GI Updates
Diarrhea/IBS

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Disclosure: Dr. Zisman has no significant financial interest in any of the products or manufacturers mentioned.
Definitions

• Diarrhea: increased frequency, looser consistency or increased volume of stool

• Acute diarrhea: < 14 days
• Persistent diarrhea: more than 14 days
• Chronic diarrhea: > 30 days
Etiology

• Acute diarrhea is self-limited and nearly always due to infection

• **Viruses**: norovirus, rotavirus, adenovirus, etc.

• **Bacteria**: campylobacter, salmonella, shigella, E. coli (ETEC), C. difficile, etc.

• **Protozoa**: giardia, entamoeba, cryptosporidium, etc.
## Indications for diagnostic evaluation

<table>
<thead>
<tr>
<th>Diarrheal illness-related factors</th>
<th>Patient-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Hospitalized patients (or recent antibiotics)</td>
</tr>
<tr>
<td>Fever</td>
<td>Elderly</td>
</tr>
<tr>
<td>Severe abdominal pain</td>
<td>Medically fragile</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Immunocompromised</td>
</tr>
<tr>
<td>≥ 6 loose stools/24 hrs</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
Diagnostic testing

- Stool studies: culture, ova & parasites, C. difficile
- If risk factors: giardia antigen, E. coli O157:H7
- Endoscopy: indicated in patients with established IBD or immunocompromised patients in whom CMV is suspected
Treatment of acute diarrhea

• Hydration:
  – Oral rehydration solution best
  – Sports drinks may be adequate if mild diarrhea
  – Dilute fruit juice with saline crackers
  – IV hydration if needed
  – Avoid fatty foods or lactose

• Antidiarrheals:
  – Loperamide and/or diphenoxylate atropine

• Bismuth subsalicylate

• Probiotics:
  – Lactobacillus and bifidobacterium species beneficial
Antibiotics for Acute Diarrhea

• Indications:
  – > 4 BMs/day, fever, blood/pus/mucus in stool
  – > 8 stools/day, volume depletion
  – Symptoms lasting > 7 days
  – Immunocompromised
  – C. difficile infection

• Avoid antibiotics if EHEC suspected (bloody diarrhea and pain but no fever) or confirmed
  – No benefit in reducing duration of symptoms
  – Increased risk of hemolytic uremic syndrome

• Choice of antibiotic:
  – Ciprofloxacin 500mg BID or levofloxacin 500mg daily x 3-5d
  – Azithromycin 500mg daily for 3 days
  – Rifaximin 200mg TID for 3 days (not for invasive infections)
Prevention of Traveler’s Diarrhea

• “Boil it, cook it, peel it, or forget it!”
• Rifaximin reduces diarrhea rate by 70%
• Bismuth subsalicylate reduces diarrhea 40-65%
• Probiotics beneficial in some studies

Pawlowski SW, Gastro 2009
Chronic Diarrhea
Classification of chronic diarrhea

• Fatty
• Bloody
• Watery
  – Osmotic
  – Secretory
  – Functional
Initial evaluation-History

- Stool frequency and consistency, duration of sx
- “Red flag” sx: nocturnal BMs, blood, wt loss
- Recent travel
- Dietary triggers (eg lactose, wheat, fatty foods)
- New medications, herbal therapies, antibiotic use
- Family history of celiac, Crohn’s, ulcerative colitis
- Prior abdominal surgeries (eg cholecystectomy, fundoplication, bowel resection)
Diagnostic testing

• Blood tests:
  – CBC, comprehensive metabolic panel, ESR, CRP, TSH, celiac testing

• Stool tests:
  – C. difficile, fecal leukocytes or calprotectin, fecal occult blood test
Bloody (Inflammatory) Diarrhea

• Classic features:
  – Visible blood, abdominal pain, nocturnal BMs

• Causes:
  – Crohn’s disease, ulcerative colitis, ischemic colitis, radiation enteritis/colitis, segmental colitis associated with diverticulosis, infections

• Workup:
  – colonoscopy (refer to GI)
Fatty Diarrhea

• Classic features:
  – Gas/bloating, oily stools, weight loss

• Causes:
  – pancreatic insufficiency, bile salt deficiency, small intestinal bacterial overgrowth, celiac disease, infections (giardia, cryptosporidium, cyclospora)

• Workup:
  – Spot fecal fat (Sudan stain), normal < 20 drops/hpf
  – 24 hr quantitative fecal fat
  – Vit A, D, E
  – Celiac serology
  – Breath test for bacterial overgrowth
  – Empiric trial of pancreatic enzymes or antibiotics
# Watery Diarrhea

<table>
<thead>
<tr>
<th>Secretory</th>
<th>Osmotic</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large volume (&gt;1 L/day)</td>
<td>Moderate volume</td>
<td>Small to moderate volume</td>
</tr>
<tr>
<td>No change with fasting</td>
<td>Resolves with fasting</td>
<td>Improves with fasting</td>
</tr>
<tr>
<td>Stool osmolar gap &lt; 50</td>
<td>Stool osmolar gap &gt; 125</td>
<td>Stool osmolar gap &lt;50</td>
</tr>
</tbody>
</table>

**Common causes:**
- Post-cholecystectomy
- Non-osmotic laxatives
- Neuroendocrine tumors
- Microscopic colitis
- Infections (cholera)

**Common causes:**
- Lactose intolerance
- Fructose intolerance
- Osmotic laxatives

**Common causes:**
- Irritable bowel syndrome
- Factitious diarrhea
When to refer to GI

- Anemia
- Weight loss
- Melena, BRBPR (or positive occult blood test)
- Nocturnal BMs
- Family history of celiac, IBD, colon CA
Celiac disease

• Immune-mediated enteropathy triggered by gluten
• Approximately 1% prevalence in Caucasians
• Diagnosis:
  – Anti-tissue transglutaminase (TTG) IgA or Anti-endomysial IgA, total IgA
  – Do not order anti-gliadin antibody or HLA type
  – Gold standard: duodenal biopsy
• Treatment:
  – Gluten-free diet
  – Screen annually for diabetes, thyroid disease, anemia
Post-cholecystectomy diarrhea

• Occurs in 5-10% of patients after cholecystectomy
• Secretory and malabsorptive components
• Treatment:
  – Low fat diet
  – Bile salt binding medication (eg cholestyramine) prescribed at bedtime
Inflammatory Bowel Disease

**Ulcerative Colitis**
- Continuous distribution
- Variable extent, but always involves rectum
- Colon only
- Superficial inflammation

**Crohn’s Disease**
- Continuous or patchy distribution
- May spare the rectum
- Involves any part of GI tract
- Full-thickness inflammation
- Fistulas and strictures
C. difficile-Associated Diarrhea

• Metronidazole for mild to moderate disease
• Vancomycin first line for severe disease, immunocompromised patients or IBD
• Recurrent/refractory cases:
  – Vanco pulse/taper
  – Saccharomyces boulardii (Florastor)
  – Rifaximin
  – Fidaxomicin
  – Fecal microbiota transplantation
Irritable Bowel Syndrome
IBS-Definition

• Rome III Criteria:
  – Recurrent abd pain/discomfort lasting at least 3 days/mo for at least 3 mo
  – Improvement with defecation
  – Onset assoc w/ change in stool form or frequency

• Other common sx include bloating, urgency, straining, sense of incomplete evacuation

• 3 subtypes: constipation or diarrhea predominant, or mixed
IBS-Epidemiology

• Estimated 7-15% of US population\textsuperscript{1,2}
• More common among:
  – Women
  – Age <50
  – Lower socioeconomic status
  – Gulf war veterans
• HRQOL lower in IBS than in GERD, depression, chronic renal failure

\textsuperscript{1}Longstreth GF, Gastro 2006
\textsuperscript{2}Drossman DA, Gastro 2002
Pathophysiology

• Dysregulation in brain-gut interaction, resulting in alterations in:
  – Autonomic response
  – Immune function
  – Gut motility
  – Visceral perception

• Multifactorial:
  – Enteric infection, psychosocial stress, genetics
Diagnostic Evaluation in IBS

• Symptom-based diagnosis. Not a dx of exclusion.

• **WARN**ing features that require workup:
  – **W**eight loss
  – **A**nemia
  – **R**ectal bleeding
  – **N**octurnal bowel movements
  – Family history of colon CA, IBD, celiac
  – Onset at age >50
## Diagnostic testing

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Not generally recommended</th>
</tr>
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<tbody>
<tr>
<td>CBC</td>
<td>H. Pylori testing</td>
</tr>
<tr>
<td>Metabolic panel</td>
<td>Lactose breath test</td>
</tr>
<tr>
<td>Albumin</td>
<td>SIBO breath testing</td>
</tr>
<tr>
<td>TSH</td>
<td>Food allergy testing</td>
</tr>
<tr>
<td>ESR, CRP</td>
<td>Stool studies</td>
</tr>
<tr>
<td>Anti-TTG IgA, total IgA</td>
<td>Colonoscopy</td>
</tr>
</tbody>
</table>
Diet in IBS

- Up to 70% of IBS patients attribute sx to food\textsuperscript{1}
- However, general exclusion diets have not been shown to be helpful
- Poor correlation between food allergy testing and response to specific exclusion diet
- Gluten-free diet and FODMAP diet have the most promising evidence

\textsuperscript{1}Monsbakken KW, Eur J Clin Nutr 2006
FODMAPs
(Fermentable oligo-, di- and monosaccharides and polyols)

• Short chain carbohydrates and sugar alcohols
• Fermented by bacteria to hydrogen, CO$_2$ and short chain fatty acids
• Osmotic load and gas $\rightarrow$ bloating and loose stool
• Sources:
  – Fructose $>$ glucose: apples, pears
  – Fructan-containing veggies: onion, asparagus, artichokes
  – Wheat-based products: bread, pasta
  – Sorbitol-containing foods: plums, cherries, artificial sweeteners
  – Raffinose containing foods: cabbage, lentils
Fiber and bulking agents

- Soluble fiber (psyllium) more effective than insoluble fiber (wheat bran)

Bijkerk C, BMJ 2009
Laxatives

- Generally not well studied in RCTs for IBS-C
- Effective for increasing stool frequency
- Not effective for abdominal discomfort, global IBS symptom severity or quality of life
Lubiprostone

• Chloride channel agonist
  – Increases intestinal secretion of fluid
  – Secondary stimulation of peristalsis

• 2 RCT’s demonstrate superiority over placebo

• Dosing:
  – 8mcg BID for IBS-C
  – 24mcg BID for chronic constipation

• Side effects:
  – Nausea (31%), diarrhea (12%), headache (11%)
Antidiarrheals
(loperamide, diphenoxylate atropine)

• Effective for decreasing stool frequency and incontinence and improving stool consistency
• Not effective for relief of abd pain or global symptoms of IBS in 2 prospective trials

1Hovdena N, Scand J Gastroenterol 1987
2Lavo B, Scand J Gastroenterol 1987
Alosetron

• 5-HT₃ receptor antagonist approved for treatment of IBS-D
• Superior to placebo for improving abd pain, urgency, global IBS symptoms, diarrhea
• Side effects: severe constipation and ischemic colitis (>1 case per 1000 patient-yrs)
• Only available under a regulated prescribing program for patients with IBS-D not responding to other therapies.
Rifaximin for IBS without constipation

• Non-absorbable oral antibiotic
• Broad coverage of enteric organisms
• Low risk of bacterial resistance
• FDA approved for traveler’s diarrhea and hepatic encephalopathy
• Two large RCTs in IBS (TARGET 1 and 2 trials)
  – 1260 patients received rifaximin or placebo x 14 d
  – Followed for 10 more weeks
  – Primary outcome: adequate relief of global IBS symptoms

Pimentel M, NEJM 2011
Rifaximin for IBS without constipation

Pimentel M, NEJM 2011
Antispasmodics
(hyoscyamine, dicyclomine)

• Most trials done with agents not available in the US (otilonium, trimebutine, cimetropium, etc)
• Generally useful for short term relief of abd pain/discomfort
• Particularly helpful for post-prandial sx if taken 30 min before meals
• Long term efficacy and safety unknown
Antidepressants

• Result in central modulation of visceral afferent input

• Meta-analysis of 9 studies showed tricyclic antidepressants superior to placebo (41% persistent sx vs 60%). Useful for IBS-D.

• SSRIs improve overall well-being and anxiety, but not abd pain. More useful in IBS-C.
Probiotics for IBS

• 3 systematic reviews suggests overall efficacy of probiotics, RR of IBS not improving 0.71 (NNT=4)
  – Most robust data for *Bifidobacterium infantis* 35624
  – VSL#3 improves bloating and flatulence symptoms
  – Combination probiotics generally effective
  – Lactobacillus species not consistently effective

Moayyedi P, Gut 2010
McFarland LV, World J Gastroenterol 2008
Hoveyda N, BMC Gastroenterol 2009
Brenner DM, Am J Gastroenterol 2009
Patients with IBS dx by Rome III criteria (n=80)

Randomized to receive placebo (without deception) or no treatment

Results:
Placebo superior to no treatment for global improvement, adequate relief of IBS symptoms, symptom severity reduction and quality of life

Conclusion: placebo without deception may be effective for IBS

Kaptchuk TJ, PLoS ONE 2011
Summary of IBS recommendations

• Clinical diagnosis based on abd discomfort and change in stool frequency or consistency
• If no alarm signs/sx, then minimal workup needed: CBC, TSH, celiac testing (anti-tTG)
• Trial of gluten-free diet or FODMAP diet
• IBS-C: fiber (psyllium), laxatives, lubiprostone
• IBS-D: loperamide, diphenoxylate, rifaximin
• Pain: antidepressants (TCAs, SSRIs), antispasmodics (dicyclomine, hyoscyamine)
Constipation
Constipation

• Rule out secondary constipation
  – Opioid-induced, other medications, obstruction, metabolic/endocrine, etc.

• Primary constipation
  – Slow transit constipation
  – Dyssynergia
  – Constipation-predominant IBS
# Laxatives

<table>
<thead>
<tr>
<th>Class</th>
<th>Medications</th>
<th>Mechanism</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk (fiber) agents</td>
<td>Psyllium</td>
<td>Retain water</td>
<td>Flatulence</td>
</tr>
<tr>
<td></td>
<td>Methylcellulose</td>
<td>Increase bulk</td>
<td>Bloating</td>
</tr>
<tr>
<td>Stool softeners</td>
<td>Docusate</td>
<td>Detergent-like action</td>
<td>Cramping</td>
</tr>
<tr>
<td>Stimulant laxatives</td>
<td>Senna</td>
<td>Increase peristalsis</td>
<td>Abd discomfort</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl</td>
<td></td>
<td>Melanosis coli</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Tolerance</td>
</tr>
<tr>
<td>Osmotic laxatives</td>
<td>Lactulose</td>
<td>Osmotic water binding</td>
<td>Bloating</td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td></td>
<td>Flatulence</td>
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<tr>
<td></td>
<td>Magnesium</td>
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<td>PEG</td>
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About half of patients with chronic constipation do not have adequate relief with these conventional therapies.
Practical Advice

• Treatment strategies:
  – Bowel purge (may need oral and rectal)
  – Antibiotics
  – Maintenance (miraIax +/- lubiprostone)
  – Periodic purge (Mg citrate if no BM in 3 days)

  – Don’t forget fiber, water and exercise!
### Opiate receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnatrexone (Relistor)</td>
<td>Opiate-induced constipation Post-op ileus</td>
<td>0.15-0.3mg/kg Subcutaneous</td>
<td>Abd pain (29%) flatulence (13%) nausea (12%)</td>
<td>Rare reports of intestinal perforation</td>
</tr>
<tr>
<td>Alvimopan (Entereg)</td>
<td>Opiate-induced constipation Post-op ileus</td>
<td>6-12mg before surgery, then BID for 7 days</td>
<td>Nausea/vomiting Hypokalemia Dyspepsia</td>
<td>Concern for cardiac events Restricted use for inpatients only</td>
</tr>
</tbody>
</table>

Both of these medications block peripheral opiate effect but do not cross the blood brain barrier.
On the Horizon

• Linaclotide
  – Activates guanylate cyclase C receptor on enterocytes
  – Results in increased fluid secretion and peristalsis
  – 2 large phase 3 RCTs showed efficacy in constipation

• Prucalopride
  – Highly selective 5-HT$_4$ agonist
  – 3 large phase 3 RCTs demonstrate efficacy for chronic constipation and IBS-C
Questions