

# Chronic Diarrhea: Differential Diagnosis and Treatment

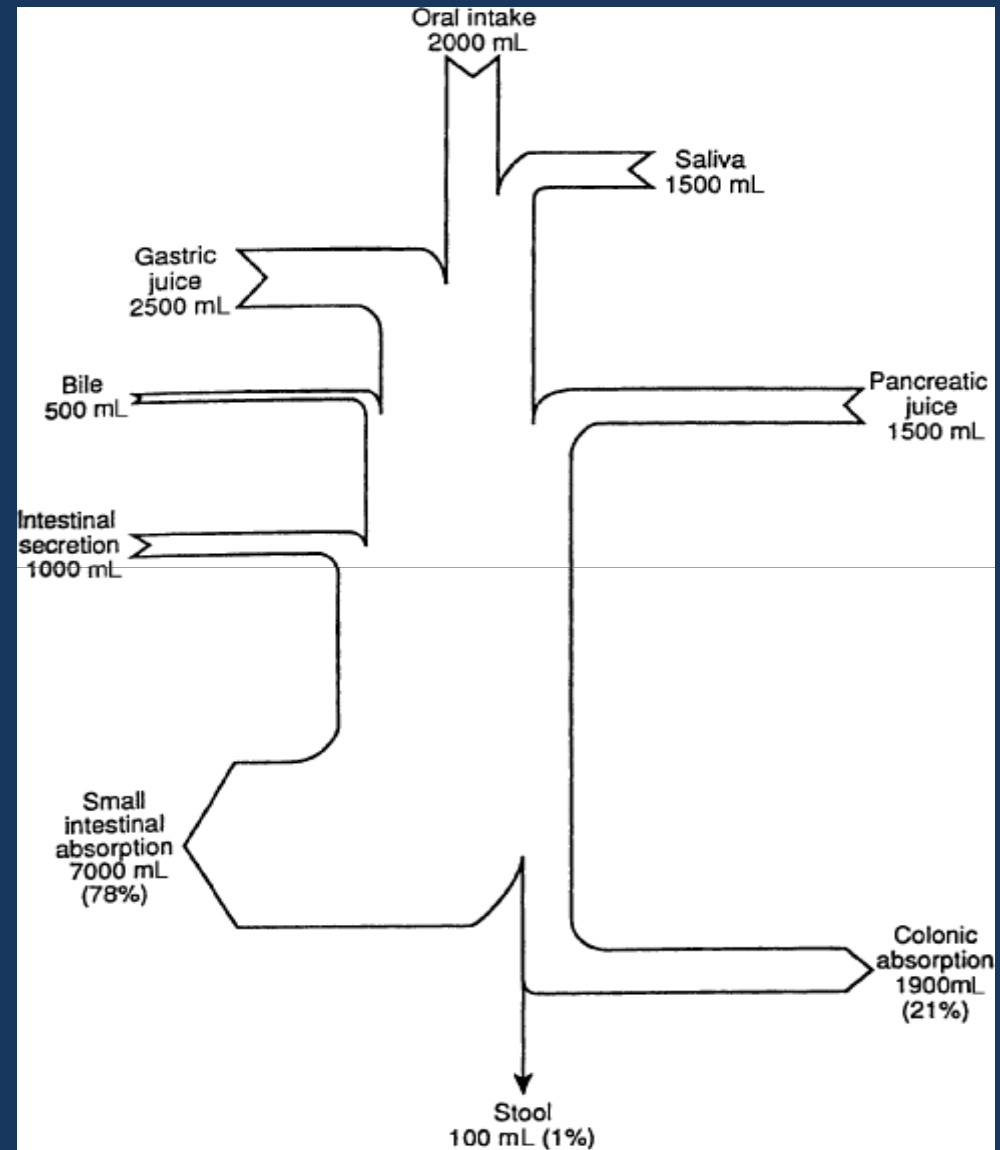
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# Definitions

- Derived from Greek “to flow through”
- Increased stool water content / fluidity
- Increased stool weight
  - > 200 gram/d
- 3 or more stool daily is generally abnormal
- Rule out fecal incontinence
- Timing
  - Acute diarrhea: <2 weeks
  - Persistent diarrhea: 2-4 weeks
  - Chronic diarrhea: > 4 weeks

# Normal stool fluids processing

- 8-9 L/d enter GI system
  - Ingest 1-2 L/d
  - Create approx 7 L/d
    - saliva, gastric, biliary, pancreatic secretions
- Small bowel reabsorbs 6-7 L/d
- Large bowel absorbs 1-2 L/d
- 100-200 gram/d stool created
- **Reduction of water absorption, due to decrease in absorption or increase in secretion, by as little as 1% can lead to diarrhea**



Source: Barrett KE: *Gastrointestinal Physiology*:  
<http://www.accessmedicine.com>

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# Types of Diarrhea

- Osmotic Diarrhea
  - Caused by ingestion of poorly absorbed osmotically active substance (non-electrolytes) that retains fluid within the lumen
    - Ions = Magnesium, Sulfate, Phosphate
    - Sugars or Sugar Alcohols = Mannitol, Sorbitol, Lactase Deficiency, Lactulose
- Secretory Diarrhea
  - Disordered electrolyte transportation
    - Net secretion of anions (chloride or bicarbonate)
    - Net inhibition of sodium absorption (and therefore water)

# Causes of Diarrhea

## Osmotic

- Ingestion of poorly absorbed agent (magnesium)
- Loss of nutrient transporter (lactase deficiency)

## Secretory

- Exogenous secretor (cholera toxin)
- Endogenous secretor (NE tumor)
- Absence of ion transporter (congenital chloridorrhea)
- Loss of intestinal surface area (diffuse mucosal disease – IBD, celiac; surgical resection)
- Intestinal ischemia
- Rapid intestinal transit (dumping syndrome)

# Initial Evaluation I: History

- Duration, pattern, epidemiology
- Severity, dehydration
- Stool volume & frequency
- Stool characteristics (appearance, blood, mucus, oil droplets, undigested food particles)
- Nocturnal symptoms
- Fecal urgency, incontinence
- Associated symptoms (abd pain, cramps, bloating, fever, weight loss, etc)
- Extra-intestinal symptoms
- Relationship to meals, specific foods, fasting, & stress
- Medical, surgical, travel, water exposure
- Recent hospitalizations, antibiotics
- History of radiation
- **Current/recent medications**
- Diet (including excessive fructose, alcohols, caffeine)
- Sexual orientation
- Possibility of laxative abuse

# Common medications and toxins associated with diarrhea

- Acid-reducing agents (H2 blockers, PPIs)
- Magnesium-containing antacids
- Anti-arrhythmics (eg, digitalis, quinidine)
- Antibiotics
- Anti-neoplastic agents
- Antiretrovirals
- Beta blockers
- Colchicine
- Levothyroxine
- Statins
- SSRIs
- Furosemide
- Metformin
- NSAIDs, ASA
- Prostaglandin analogs (misoprostil)
- Theophylline
- Amphetamines
- Caffeine
- Alcohol
- Narcotic/opioid

# Initial Evaluation II: Physical Examination

- Most useful in determining severity of diarrhea
  - Orthostatic changes
  - Fever
  - Bowel sounds
  - Abdominal distention, tenderness, masses, evidence of prior surgeries
  - Hepatomegaly
  - DRE (digital rectal exam) including FOBT (fecal occult blood testing)
  - Skin, joints, thyroid, peripheral neuropathy, murmur, edema



# Initial Evaluation III: Testing

- CBC w/ differential (Hct, MCV, WBC count)
- electrolytes, BUN, glucose, LFTs, Ca, albumin
- TSH, B12, folate, INR/PTT, Vit D, iron, ESR, CRP, Amoeba Ab, anti-transglutaminase IgA Ab, anti-endomysial IgA Ab, HIV
- Stool studies
  - Culture (more useful only for acute), O&P, Giardia Ag, C diff, Coccidia, Microsporidia, Cryptosporidiosis
  - Fecal leukocytes (or marker for neutrophils: lactoferrin or calprotectin)
  - Fecal occult blood
  - Stool electrolytes for osmolar gap =  $290 - 2[\text{Na} + \text{K}]$
  - Stool pH (<6 suggests CHO malabsorption due to colonic bacterial fermentation to CO<sub>2</sub>, H<sub>2</sub>, and short chain FA)
  - Fat content (48h or 72h quantitative or Sudan stain)
  - Laxative screen (if positive, repeat before approaching pt)

# Clinical classification

- Fatty
  - Bloating, flatulence, greasy malodorous stools that can be difficult to flush, weight loss, s/s of vitamin deficiencies (periph neuropathy, easy bruising)
  - Anemia, coagulopathy, hypoalbuminemia, osteopenia
- Watery
  - Large volume, variable presentation
- Inflammatory
  - Blood, mucus, pus, abd pain, fever, small volume
  - Positive fecal leukocytes, gross or occult blood, ESR/CRP, leukocytosis

# Differential Diagnosis: Acute Diarrhea

- Infection
- Food allergies
- Food poisoning/bacterial toxins
- Medications
- Initial presentation of chronic diarrhea

# Differential Diagnosis: Fatty Diarrhea

Maldigestion = inadequate breakdown of triglycerides

- Pancreatic exocrine insufficiency (eg, chronic pancreatitis)
- Inadequate luminal bile acid concentration (eg, advanced primary biliary cirrhosis)

Malabsorption = inadequate mucosal transport of digestion products

- Mucosal diseases (eg, Celiac sprue, Whipple's disease)
- Mesenteric ischemia
- Structural disease (eg, short bowel syndrome)
- Small intestinal bacterial overgrowth (bile salt deconjugation)

# Review of Nutrient/Vitamin Absorption

Duodenum/Jejunum	Ileum	Colon
Carbohydrates / simple sugars	Vitamin B12	Short-chain fatty acids
Fats	Bile salts	Vitamin K**
Amino acids	Magnesium	Biotin**
Iron		
Fat-soluble vitamins (A, D, E, K)		
Calcium		
Magnesium		
Other Vitamins		
Minerals		

\*\* In part produced by bacterial gut flora

# Differential Diagnosis: Watery Diarrhea

## Osmotic (poorly absorbable substance in lumen)

- Carbohydrate malabsorption (eg, lactase deficiency, diet high in fructose or sugar alcohols)
- Osmotic laxatives (Mg, PO<sub>4</sub>, SO<sub>4</sub>)

## Secretory (malabsorption or secretion of electrolytes, H<sub>2</sub>O)

- Very broad differential – see next slide

# Differential Diagnosis: Watery (Secretory) Diarrhea

- Bacterial toxins
- Abnormal motility
  - DM-related dysfunction
  - IBS
  - Post-vagotomy diarrhea
- Diverticulitis
- Ileal bile acid malabsorption
- Malignancy
  - Colon CA
  - Lymphoma
  - Rectal villous adenoma
- Vasculitis
- Congenital chloridorrhea
- Inflammatory
  - Microscopic colitis
- Endocrinopathies
  - Hyperthyroidism
  - Adrenal insufficiency
  - Carcinoid syndrome
  - Gastrinoma, VIPoma, Somatostatinoma
  - Pheochromocytoma
- Idiopathic
  - Epidemic (Brainerd)
  - Sporadic
- Medications, stimulant laxative abuse, toxins

# Differential Diagnosis: Inflammatory Diarrhea

- IBD (Crohn's, UC)
- Ischemic colitis
- Malignancy
  - Colon CA
  - Lymphoma
- Diverticulitis
- Radiation colitis
- Infectious
  - Invasive bacterial (*Yersinia*, TB)
  - Invasive parasitic (Amebiasis, strongyloides)
  - Pseudomembranous colitis (*C diff* infection)
  - Ulcerating viral infections (CMV, HSV)



# Additional studies

- Imaging
  - Small bowel series
  - CT/MRI or CT/MR enterography
- Endoscopy vs Push Enteroscopy with small bowel biopsy
- Colonoscopy vs Flexible Sigmoidoscopy, including random biopsies

# Treatment

- Correct dehydration and electrolyte deficits
  - Oral rehydration therapy (cereal-based best)
  - Sports drinks + crackers/pretzels
- Generally, empiric course of antibiotics is not useful for chronic diarrhea
- Empiric trials of (in appropriate clinical setting):
  - Dietary restrictions
  - Pancreatic enzyme supplementation
  - Opiates (codeine, morphine, loperamide, tincture of opium)
  - Bile acid binding resins
  - Clonidine (diabetic diarrhea)
  - Octreotide (for carcinoid syndrome, other endocrinopathies, dumping syndrome, chemotherapy-induced diarrhea, AIDS-related diarrhea)
  - Fiber supplements (psyllium) and pectin

# Case 1 (a reminder)

61 yo M with no signif PMHx (although hasn't been to MD in >10 yrs), presents w/ 3-4 years of watery diarrhea, now worse for last 1 mos. Endorses 12-14 BMs, fairly large volume, daily. Denies hematochezia or melena, weight loss. For last 1 mos, has also developed N/V and dyspepsia. No travel, but does endorse occasional well water for the last 2 yrs.

- PHMx: none
- Meds: none
- PE: stlightly tachycardic to 105, normotensive, mild epigastric abd TTP, DRE: brown liquidy stool in vault
- Labs: CBC normal, BMP notable only for BUN 30, Cr 1.8, Stool cx = neg; Stool Osm Gap = 23; Fecal leuks = neg

## Case 1 (con't)

- EGD – Erosive esophagitis, hypertrophied gastric rugae w/ edema, multiple diffuse small gastric nodules w/o active bleeding, multiple deep non-bleeding ulcers in first and second portion of duodenum, some w/ eschar-like base and more ulcers visible when looking down-stream in duodenum. Bx = normal.
- Colonoscopy – Few diverticuli, otherwise normal to ileum.

## Case 1 (con't)

- EGD w/ hypertrophic rugal folds and multiple duodenal ulcers is highly suggestive of Zollinger-Ellison syndrome (ie, gastrinoma).
- Gastrin level = 184 (normal 10-100, >1000 diagnostic of ZE)
- CT abd = normal
- Octreotide scan = normal
- Secretin stim test = diagnostic for ZE
- EUS = pending
- Tx: started on high-dose PPI and diarrhea now resolved

## Case 2

23 yo F administrative assistant, reported 6 months of diarrhoea. She had been passing up to 4 loose stools each day, although there were periods of up to a week when her bowel habit was normal.

- What further information do you want?
- What is on your differential diagnosis?

# Etiologies to consider

- **Lactose intolerance**
  - Flatulence, bloating, soft stools with lactose ingestion
  - Acquired lactase deficiency
  - African Americans (70%), Asians (85%)
- **Irritable bowel syndrome**
  - Alternating constipation, diarrhoea, mucus in stool
  - Relief with defecation, worse with stress
  - No night-time symptoms
- **Giardia infection**
  - Foul smelling stool, steatorrhea, flatulence, cramping
  - Exposure to contaminated water
- **Thyrotoxicosis**
  - Palpitations, wt loss, tremor, heat intolerance
  - Trouble sleeping, anxiety
- **Medications/substances**
  - SSRI, metformin, NSAIDs, allopurinol, chemotherapy, antibiotics, etc
  - Amphetamines, narcotic withdrawal

## Case 2 (continued)

She had colicky lower abdominal pain, relieved by defecation. She also had abdominal bloating.

She had not had any diarrhea at night. There was no blood in the stools. Her weight had not altered over this time. She did notice occasional mucus in the stools, but denied joint pains.

She had been under considerable stress at work. Her firm was undergoing restructuring and she was concerned that she would lose her job.



# Irritable bowel syndrome: diagnosis of exclusion

- R/O “red flags” for inflammation &/or malabsorption
  - Fever, night sweats
  - wt loss, inability to gain wt
  - bloody stool
  - joint pains
  - night-time symptoms
  - reactive arthritis syndrome with genital infections, bacterial diarrhoea (eye, skin, joints, GU)
  - nutritional deficits: Hb, Ca, INR, albumin
- Exclude other common things
  - Giardia
  - Lactose intolerance, wheat allergy
  - Laxative abuse
  - Hyperthyroidism
  - Medications
- IBS vs functional diarrhea

## Case 3

29 yo F, reported several months of diarrhea and general malaise. She has had 6 – 8 loose to watery stools daily. She denies hematochezia or melena. She endorses increased fatigue and lethargy. Her appetite had been poor and she thought she had lost 10-12 lb. She also reports intermittent joint pains, particularly in her knees. She denies fever, but has had night sweats on several occasions. She denies palpitations, increased hunger or tremor.

On exam temperature was 37.8°C. Abd exam notable for RLQ tenderness. Examination of her knees was normal.

Stool tests: WBC seen, positive FOBT, no ova, cysts or parasites, neg bacterial cx

Labs: Hct 32, WBC 13.5, ESR 38, CRP 21.2

What diagnosis is most likely?

# IBD Key Features

- Crohn's disease
  - skip lesions from mouth to anus
  - perianal abscesses and fistulas
  - bloody stool may not be as obvious
  - frequently involves terminal ileum (RLQ)
- Ulcerative colitis
  - Tenesmus, bloody stool
  - Involves rectum, and contiguous section of colon
- Diagnose by colonoscopy w/ biopsy
  - UC: crypt abscesses, crypt branching, atrophy of glands, loss of mucin in goblet cells
  - Crohn's: transmural inflammation, granulomas

# Systemic manifestations of IBD

- Joints
  - Reactive arthritis
- Eyes
  - Uveitis, iritis, episcleritis
- Skin / Mucus Membranes
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Aphthous stomatitis
- Liver/GI
  - Primary sclerosing cholangitis with elevated GGT, ALP
  - Cholelithiasis
  - Pancreatitis
- Heme/Onc
  - Hypercoagulability
  - Increased risk for colorectal cancer



Annals of Medicine. 2010; 42: 97–114



Source: Wolff K, Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ: Fitzpatrick's Dermatology in General Medicine, 7th Edition: <http://www.accessmedicine.com> Copyright © The McGraw-Hill Companies, Inc. All rights reserved.



Source: McPhee SJ, Papadakis MA: Current Medical Diagnosis and Treatment 2010, 49th Edition: <http://www.accessmedicine.com> Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

## Case 4

24 yo M p/w 4 months of diarrhea, 5-6 loose stools each day, which he said were pale and difficult to flush. He endorses abdominal bloating, 8 lb weight loss without dieting, and intermittent itchy rash. He travelled to Africa 9 mos ago. He denies reactive arthritis and hyperthyroid symptoms.

Physical examination was normal.

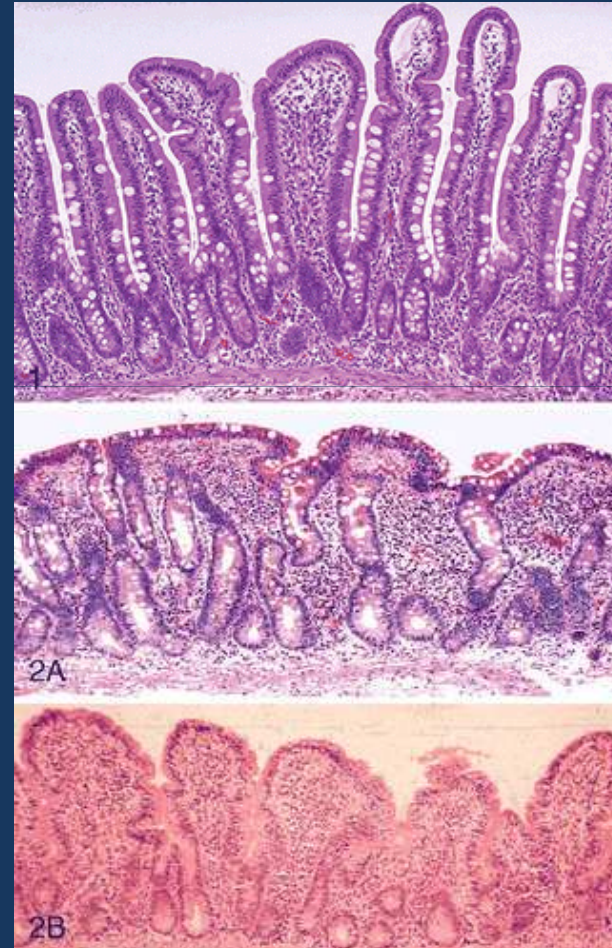
Notable labs/testing:

- Stool cultures, ova and parasites all negative; Giardia Ag negative; FOBT negative.
- Hb 31, MCV 75, Ferritin 10
- Colonoscopy -- negative, including terminal ileum

What additional testing would you like?

# Further investigations

- Small bowel biopsy
  - Blunting of intestinal villi, crypt hypertrophy
  - Lamina propria infiltration with excess lymphocytes and plasma cells
- Auto-antibodies
  - Anti-endomyseal IgA Ab
  - Anti-transglutamase IgA Ab
  - Antigliadin IgG and IgA Ab
  - IgA deficiency can occur in 10% and give false negative results for the IgA Ab
  - IgA antibodies disappear on gluten-free diet



# Celiac sprue

- 1:250 Caucasians
- Gluten sensitive enteropathy
- Usually resolves on gluten-free diet
- Affects distal duodenum, proximal jejunum
- Causes malabsorption of multiple nutrients

# Celiac sprue: signs and symptoms

- wt loss (growth retardation)
- chronic diarrhoea
- abdominal distension
- dermatitis herpetiformis
  - pruritic papular rash
- iron and/or B12 deficiency anemia
- Protein loss
- Fat soluble vitamin deficiencies:
  - Vit A: poor night vision, follicular hyperkeratosis
  - Vit D: hypocalcemia, osteoporosis
  - Vit K: easy bruising & bleeding, elevated INR

