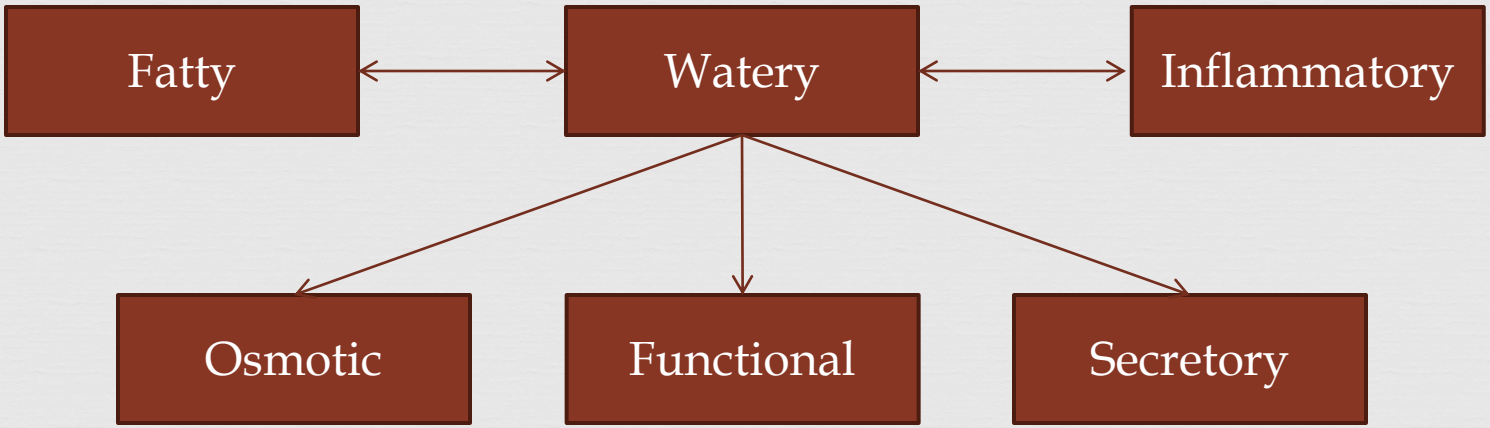
Chronic Diarrhea

Basics

- Definition varies from person to person
- AGA consensus definition
  - Decrease in fecal consistency lasting > 4 weeks
- Estimated 3-5% of population and 350 M economic burden annually
- Huge differential diagnosis!!

Categorization



History

- Volume, frequency, consistency, duration
- Night symptoms – suggesting secretory
- Travel/HIV risk factors
- Fecal incontinence – often confused with diarrhea
- Systemic symptoms (IBD) – fevers, arthralgia, mouth ulcers, eye redness
- Meds including OTC
- Weight loss
- Diet – dairy/food allergens/sugar alcohols
- FHx of IBD
- Subcategories
  - Fatty – greasy, floating, malodorous indicating malabsorption
  - Inflammatory – blood and pus
  - Watery
    - Osmotic – typically improve with fasting (or removing offending agent)
    - Secretory – high volume (> 1 L/day), occur at night and despite fasting,
    - Functional – smaller volumes (< 350 ml/day), occur during day

Physical Exam

- General
  - Weight loss
  - Lymphadenopathy
- Eye
  - Episcleritis (IBD)
  - Exophthalmia (Hyperthyroidism)
- Skin
  - Dermatitis herpetiformis (15-25% of celiac patients)
    - Itchy symmetric rash on scalp, shoulders, buttocks, elbows, knees
- Abdomen
  - Surgical scars, tenderness, masses
- Anorectal
  - Fistula (Crohn's)
  - FOB +/- Anoscopy (ulcerations or impaction)

Table 1. Differential Diagnosis of Chronic Diarrhea

Watery

Secretory (often nocturnal; unrelated to food intake; fecal osmotic gap < 50 mOsm per kg*)
- Alcoholism
- Bacterial enterotoxins (e.g., cholera)
- Bile acid malabsorption
- Brainerd diarrhea (epidemic secretory diarrhea)
- Congenital syndromes
- Crohn disease (early ileocolitis)
- Endocrine disorders (e.g., hyperthyroidism [increases motility])
- Medications (see Table 3)
- Microscopic colitis (lymphocytic and collagenous subtypes)
- Neuroendocrine tumors (e.g., gastrinoma, vipoma, carcinoid tumors, mastocytosis)
- Nonosmotic laxatives (e.g., senna, docusate sodium [Colace])
- Postsurgical (e.g., cholecystectomy, gastrectomy, vagotomy, intestinal resection)
- Vasculitis

Osmotic (fecal osmotic gap > 125 mOsm per kg*)
- Carbohydrate malabsorption syndromes (e.g., lactose, fructose)
- Celiac disease
- Osmotic laxatives and antacids (e.g., magnesium, phosphate, sulfate)
- Sugar alcohols (e.g., mannitol, sorbitol, xylitol)

Functional (distinguished from secretory types by hypermotility, smaller volumes, and improvement at night and with fasting)
- Irritable bowel syndrome

Fatty (bloating and steatorrhea in many, but not all cases)

Malabsorption syndrome (damage to or loss of absorptive ability)
- Amyloidosis
- Carbohydrate malabsorption (e.g., lactose intolerance)
- Celiac sprue (gluten enteropathy)–various clinical presentations
- Gastric bypass
- Lymphatic damage (e.g., congestive heart failure, some lymphomas)
- Medications (e.g., orlistat [Xenical; inhibits fat absorption], acarbose [Precose; inhibits carbohydrate absorption])
- Mesenteric ischemia
- Noninvasive small bowel parasite (e.g., *Giardia*)
- Postresection diarrhea
- Short bowel syndrome
- Small bowel bacterial overgrowth (> 10^5 bacteria per mL)
- Tropical sprue
- Whipple disease (*Tropheryma whippelii* infection)

Maldigestion (loss of digestive function)
- Hepatobiliary disorders
- Inadequate luminal bile acid
- Loss of regulated gastric emptying
- Pancreatic exocrine insufficiency

Inflammatory or exudative (elevated white blood cell count, occult or frank blood or pus)

Inflammatory bowel disease
- Crohn disease (ileal or early Crohn disease may be secretory)
- Diverticulitis
- Ulcerative colitis
- Ulcerative jejunoileitis

Invasive infectious diseases
- *Clostridium difficile* (pseudomembranous) colitis–antibiotic history
- Invasive bacterial infections (e.g., tuberculosis, yersiniosis)
- Invasive parasitic infections (e.g., *Entamoeba*)–travel history
- Ulcerating viral infections (e.g., cytomegalovirus, herpes simplex virus)

Neoplasia
- Colon carcinoma
- Lymphoma
- Villous adenocarcinoma

Radiation colitis

Lab Evaluation

- Minimum evaluation in most patients
  - CBC
  - ESR
  - TSH
  - CMP

Lab Evaluation

- Points to consider for additional testing
  - Celiac testing
    - Fe def anemia, FH celiac, weight loss, malabsorption, T1DM, autoimmune thyroid disease, or elevated transaminases
    - Presumptive treatment for IBS and no improvement after diet modification
- Fecal electrolytes (Na and K) to help differentiate between an osmotic and secretory diarrhea
  - Stool Osmolal Gap (SOG)
    - StoolOsm (usual value is 290) – (2*(Stool Na+ Stool K))
      - SOG < 50 compatible with secretory diarrhea
      - SOG $\geq$ 50 and $\leq$ 125 indeterminate
      - SOG > 125 compatible with osmotic diarrhea

Lab Evaluation

- Check for C difficile toxin for diarrhea developing after any recent hospitalization (past few days) or antibiotic use (in the past three months)
- If travel outside of country
  - Giardia and Cryptosporidium stool antigens
    - Can be frequently missed on O&P
    - If no travel but utilizes well water or recent camping trip consider checking these only
  - O&P x 3 (only performed at Deaconess on special request and documented foreign travel to resource-poor area)

What about endoscopy?

- Appropriate in the following circumstances based on presumed categorization
  - Fatty diarrhea
  - Inflammatory diarrhea (assuming no fulminant colitis)
  - Secretory diarrhea
- In general think about referral for the following circumstances
  - Is not a clear cut IBS/osmotic diarrhea case
  - Not responding to presumptive treatments

Common Etiologies

Irritable Bowel Syndrome (IBS) = Functional

- Crampy abdominal pain + altered bowel habits (either diarrhea or constipation)
- Watery small volume diarrhea occurs while awake, often after meals
- Pain improves with defecation
- Mucus noted in 50% of patients
- Prevalence twice as much in women
- Think something else if nocturnal symptoms, progressive pain, weight loss, FOB +

IBS

- Usually exacerbated by stress or eating but can transiently occur after gastroenteritis
- Even though diagnosis of exclusion, exhaustive work-up unnecessary in healthy young patients meeting Rome IV criteria that respond to exercise and diet modifications

- Rome IV Criteria
  - Recurrent abdominal pain, on average $\geq$ 1 day/week in last 3 months + $\geq$ 2 of following
    - Related to defecation
    - Associated with change in stool frequency
    - Associated with change in stool form (appearance)

Inflammatory Bowel Disease (IBD)

- Bimodal distribution
  - Usually between 15-40
  - Second peak between 50-80
- Crohn's disease
  - Sometimes subtle presentation and can take years to diagnose (may be misdiagnosed as IBS)
  - Diarrhea, abdominal pain, weight loss, fever
  - Typically starts in TI but can involve the entire GI tract from mouth to perianal area
  - FOB common but gross bleeding much less common
- Ulcerative colitis
  - Variable presentation depending on extent of disease
    - Rectal bleeding, diarrhea, pain, tenesmus, progressing to bloody diarrhea, weight loss, fever, anemia
  - Mild – Proctitis or proctosigmoiditis
  - Moderate – Left-sided colitis to splenic flexure
  - Severe – Extensive colitis but might not extend to cecum (pancolitis)

Microscopic Colitis

- Chronic secretory diarrhea without bleeding or inflammation in stool
  - Usually in middle age patients but can occur in all ages
- Two types diagnosed histologically, often gross appearance on endoscopy is unremarkable
  - Collagenous colitis
  - Lymphocytic colitis
- Biopsies from right colon preferred as severity of histology declines from proximal to distal colon
- Cause unknown but evidence suggests long term NSAID use increases risk

Malabsorption

- Most common causes
  - Celiac disease
  - Intestinal bypass
  - Mesenteric ischemia
  - Small bowel bacterial overgrowth
  - Giardiasis
  - Pancreatic insufficiency
  - Bile acid related

Malabsorption

- Classic symptoms are rare
- Most patients may present with IBS like picture
  - Anorexia, flatulence, abdominal distension, borborygmi may be only symptoms to suggest malabsorption

Celiac Disease

- Small intestine malabsorption from gluten
- Underdiagnosed
  - 2 million in US (1 in 133 persons)
  - 1 in 22 if first degree relative with disease
- Screen with celiac panel
  - Total IgA
  - Tissue transglutaminase IgA
- Confirm with EGD and small bowel biopsy
- Gluten free diets can give false negative results

Lactose Intolerance

- Not a food allergy
- Deficiency of lactase enzyme
- Ethnic association
  - >90% in some eastern Asian populations
  - 80-95% Native Americans
  - 65-75% Africans and African Americans
  - 50% Hispanics
  - 7-20% Caucasians

Lactose Intolerance

- Suggested by high stool osmotic gap and improvement of symptoms on fasting
- Can be confirmed with hydrogen breath test
- Rule out secondary causes if positive
  - Bacterial overgrowth
  - Infectious enteritis (Giardiasis)
  - Mucosal injury
    - Celiac
    - IBD – especially Crohn's
    - Drug- or radiation-induced enteritis

Bacterial Overgrowth

- Most frequent presenting symptoms abdominal pain, diarrhea, weight loss, bloating, excess flatulence, malabsorption, anemia
- Suspicion should be high in patients with associated conditions
- Work up with UGI w/ SBFT and can confirm with hydrogen breath test showing early peak from SIBO in addition to peak from colon

Disorders associated with bacterial overgrowth

Small intestinal stasis
Anatomic abnormalities
Small intestinal diverticulosis
Surgically created blind loops (end-to-side anastomosis)
Strictures (Crohn's disease, radiation, surgery)
Abnormal small intestinal motility
Diabetes mellitus
Scleroderma
Idiopathic intestinal pseudoobstruction
Radiation enteritis
Crohn's disease
Abnormal communication between the proximal and distal gastrointestinal tract
Gastrocolic or jejunocolic fistula
Resection of the ileocecal valve
Associations usually with multifactorial causes
Hypochlorhydria due to atrophic gastritis or medications. These are usually not clinically significant unless there coexist concomitant motility disturbances of the small bowel
Immunodeficiency states (common variable immunodeficiency, AIDS, severe malnutrition)
Chronic pancreatitis
Cirrhosis
Alcoholism
End stage renal disease
Advanced age

Cholecystectomy

- 5-12% of patients have diarrhea post-procedure
- Most cases resolve or improve over weeks to months
- Bile drains directly and more continuously in the small bowel
- If exceeds TI reabsorptive capacity, enter colon and precipitate diarrhea
- Treat with bile-acid binding resins

Chronic Infections

- Usually are self limited but can progress to chronic diarrhea
- History of travel, camping, well water, antibiotic use, infectious contacts, day care attendance
- Stool culture, C diff toxin, or parasitic antigens depending on likely cause
- Shiga toxin for any history of bloody diarrhea

Drug-Induced

- Variety of different mechanisms
- Symptoms resolve with removal of offending agent
- A good example of a substance causing osmotic diarrhea

Table 3. Drugs Associated with Diarrhea

Osmotic

Citrates, phosphates, sulfates

Magnesium-containing antacids and laxatives

Sugar alcohols (e.g., mannitol, sorbitol, xylitol)

Secretory

Antiarrhythmics (e.g., quinine)

Antibiotics (e.g., amoxicillin/clavulanate [Augmentin])

Antineoplastics

Biguanides

Calcitonin

Cardiac glycosides (e.g., digitalis)

Colchicine

Nonsteroidal anti-inflammatory drugs (may contribute to microscopic colitis)

Prostaglandins (e.g., misoprostol [Cytotec])

Ticlopidine

Motility

Macrolides (e.g., erythromycin)

Metoclopramide (Reglan)

Stimulant laxatives (e.g., bisacodyl [Dulcolax], senna)

Malabsorption

Acarbose (Precose; carbohydrate malabsorption)

Aminoglycosides

Orlistat (Xenical; fat malabsorption)

Thyroid supplements

Ticlopidine

Pseudomembranous colitis (*Clostridium difficile*)

Antibiotics (e.g., amoxicillin, cephalosporins, clindamycin, fluoroquinolones)

Antineoplastics

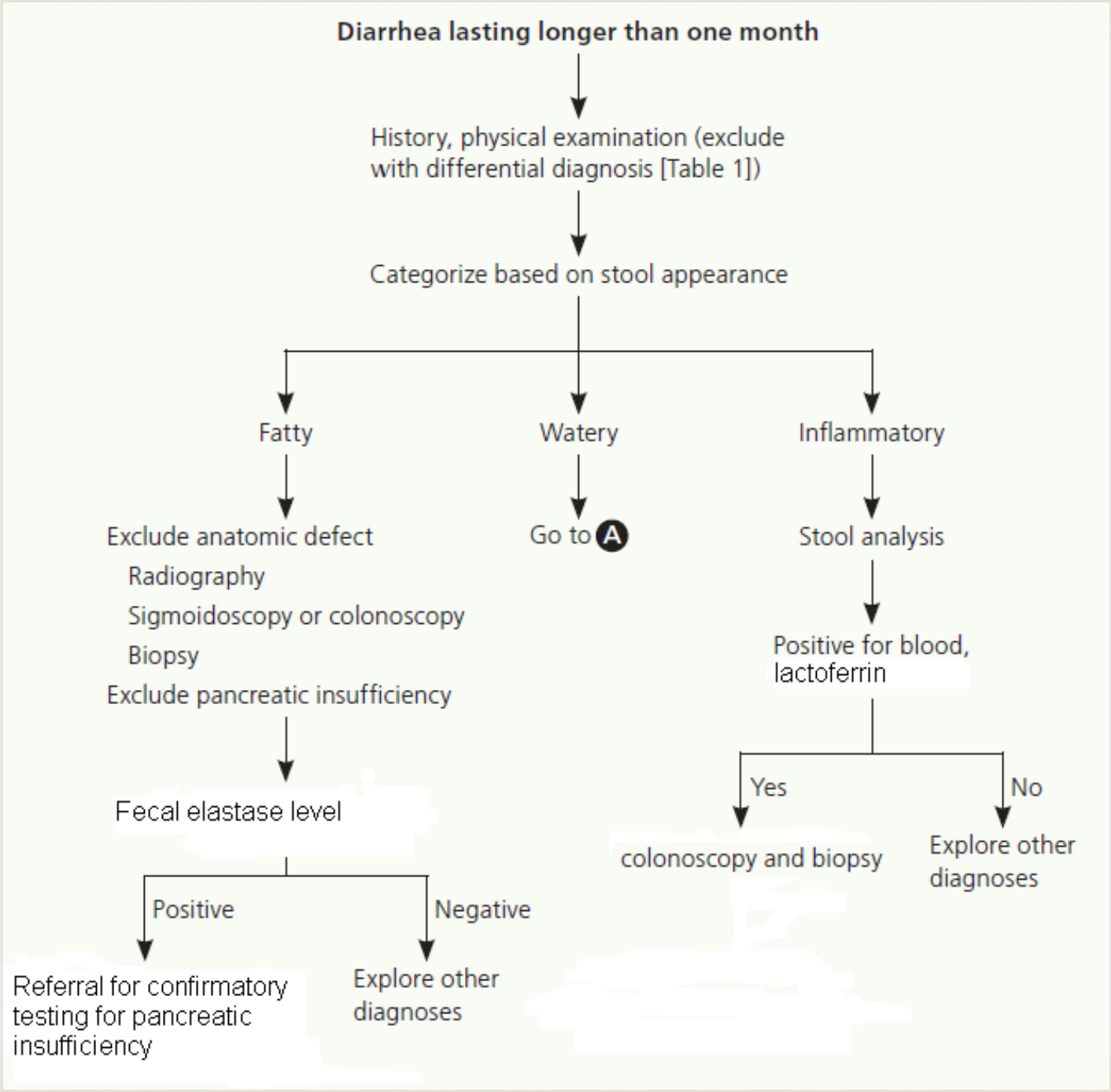
Immunosuppressants

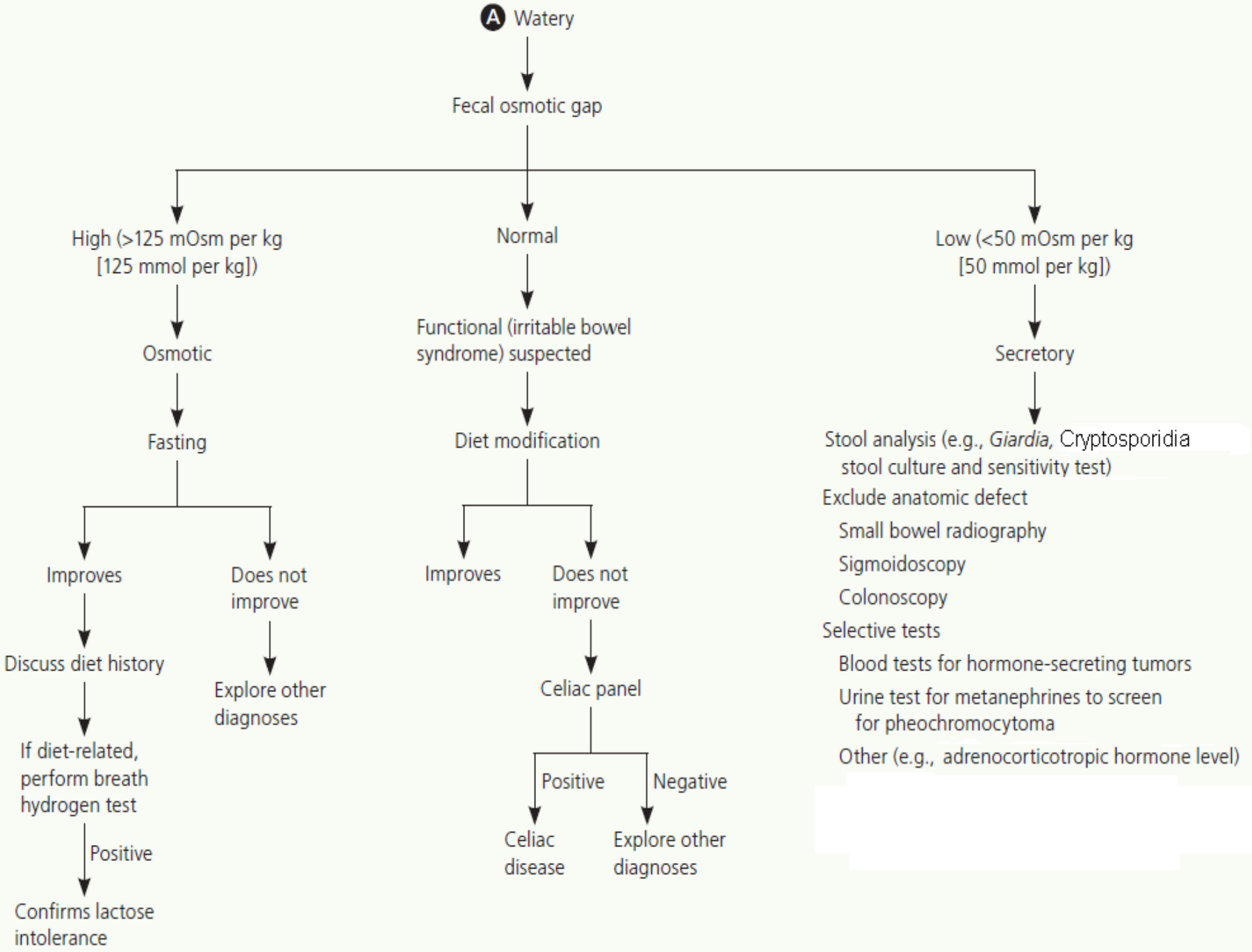
Zebras

- Endocrine
  - Addison's disease
  - Carcinoid
  - VIPoma
  - Gastrinoma
  - Mastocytosis
- Don't screen for these unless there are other symptoms to suggest

Treatment

- Primarily through treating the underlying disorder
- Empiric therapy as an exception and not the rule
- Symptomatic therapy
  - Never in anyone with inflammatory symptoms
- Many options
  - Loperamide
  - Lomotil (watch anti-cholinergic effects from atropine)
  - Psyllium in small doses


Diarrhea lasting longer than one month
History, physical examination (exclude with differential diagnosis [Table 1])
Categorize based on stool appearance
Fatty
Watery
Inflammatory
Exclude anatomic defect
Radiography
Sigmoidoscopy or colonoscopy
Biopsy
Exclude pancreatic insufficiency
Go to A
Stool analysis
Positive for blood, lactoferrin
Yes
No
colonoscopy and biopsy
Explore other diagnoses
Fecal elastase level
Positive
Negative
Referral for confirmatory testing for pancreatic insufficiency
Explore other diagnoses


A Watery
Fecal osmotic gap
High (>125 mOsm per kg [125 mmol per kg])
Normal
Low (<50 mOsm per kg [50 mmol per kg])
Osmotic
Functional (irritable bowel syndrome) suspected
Secretory
Fasting
Diet modification
Stool analysis (e.g., Giardia, Cryptosporidia stool culture and sensitivity test)
Exclude anatomic defect
Small bowel radiography
Sigmoidoscopy
Colonoscopy
Selective tests
Blood tests for hormone-secreting tumors
Urine test for metanephrines to screen for pheochromocytoma
Other (e.g., adrenocorticotropic hormone level)
Improves
Does not improve
Improves
Does not improve
Discuss diet history
Explore other diagnoses
Celiac panel
If diet-related, perform breath hydrogen test
Positive
Negative
Positive
Celiac disease
Explore other diagnoses
Confirms lactose intolerance

Takeaways

- Narrow your differential and work-up based on stool appearance and history
- Send patients for colonoscopy for any type other than osmotic or other diagnosis not improving with usual treatment
- Remember to test for celiac disease in patients with risk factors