, and the fluoroquinolones.

Chemotherapeutic agents, particularly those with antimicrobial properties, have also been associated with the development of CDI.

The second step is acquisition of a toxigenic strain of *Clostridium difficile*.

The organism is primarily a nosocomially acquired pathogen and its spores can be found in the hospital environment.

Once a patient has acquired *C. difficile*, he or she will develop clinical disease or will remain asymptptomatically colonized, the final step in the process.

Although the exact incubation time for CDI is unknown, the time from acquisition to disease is relatively short, perhaps no longer than 7 days.
Treatment

- In about 20% of patients, *Clostridium difficile* infection will resolve within 2-3 days of discontinuing the antibiotic to which the patient was previously exposed.
- The infection can usually be treated with an appropriate course (about 10-14 days) of antibiotics, including metronidazole, vancomycin (administered orally), or recently approved fidaxomicin.
- After treatment, repeat *Clostridium difficile* testing is not recommended if the patients’ symptoms have resolved, as patients may remain colonized.

How can we prevent this

- Use antibiotics judiciously (are they truly necessary?)
- Use Contact Precautions for patients with known or suspected *Clostridium difficile* infection; can stop when diarrhea ceases.
- Because alcohol does not kill *Clostridium difficile* spores, use of soap and water is more efficacious than alcohol-based hand rubs.
- Use gowns when entering patients’ rooms and during patient care.
- Dedicate or perform cleaning of any shared medical equipment.
- Continue these precautions until diarrhea ceases.
- Because *Clostridium difficile*-infected patients continue to shed organism for a number of days following cessation of diarrhea, some institutions routinely continue isolation for either several days beyond symptom resolution or until discharge, depending upon the type of setting and average length of stay.
- Cleansing programs at institutions.
Diagnosis

- Stool analysis: PCR (highly specific and sensitive)
- What about sigmoidoscopy or colonoscopy?
  - When should this be done??

Endoscopic view....

Treatment

- Historically, as many as 50% of patients will respond to stopping the precipitating antibiotic, however the emerging trends of CDI demonstrate that this is a potentially devastating infection that requires treatment.
- Adequate hydration and electrolyte replenishment should accompany medical and surgical therapy.
- Antiperistaltics should be avoided because these can exacerbate toxin-mediated damage to the mucosa.
Treatment

- Metronidazole (500mg 1 po TID or IV for 2 weeks)
- Effective, comparable to vancomycin but less expensive (and less chance of developing VRE!)
- Oral vanco used for intolerance to metronidazole, lack of response to metronidazole or more severe disease
- No documented resistance to these two drug by Cdiff
- When should we start seeing results??
  - Hopefully by a few days

Treatment

- Severe disease
  - Can use vanco enemas
  - May need surgical eval

Treatment

- IVIG
- Probiotics
- Fidaxomicin (Dificid)
- Rifaximin: Small case series have suggested that sequential therapy with vancomycin followed by rifaximin may be effective for the treatment of recurrent CDI
Recurrence

- 20% after 1st episode
- 45% after 1st recurrence
- 65% after 2 or more recurrences

Recurrence

- Historically, we are taught to give another trial of what we first tried
- CDI can recur after treatment with metronidazole or vancomycin with rates ranging from 15% to 30%
- After the first relapse; prolonged vancomycin taper is recommended
Fecal Transplant

- Fecal bacteriotherapy
- Attempts to reconstitute the protective flora with fecal infusions via nasogastric tube or rectally have been reported to have great success


Toxic Megacolon

Clostridium difficile colitis and Toxic Megacolon

http://www@Enablement.org/normal-anatomy.png

http://www.Enablement.org/pre-inflammation-complex.png

http://www.Enablement.org/toxic-megacolon.png

http://www.Enablement.org/toxic-megacolon-radiograph.png
Surgery

- Early surgical consultation should be considered for severe CDI, especially if toxic megacolon is present, because operative intervention can be lifesaving.
- Various surgical procedures have been described, including diversion of fecal stream by ileostomy, decompressive colostomy, or subtotal colectomy, the procedure of choice with toxic megacolon.
- Cases requiring surgery carry high mortality rates, ranging from 30% to over 50%.