Approach to Chronic Diarrhea

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Definition of Diarrhea

- Can be misused by patients
  - Loose stools, urgency, more than 1 bowel movement per day
- "Pseudodiarrhea"
  - Frequent defecation but normal stool consistency
- Defined by any one of three criteria
  - Stool frequency of >/= 3 bowel movements per day
  - Soft, mushy, watery stools (include Bristol stool chart, types 5-7)
  - Stool weight <200g/day
- Duration: Chronic = at least 4 weeks
- Obstipation
  - Overflow diarrhea

Hammer HF. *Digestive Diseases.* 2021;39:615-621

Etiology

- Functional / IBS- Diarrhea
- Organic
  - Secretory
  - Osmotic
- Fatty (steatorrhea)
- Inflammatory
- Dysmotility

Etiology

Organic

- Secretory
  - Watery, large volume, persists with fasting
  - Causes: drug induced diarrhea, bile acid diarrhea, hormone secreting/ endocrine tumors, bacterial infections
- Osmotic
  - Watery, less voluminous than secretory, improves with fasting
  - Causes: drug induced diarrhea, dietary (lactose intolerance, poor absorbed sugars/sugar alcohols), malabsorption issues like celiac

Etiology

Organic

- Fatty (Steatorrhea)
  - Bulky malodorous pale stool
  - Causes: malabsorption like celiac, exocrine pancreatic insufficiency (EPI), and inflammatory bowel disease (IBD)
- Inflammatory
  - Liquid loose with blood
  - Causes: IBD, infectious, other inflammatory causes (ischemic, radiation)

Etiology

- Dysmotility
  - Diabetes diarrhea
  - Other systemic diseases like scleroderma, amyloidosis

How I Approach Evaluating Diarrhea

1) History should give you most of the diagnosis
   1) Duration
   2) Frequency
   3) Characteristics of the stool
   4) Associated symptoms
   5) Red flag concerns
   6) Association of stress and depression
   7) Recent travel
   8) New/ change in medications
   9) Dietary history
   10) Abdominal surgeries
   11) Abdominal radiation
   12) Family history

History

Evaluate for causes of diarrhea:

- Stools during fasting
  - Secretory diarrhea
- Resolution with fasting
  - Osmotic diarrhea
- Tenesmus
  - Feeling of need to constantly pass a stool
  - Inflammatory diarrhea
- Foul smelling, floating stools with bloating
  - Suggests fatty stools
  - Malabsorption
- Nocturnal stools
  - Suggests organic rather than functional cause
- Started after cholecystectomy
  - Consider bile acid diarrhea

Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669

History

- Association with food intake? Think:
- Lactose or fructose intolerance
  - 36% of US population is lactose intolerant
  - Fructose is absorbed by facilitated diffusion with limited capacity; when the amount ingested exceeds that capacity, malabsorption and diarrhea may occur.
    - High fructose corn syrup
- Presence of poorly absorbed sugar alcohols
  - Sorbitol, sucralose, mannitol, Xylitol
  - Present in diet drinks and snacks
- Caffeine intake
  - Can stimulate gut motility

Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669

History

- History of radiation treatment
  - Can cause diarrhea years after exposure
  - Radiation enteritis occurs in up to 20% of patients treated with pelvic irradiation, typically 1.5-6 years after irradiation
  - Caused by direct damage to enterocytes and ischemia that is due to blood vessel damage. Submucosal fibrosis and lymphatic damage are commonly seen. The damaged bowel loses absorptive capacity and is predisposed to SIBO, particularly if strictures develop. If the distal ileum is involved, bile acid malabsorption can be present.
- Abdominal surgery
  - Can lead to vagotomy, SIBO, bile acid malabsorption, short bowel syndrome

Author: Jakembradford - CC BY-SA 4.0

Theis et al. Chronic radiation enteritis. Clin Oncol (R Coll Radiol) 2010; 22: 70-83

Medications

- Medications are a common cause of chronic diarrhea.
- Review medications - both prescription and over the counter
- Don't forget about vitamins, minerals, herbal and nutritional supplements

Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669

Medications List

- Magnesium supplements
  - Mg gluconate, Mg glycinate less likely
- Weight loss teas or supplements
  - Might contain laxatives or thyroxine-like thyroid replacements
- Metformin, gliptins
- Antibiotics, including macrolides
- NSAIDS and SSRIs
  - Associated with microscopic colitis
- Beta blockers
- Furosemide
- Olmesartan
  - Associated with celiac sprue like enteropathy
- Antineoplastic agents

How I Approach Evaluating Diarrhea

1) History should give you most of the diagnosis
2) Look for red flags

Red Flags

- Blood in stool
- Anemia
- Progressive abdominal pain
- Unintentional Weight loss
- Fever
- Tenesmus
- Nocturnal stools
- Immunosuppressed patient
- Family history of IBD or GI malignancy

Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669

How I Approach Evaluating Diarrhea

1) History should give you most of the diagnosis
2) Look for red flags/suggestions of alternative diagnoses
3) Don't consider IBS a diagnosis of exclusion. Use the ROME IV Criteria

ROME IV Diagnostic Criteria for IBS-Diarrhea

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with **two or more** of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

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

Types of Irritable Bowel Syndrome

- IBS – Diarrhea
  - > 25% Bristol 6-7, <25% Bristol 1-2
- IBS – Mixed
  - > 25% Bristol 6-7 AND > 25% Bristol 1-2
- IBS – Constipation
  - > 25% Bristol 1-2, <25% Bristol 6-7
- IBS - Unspecified

Source: Pixabay

Issues with the ROME Criteria

- Sensitivity only 82%, Specificity 83%
- Focused too much on pain
  - Rome III had discomfort in addition to pain
- Strict IBS subtyping not super helpful
  - Fluctuating symptoms
- Recall bias
  - Patients need to recall last 3-6 months
  - Exaggerated symptoms

Black et al. *Gut*. 2020

How I Approach Evaluating Diarrhea

1) History should give you most of the diagnosis
2) Look for red flags/suggestions of alternative diagnoses
3) Don't consider IBS a diagnosis of exclusion. Use the ROME IV Criteria
4) Limited laboratory work up
   1) Complete blood count (CBC)/chemistry
   2) Celiac Testing
   3) Fecal Calprotectin
   4) Giardia testing (if risk factors)

Testing

CBC
- Anemia

Chemistry
- Monitor electrolytes if concerned for severe diarrhea

Celiac Testing
- Serum IgA Tissue transglutaminase
  - Must test for IgA deficiency (IgA level) – incidence of 1:223
- If IgA deficiency – either
  - IgG tissue transglutaminase
  - IgG deaminated gliadin peptides
- Positive serologies requires histologic confirmation on EGD/endoscopy

Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669c

Stool Testing

Fecal Calprotectin
- Could use lactoferrin or ESR/CRP if calprotectin not available
- Directly proportional to neutrophil migration into GI tract
- Cut off of 50 ug/g provides 81% sensitivity and 87% specificity for IBD vs IBS
- Meta analysis data suggests <1% probability of IBD if <40 ug/g
- Data also suggests its useful in finding microscopic colitis

Giardia
- Common cause of watery diarrhea
- Stool antigen or PCR testing (>95% sensitive/specific)
- Reasonable in most patients

Smalley W et al. *Gastroenterology.* 2019;157:851-854
Schiller LR. *The American Journal of Gastroenterology.* 2018:113:660-669

Testing – Less used

C. difficile testing – only in severe cases
- More severe than IBS-D
- Usually have risk factors
  - Antibiotic use
  - Recent hospitalization
  - Resident at long term care facility
- Carriers exist (pcr positive, toxin negative)

- **Stool O&P**
  - Not routinely recommended
  - Really need three samples to get good sensitivity
  - Reasonable if
    - Travel to endemic regions (Asia, sub-Saharan Africa)
    - Recent immigration from these areas

Smalley W et al. *Gastroenterology.* 2019;157:851-854

Testing – Less used

Bile acid diarrhea
- Measurement of total bile acids in a 48-hour stool collection (abnormal= increased fecal bile acids)
  - Not readily available or FDA approved
- More commonly: empiric treatment with bile acid binders

Stool electrolytes
- Calculate osmotic gap
  - 290 mOsm/kg – 2x (fecal sodium + fecal potassium)
    - < 50 mOsm/kg secretory diarrhea
    - > 75 mOsm/kg osmotic diarrhea

Testing – Less used

Indirect pancreatic testing

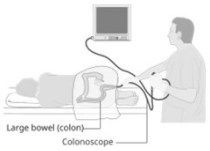
- Serum trypsin, fecal chymotrypsin, fecal elastase assays
  - Limited sensitivity
- More commonly: empiric trials of pancreatic enzyme replacement therapy or imaging

Small intestinal bacteria overgrowth

- Hydrogen breath test (uses glucose or lactulose)
- Bacteria in the small intestine degrade nutrients before they can be absorbed→ producing H2 which diffuses across the gut wall into the bloodstream
- Risk factors: anatomic or functional abnormalities of the intestines

Who needs a Colonoscopy?

- Anyone due to colon cancer screening
  - > 45 years old
  - 10 years prior to first family member with colon cancer
- Red flag symptoms
- Concern for inflammatory bowel disease
  - Elevated fecal calprotectin/lactoferrin
  - Consider if family history of IBD
- Refractory to therapy



Schiller LR. *The American Journal of Gastroenterology*. 2018:113:660-669

Endoscopy Considerations

- Upper endoscopy/EGD: unexplained steatorrhea
  - Biopsy small intestine to evaluate for malabsorptive disease
- Lower endoscopy/colonoscopy: inflammatory and secretory diarrhea
  - Evaluate and biopsy for IBD and microscopic colitis

How good is the limited test approach?

- This limited diagnostic approach rules out organic disease in over 95% of patients
- Systemic review of 14 studies of clinic-based IBS patients
  - Only 2-5% of patients were diagnosed with an alternative condition

El-Serag HB et al. Ali Pharm Ther. 2004:19:861-870

Imaging Considerations

- Imaging studies are useful in some patients with steatorrhea and secretory or inflammatory diarrhea
  1. Help to define anatomic abnormalities
  2. Delineate the degree and extent of inflammation in IBD
  3. Diagnose chronic pancreatitis
  4. Demonstrate hormone-secreting tumors.

Consider

- IBD: CT enterography or MR enterography
- Chronic pancreatitis: CT/MR pancreas protocol
- Overflow diarrhea: KUB with sitz markers

Pathophysiology

Helps us understand treatments

- Irritation from products of digestion
- Mucosal immune activation
- Changes in
  - Neurotransmitters
  - Mucosal permeability
  - Gut microbiome
- Leads to symptoms via
  - Altered motility
  - Visceral hypersensitivity

Lacey BE. *International Journal of General Medicine*. 2016:9:7-17.
Carco et al. Front Cell Inf Micro 2020:10:468

Your Functional Diarrhea Toolbox

- Dietary Changes
- Fiber supplements
- Natural supplements
- ?Probiotics
- Anti-spasm medications
- Anti-diarrheal agents
- Bile acid binders
- Neuromodulators
- Rifaximin (Xifaxan)
- 5HT3 receptor antagonists (Alosetron)
- Eluxadoline (Viberzi)

First Things First

- Provide reassurance
- Physician-patient relationship is important
- Set expectations
  - 30-50% had unchanged symptoms
  - 2-18% had progressive symptoms
  - 12-38% had improvement in symptoms
- Goal: not one bowel movement per day, but improved quality of life
  - Reduce/eliminate urgency
  - Reduce/eliminate pain
  - Consistently of stool not as important

El-Serag HB et al. Ali Pharm Ther. 2004:19:861-870

Dietary Changes

- Patients will often have tried these
- Especially important in those with meal-related symptoms
- Trial of a Lactose Free Diet
  - More common in African Americans, Asian Americans, and Native Americans
  - Up to 36% in the US
  - Intolerance not increased in IBS-D
    - May have exaggerated symptoms due to visceral hypersensitivity

Lacey BE. *International Journal of General Medicine*. 2016:9:7-17

Dietary Changes

- Gluten free diet trial
  - Non-celiac gluten sensitivity (NCGS)
  - Gluten increases small bowel but not colonic permeability
  - Data on GF diet in IBS is mixed
  - Could be related to removal of fructans instead
    - 59 pts self reported NCGS
    - Gluten without fructans vs. fructans without gluten vs. Placebo
    - GI symptoms scores and bloating higher with fructan exposure than gluten exposure

Vazquez-Roque MI et al. Gastro. 2013;144(5):903-911

Low FODMAP Diet

- Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
  - Short-chain carbohydrates
  - Not absorbed well by intestine
  - Osmotically active
  - Feeds gut bacteria
    - Producing short chain fatty acids -> visceral hypersensitivity
    - Hydrogen and methane -> bloating
- Low FODMAP diet helps alleviate symptoms in 75% of IBS patients

Smalley W et al. *Gastroenterology*. 2019;157:851-854

Low FODMAP Diet

How do I use this thing?

- Standard - Three phases
  1. Restriction (6-8 weeks)
  2. Reintroduction
  3. Avoidance of triggering foods
- Trigger finding
- Lots of Apps and online resources
  - Monash University FODMAP diet - $8
- Nutritionists do a Low FODMAP class

Smalley W et al. *Gastroenterology*. 2019;157:851-854

Fiber

- Increases stool bulk
- May change microbiome
- May decrease fermentation in the bowel
- **Soluble** fiber
  - Psyllium fiber or methylcellulose
  - Avoid wheat bran and other insoluble fibers (fermentable)
- I find people have less bloating with methylcellulose than psyllium
- Start with 3-4g per day and increase as needed

Vazquez-Roque MI et al. Gastro. 2013;144(5):903-911

So you want to go natural? – Peppermint

- Natural anti-spasm agent
  - Suggested mechanisms of action:
    - L-menthol blocks calcium channels in the gut leading to smooth muscle relaxation
- Found in
  - Teas
  - Peppermint mints (Altoids)
  - Oil
  - IBgard- over the counter

- Alammar et al. Meta-analysis that evaluated 12 RCTs including 835 patients comparing daily use of peppermint oil to placebo
  - NNT for overall IBS symptoms was 3

Alammar N, Wang L, Saberi B et al. The impact of peppermint oil on the irritable bowel syndrome: A meta-analysis of the pooled clinical data. BMC Compliment Altern Med. 2019;19:21.

Iberogast

- Combination of several herbs
  - Bitter candytuft (Iberis amara totalis recens)[1]
  - Dried angelica root (Angelicae radix)
  - Dried chamomile flower head (Matricariae flos)
  - Dried caraway fruit - commonly known as seeds (Carvi fructus)
  - Milk thistle dried fruit (Silybi mariani fructus)[2]
  - Dried balm leaf (Melissae folium)
  - Dried peppermint leaf (Menthae piperitae folium)
  - Dried celandine (Chelidonii herba)
  - Dried liquorice root (Liquiritiae radix)
- On the market for 30 years
- Effects thought to be through serotonin, acetylcholine and opiate GI receptors
- Recognized by ACG task force on IBS as possible complementary treatment
- Has been linked to rare cases of liver injury, including acute liver failure

Vazquez-Roque MI et al. Gastro. 2013;144(5):903-911

Probiotics

- Data on both sides
- Meta-analysis showed a pooled effect for combination probiotics but there was significant heterogeneity in the studies
- ACG and AGA recommend against use of probiotics
- There are small studies suggesting benefit in IBS with
  - *Bifidobacteria* spp
    - *B. intantis* – Align, VSL #3
    - *B. lactis BB12* –USANA probiotic
    - *B. animalis/regularis* - Activia
  - *Lactobacillus* spp
    - *Lactobacillus GG* - Culturelle

ACTIVIA

Lacey BE et al. *Am J Gastroenterology.* 2021:116:17-44
Lembo A et al. *Gastroenterology.* 2022:163:137-151

Anti-Spasm agents

- Cause intestinal smooth muscle relaxation
- Great because can use as needed for symptom relief
- Recommended for IBS associated abdominal pain
- Can use daily if needed
- Dicyclomine
  - Anticholinergic
- Hyoscyamine
  - Anticholinergic
  - Sublingual form
- Page et al. Double-blind randomized study of 97 patients compared dicyclomine to placebo for 2 weeks
  - 84% of treatment group vs 54% placebo group reported improvement

Page JG, Dimberger GM. Treatment of irritable bowel syndrome with Bentyl (dicyclomine hydrochloride). J Clin Gastroenterol. 1981;3:153-6.

Anti-Diarrheal Agents

- Loperamide
  - Opioid agonist
    - Inhibits peristalsis and prolong transit time
  - Consider 2mg about 45 minutes prior to meals if diarrhea occurs after meals
  - Consider bedtime or early morning dosing for morning-predominant diarrhea
  - Scheduled and not "as needed"
  - Trials are small, but show improvement in abdominal pain, stool consistency and global symptoms
  - Be careful if IBS-Mixed

Lembo A et al. *Gastroenterology.* 2022:163:137-151

Bile Acid Binders

- Bile acid diarrhea is seen in up to 50% of patients with functional diarrhea
- Bile -> increased colon mucosal permeability, motility and mucous secretion
- Bile acids typically absorbed in ileum
  - If reaches the colon, it can cause irritation leading to diarrhea
- Colestipol (tablet) or cholestyramine (powder)
- Side effect: flatulence, constipation, bloating
- Caution in timing of medications
- Consider in cholecystectomy patients

*Not FDA approved for this indication

Lacey BE et al. *Am J Gastroenterology.* 2021:116:17-44
Naumann S et al. *Int. J. Mol. Sci.* 2020:21:6495

Tricyclic Antidepressants

- Could consider early if strong depression/anxiety component
- Most GI effects via anticholinergic properties
  - Slow intestinal transit time
- Amitriptyline, nortriptyline, desipramine and imipramine
  - 2^o amines (desipramine, nortriptyline) have less H_1 and M_1 side effects
- Start 10-25mg at bedtime
- Side effects:
  - Suicidal ideations (usually younger individuals)
  - QTc prolongation
  - Daytime sedation
  - Dry mouth
  - Urinary retention
- EKG at baseline and consider with titration of medication

Lembo A et al. *Gastroenterology.* 2022:163:137-151

Rifaximin (Xifaxan)

- FDA approved for treatment of IBS-D
  - Not approved for SIBO. Commonly used for "off label"
- Non-absorbable antibiotic used to treat the abnormal microbiome in patients with IBS-D
- Two-week course of 550mg three times a day
- Guidelines recommend retreatment two more times if improvement
- Studies showed significant improvement in global symptoms, bloating, diarrhea and abdominal pain compared to placebo
- Side effects similar to placebo
- Often expensive

Lacey BE et al. *Am J Gastroenterology*. 2021:116:17-44
Lembo A, Pimentel M, Rao SS et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea predominant irritable bowel syndrome. Gastroenterol. 2016;151:1113-21.

Alosetron (Lotronex)

- Selective 5-HT3 antagonist
  - 5HT3 receptors are on enteric motor neurons
  - Modulate visceral pain, slows colonic transit and increases fluid absorption
- Approved for women with severe IBS-D that has failed other treatments
  - Studies showed lack of improvement in men
- Alosetron 0.5-1 mg twice daily

Lembo A et Al. Gastroenterology. 2022.163

Alosetron (Lotronex)

- Previously withdrawn from the market 2020-2022 due to concerns of ischemic colitis and severe constipation
  - Systemic review from FDA showed risk of ischemic colitis was higher than placebo (0.15 vs 0.0 percent)
  - Additional data showed very low incidence 1.03 cases/1000 pt years).
- Severe constipation (28 vs 5% compared to placebo)

Eluxadoline (Viberzi)

- Minimally absorbed mixed mu and kappa receptor agonist and delta opioid receptor antagonist
- FDA approved for treatment of IBS-D
- Typical dose is 100 mg twice daily
  - Decrease to 75mg twice daily in those who experience intolerance (constipation, nausea) or those with moderate kidney hepatic impairment
- Side effect: acute pancreatitis

Lacey BE et al. *Am J Gastroenterology*. 2021:116:17-44

Eluxadoline (Viberzi)

- Contraindicated due to pancreatitis risk
  - Those without a gallbladder
  - History biliary disorders
  - Child-Pugh class C
  - > 3 alcoholic drinks per day or history of alcohol use disoder
- Discontinue if no improvement in 12 weeks

Lacey BE et al. *Am J Gastroenterology*. 2021:116:17-44

Summary Steps for Evaluation

- History and Physical
- Labs and stool
- If alarm findings→ endoscopic evaluation
- If functional / IBS suspected, treat symptoms from the 'Functional Diarrhea Toolbox"
  - If progressive or worsening symptoms, proceed with endoscopic evaluation, testing for hormone secreting tumors
- If underlying organic causes→ evaluate and treat specific cause

Summary

- A good history can help identify most causes of chronic diarrhea.
- If a patient has red flag symptoms, proceed with more in depth evaluation including endoscopic evaluation

Your Functional Diarrhea Toolbox

- Dietary Changes
- Fiber supplements
- Natural supplements
- ?Probiotics
- Anti-spasm medications
- Anti-diarrheal agents
- Bile acid binders
- Neuromodulators
- Rifaximin (Xifaxan)
- 5HT3 receptor antagonists (Alosetron)
- Eluxadoline (Viberzi)