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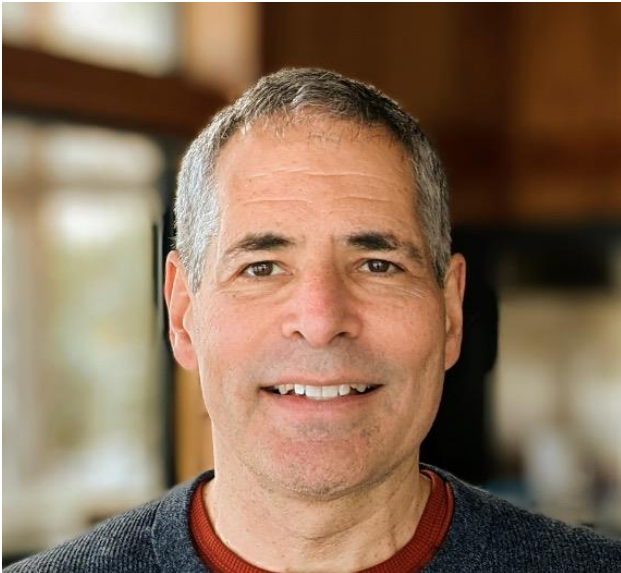
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# Commercial/Faculty Disclosures

I have no financial disclosures



# Goals

Acute and Chronic Diarrhea  
Focus on essentials  
New developments



# Topics Covered

## Definitions

## Approach to acute diarrhea

- Differential diagnosis
- Diagnostic approach
  - When to watch
  - When to test
  - When to treat

## Approach to chronic diarrhea

- Mechanisms
- Diagnostic evaluation
  - Initial testing
  - Follow-up testing



# Diarrhea: Definitions

## Objective definition

- Excessive stool weight:  $>200\text{gm/day}$

## Subjective definition

- Excessive frequency of defecation ( $\geq 3$  stools)
- Less-than-normal form and consistency

Acute diarrhea:  $< 4$  weeks duration

Chronic diarrhea:  $> 4$  weeks duration

Persistent diarrhea: 2-4 weeks duration



# Normal Intestinal Physiology

10 L of fluid enters the jejunum daily

- 2 L: Food and drink
- 8L: Salivary, gastric, biliary, pancreatic, intestinal secretions

1L enters the colon

80-100 mL excreted daily



# Abnormal Intestinal Physiology

Loosening of stools: 50-60mL increase daily fecal water

Diarrhea: 100mL (1-2%) increase in fecal water

Many disorders disrupt intestinal fluid and electrolyte absorption by at least this amount

- Frequent event
- Extensive differential diagnosis





# Acute Diarrhea: Major Causes

Infectious: Most common

- Viral: Noroviruses , Rotavirus
- Bacterial: Food poisoning, C. difficile
- Parasitic/protozoal

Noninfectious

- Medications
- Consumption of poorly absorbed sugars (e.g. sorbitol)
- Enteral feeding
- Ischemic colitis
- Fecal impaction: “paradoxical diarrhea”



# Diagnostic Evaluation

Majority of cases are mild and self-limited

90% of cases need no diagnostic evaluation

Treat symptomatically for several days

Likely etiologies:

- Viral (>75%)
  - Noroviruses (71%), Rotavirus
- Bacteria elaborating preformed toxin
  - *S. aureus*, *B. cereus*, *C. perfringens*

Stool culture positive: 1.5-5.6%



# Stool Tests for Bacterial Pathogens

- Inflammatory Diarrhea:
  - Bloody/mucoid diarrhea
  - Stool culture positive up to 87%
- Severe Illness:
  - Volume depletion: eg orthostatic, scant or dark urine
  - Severe abdominal pain (also consider imaging)
  - Temperature > 38.5°C (101.3°F)
- History of inflammatory bowel disease
- Immunocompromised or elderly ( $\geq 70$  yrs) with significant cardiovascular disease
- Pregnancy
- Public Health Concerns:
  - Food Handlers, healthcare and daycare workers



# Stool Culture

Routine culture:

- Campylobacter, Salmonella, Shigella

Notify lab:

- E. Coli O157:H7, Yersinia, Aeromonas, Vibrio

Single specimen: Bacteria shed continuously

Clostridium difficile toxin assay

- Antibiotic/Chemotherapy within preceding 2 weeks
- Hospital-acquired diarrhea

Stool cultures: Low yield if diarrhea develops after hospitalization > 72 hours.



# Multipathogen/Multiplex Molecular Diagnostic Panels

- Up to 22 pathogens with fast turnaround (few hours) and more sensitive than stool culture: Bacterial, viral and parasitic;
- Replace stool culture in select cases
  - Very sick (bloody diarrhea/fever), immunocompromised, hospitalized
  - Epidemiological risk factors: Travel, high risk food or untreated water exposure
  - Caveat: Detect genetic material: Not necessarily viable organisms
- May detect more than one organism
- Positive test for bacteria: Send confirmatory culture.
  - Susceptibility testing
  - Public health reporting



# Stool For Ova and Parasites

Cost-effective in high-risk groups

- Persistent diarrhea (>14 days)
- Community waterborne outbreak
- Exposure to untreated water (e.g. streams)
- Daycare center exposure
- Travel to Russia, Nepal
  - Giardia, Cryptosporidia
- MSM: Giardia, E.histolytica
- Advanced HIV: CD4<200cells/microL
  - Giardia, E.histolytica, Microsporidia

Intermittent shedding



- 3 specimens on consecutive days



# Who needs Endoscopic Evaluation?

Bloody diarrhea

- IBD versus infectious diarrhea
- Suspected ischemic colitis

Pseudomembranous colitis

Immunocompromised or other high-risk patients: Look for CMV

Flexible sigmoidoscopy versus colonoscopy



# Supportive Therapy

Rehydration: Glucose- $\text{Na}^+$  co transporter

- WHO oral rehydration solution (per liter of water)
  - 20gm glucose or 40gm sucrose,  $\text{NaCl}$ ,  $\text{NaHCO}_3$ ,  $\text{KCl}$
- Alternative rehydration solution (per liter of water)
  - 4 tablespoon sugar
  - $\frac{1}{2}$  teaspoon salt
  - $\frac{1}{2}$  teaspoon baking soda
- Rice-based oral rehydration solution (e.g. Cera-lyte)

Fluids for sweat replacement (e.g. Gatorade, Powerade, Propel)

- Not equivalent to ORS. Sufficient for mild cases
- Diluted fruit juice plus saltine crackers

Dietary modification

- Lactose free diet for several weeks
- Avoid food with high fat content
- Boiled starches or cereals with salt
- BRAT diet: Bananas, rice, apple sauce, toast





# Supportive Therapy: Other Measures

Stop all sugar substitutes

Review medications

Assess for fecal impaction and treat

Adjust tube feeds: Dilute, decrease rate or add fiber



# Antidiarrheal agents

Stools nonbloody and fever low-grade

Antimotility agents: Decrease peristalsis

- Loperamide (Imodium)
  - 4mg initially, then 2mg after each loose movement
  - Maximum: 16mg/day for 2 days
- Diphenoxylate atropine (Lomotil)
  - Central opiate and anti-cholinergic side-effects (atropine)
  - 1-2 tabs tid/qid

Other agents

- Pepto-Bismol: 2 tabs every 30 minutes; Can also help vomiting
- Kaopectate: Improves stool consistency
- Racecadotril, aka acetorphan: Peripherally acting enkephalinase inhibitor; Reduces the secretion of water and electrolytes



# Empiric Antibiotic Therapy

Severely ill immunocompetent individuals

- Fever, bloody diarrhea
- Dehydration
- >8 stools/day or symptoms for > 1 week

Immunocompromised patients

- AIDS, malignancy, transplant recipients

Drugs of choice

- Quinolone: Ciprofloxacin, levofloxacin, norfloxacin (3-5 days)
- Alternatives: Azithromycin (3 days) and erythromycin (5 days)
  - Suspect fluoroquinolone resistance (eg. travel to Southeast Asia)
  - Campylobacter infection
- Vancomycin: C. difficile suspected



# Probiotics: Mixed Results

## Prevention of travelers diarrhea

- Supportive studies/meta-analysis
- Lactobacillus GG and acidophilus
- Saccharomyces boulardii: N. Africa, Turkey

## Infectious diarrhea

- Mixed data: Lactobacillus species
- Reduce duration of diarrhea: about 24 hours
- 10 billion CFU within first 48 hours

Antibiotic associated diarrhea: Need more studies



# Acute Diarrhea

Select Infectious Causes



# Campylobacter jejuni

A leading cause of bacterial diarrhea: 4-11%

Source - Contaminated poultry: 50-70%

Relapsing course: 15-20%

Drugs of choice:

- Fluoroquinolones
- Azithromycin
- Rising rates of resistance
  - Check sensitivities



# Campylobacter: Complications

## Reactive arthritis/Reiter's Syndrome: 1%

- 1-2 weeks after diarrhea onset
- Self-limited: several months

## Guillain-Barré Syndrome

- Responsible for 25% cases
- Symptoms within 3 months of diarrhea onset
- May be Culture negative but serology positive

Antibiotics do not prevent these complications



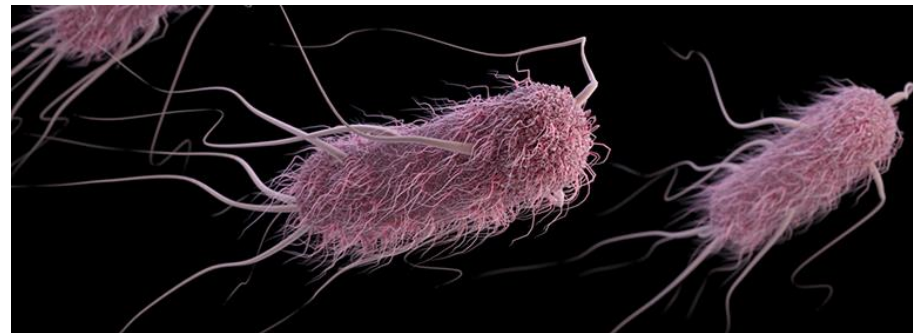
# Enterohemorrhagic E. coli (EHEC)

Most prevalent in U.S.: E. coli 0157: H7

- Undercooked meat ingestion
- Predisposing factors: Age < 10 or > 50
- Watery diarrhea → bloody diarrhea
- Often afebrile

May elaborate 2 proteins:

- Shiga toxin = verotoxine
- Intimin= Adhesine protein





# EHEC Infections: Complications

## EHEC with both proteins

- Potentially lethal
- Increase risk of Hemolytic-uremic Syndrome (HUS)
  - Acute renal failure
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia
- Selective culture required
- **Avoid Antibiotics:**
  - Increased production of shiga toxin
  - Increased risk of HUS



# Listeria (Listeriosis)

Most deadly foodborne infection  
1600 infections annually in US  
260 die



# Listeria Monocytogenes

## Periodic outbreaks: Contaminated foods

- Recalls: Ice cream, hummus, frozen vegetables, cold cuts
- Listeria may live for years on food-processing equipment

## Normal hosts:

- Self-limited febrile gastroenteritis: 2 days
- 24 hours after ingestion of large inoculum of bacteria
- Stiff neck/headache, diarrhea, nausea/vomiting, fever, arthralgias
- Diagnosis: Selective stool culture

## Immunocompromised, neonates and older adults, pregnant women

- Invasive disease: Listeriosis
- Presents more than 30 days post exposure
- Bacteremia/sepsis, meningitis, meningoencephalitis, fetal loss
- High morbidity/mortality



# L. Monocytogenes: Treatment

## Immunocompetent w/ Diarrhea: Supportive Invasive infection

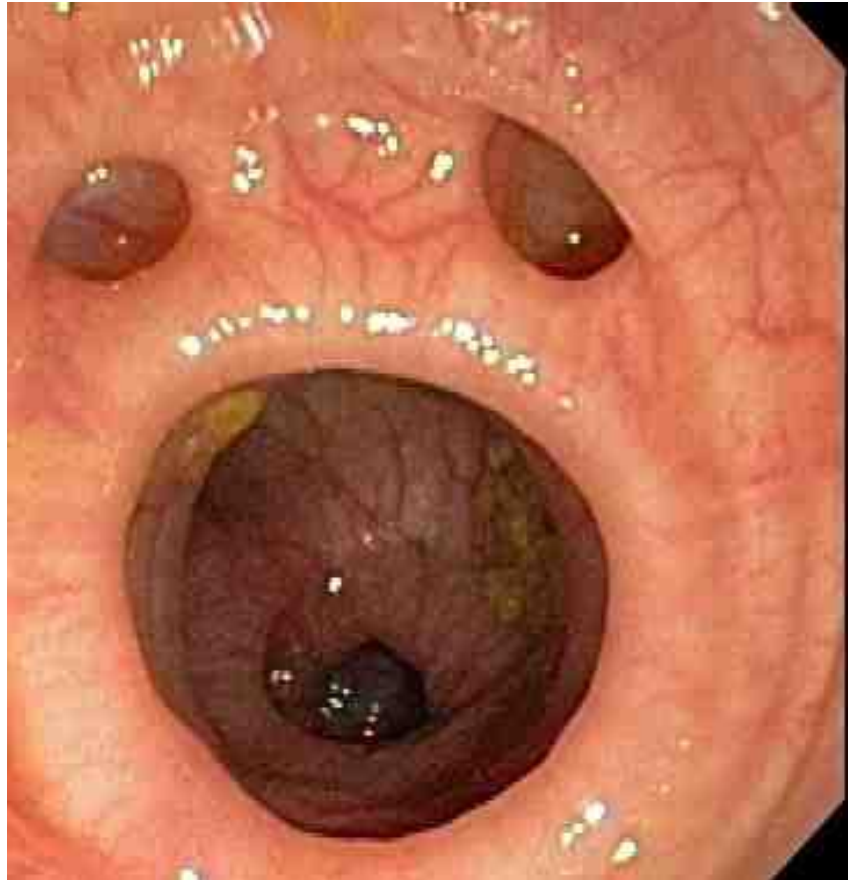
- First line: Ampicillin, penicillin G
- Gentamycin may be added for synergy in severe dz
- PCN allergic: Trimethoprim sulfamethoxazole
- Alternatives: Imipenem, meropenem

## Prevention

- Refrigeration below 40 F; Wash produce thoroughly
- High risk populations:
  - Cook foods thoroughly to high temperature
  - Avoid luncheon meats, hot dogs, soft cheeses, prepared foods



# Chronic Diarrhea: A Systematic Approach



# Chronic Diarrhea in Resource-abundant Settings

Afflicts 3-7% of the population

Myriad of disorders

Order of prevalence varies

- Practice setting

Optimum evaluation strategy

- Not established
- Expert opinion



# MAJOR CAUSES IN DEVELOPED COUNTRIES

Irritable bowel syndrome

Inflammatory bowel disease

- Ulcerative colitis, Crohn's disease
- Microscopic colitis

Malabsorption syndromes

- Lactose intolerance, Celiac disease, SIBO, Pancreatic insufficiency

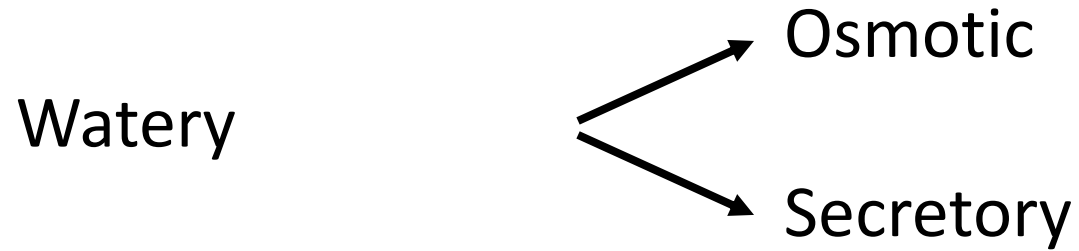
Medications

Chronic infections

- Immunocompromised
- Bacterial, parasitic



# Categorization of Diarrhea



Inflammatory

Fatty

Several mechanisms may coexist





# Osmotic Diarrhea

## Hallmarks

- Diarrhea stops with fasting
- Large osmotic gap:  $> 125 \text{ mOsm/kg}$

## Mechanism

- Ingestion of osmotically active solutes
- Retention of water in intestinal lumen
- Electrolyte absorption ( $\text{Na}^+$ ,  $\text{K}^+$ ) is normal
- Large osmotic gap between expected (290mOsm) and calculated

$$\text{Stool osmotic gap} = 290 - 2([\text{Na}^+] + [\text{K}^+])$$



# Osmotic or Malabsorptive Diarrhea

## Exogenous Causes:

- Antacids:  $\text{Mg}^+$
- Laxatives:
  - Polyethylene glycol (PEG)
  - Poorly absorbed anion ( $\text{PO}_4^{-3}$ ,  $\text{SO}_4^{-2}$ , citrate)
- Sugar substitutes: Sugar-free candy/gum or medication elixirs:
  - Sorbitol, mannitol, Splenda, lactulose
- Nonabsorbable fats: Olestra

## Endogenous Causes:

- Congenital: Disaccharide deficiencies: Lactose intolerance
- Acquired
  - Post-enteritis: Lactose intolerance
  - Pancreatic insufficiency
  - Celiac disease
    - Olmesartan (ARB): Collagenous sprue and collagenous colitis



# Secretory Diarrhea

## Hallmarks

- Persists with fasting
- Nocturnal diarrhea
- Large volume, watery
- Small stool osmolar gap  $< 50 \text{ mOsm/kg}$



# Secretory Diarrhea

## Exogenous:

- Stimulant laxatives: Bisacodyl, senna
- Prostaglandins, theophylline, colchicine
- Dietary secretagogues: Ethanol, caffeine, colas

## Endogenous:

- Bile acid malabsorption:
  - Crohn's ileitis, SB resection, bacterial overgrowth, cholecystectomy
- Hormone-producing tumors: Carcinoid, gastrinoma, VIPoma



# Bile Acid Diarrhea

IBS-D: up to 50% with bile acid malabsorption

Post cholecystectomy: 5-12%; Often improves over weeks to months

Bile acids: Stimulate colonic motility and secretion

Treatment: Bile acid sequestrants

- Colestipol (tablet): 1 gm twice daily
- Cholestyramine (powder): 4 gms daily
- Colesevelam/Welchol (tablet): 1.875gm twice daily
  - Average delay in transit time of 4 hours c/w placebo

Potential side effects: Bloating, flatulence, abdominal discomfort and constipation

- Need to be separated from other medication by > 2 hours.



# Inflammatory Diarrhea

## Hallmarks

- Mucoid, bloody stool
- Tenesmus, abdominal pain, fever
- FOBT positive
- Can be nocturnal
- Fecal leukocytes:
  - Low sensitivity (70%) /specificity (50%)

## Fecal calprotectin: Zn/Ca binding protein

- Derived from neutrophils & monocytes
- Levels increased in intestinal inflammation
- Distinguish inflammatory from noninflammatory causes of chronic diarrhea



# Inflammatory Diarrhea

IBD: Crohn's, ulcerative colitis

Chronic infections

- C. difficile
- Invasive bacteria: eg. TB, yersinia
- Invasive parasites: eg. ameba, strongyloides

Radiation or chemo-induced mucositis

Colonic ischemia



# Fatty Diarrhea

Oil droplets in stool, floating stool

## Diagnosis

- Positive Sudan III stain: Qualitative
- 72 hour stool collection
  - Abnormal: > 7gm fat/day
  - Rarely done (limited reproducibility)
- Stool acid steatocrit
  - Acidify stool
  - Separate fecal homogenate into lipid, water, solid phases; Measure lipid
  - Good correlation with quantitative fecal fat





# Fatty Diarrhea: Causes

Maldigestion and/or Malabsorption  
Pancreatic insufficiency

Inadequate luminal bile acids  
Crohn's disease  
Short bowel syndrome  
SIBO



# History

Stool characteristics: Watery, bloody, oily

Epidemiological factors: Travel, sick contacts

Aggravating/mitigating factors: Diet, stress

Presence or absence:

- Fecal incontinence, abdominal pain, weight loss

Past history:

- Diabetes, Hyperthyroidism, surgery, XRT, CAD

Medication history

Sexual history: Risk factors for HIV

Family history: IBD, neoplasm, celiac disease

Markers of eating disorder, malingering



# PHYSICAL EXAM

Extent of fluid and nutritional depletion

Skin rashes or flushing

Mouth ulcers

Thyroid masses or exophthalmos

Arthritis

Hepatomegaly or abdominal masses

Anorectal exam: sphincter tone, perianal fistula/abscess

Scars (suggesting prior abdominal surgery)



# Initial Laboratory Testing

## AGA (American Gastroenterological Association) Initial Evaluation:

- Fecal calprotectin or lactoferrin: Screen for IBD
- TTG IgA and total IgA level: Celiac disease
- Stool: Giardia
- Future: Fasting serum C4 level (serum 7 $\alpha$ -hydroxy-4-cholesten-3-one): marker of bile acid synthesis
  - Elevated in bile acid diarrhea
  - Values > 24–48 ng/mL are generally considered suggestive of bile acid diarrhea, with higher thresholds (e.g., >48 ng/mL) offering greater specificity.
  - limited availability and lack of regulatory approval
  - Empiric therapy with bile acid binders is often used instead of C4 measurement in clinical practice.



# Additional Laboratory Testing: Other Guidelines

## Also include

- CBC with differential
- Electrolyte panel
- Total protein & albumin
- Thyroid function tests
- ESR

## Strongly consider

- Iron studies, vitamin B12, Folate, Prothrombin time



# Initial Stool Testing

Fecal occult blood testing

Fecal calprotectin

C. difficile toxin: Antibiotic history

Stool culture: Include Aeromonas, Plesiomonas

Stool examination for O & P: Three samples

- Cryptosporidium, Cyclospora, E. histolytica; Microsporidium in immunocompromised patients

ELISA for Giardia antigen



# Endoscopic Evaluation

Required for evaluation of many patients

Alarm features or age-appropriate

## Flexible Sigmoidoscopy

- Reasonable exam for some patients

## Colonoscopy

- Patients with iron deficiency anemia
- Rectal bleeding
- Older patients:  $\geq 50$  yrs
- Patients with suspected Crohn's disease
- Nocturnal pain or diarrhea
- Biopsy normal-appearing mucosa
  - Collagenous/lymphocytic colitis
  - 10% right-sided only

## Upper Endoscopy

- May be useful to rule-out sprue or Whipple's



# Difficult to Diagnose Cases

## Common problems overlooked

- Lactose intolerance
- Fecal incontinence
- Review medications again

Stool culture: Aeromonas and pleisiomonas

O&P: Cryptosporidium, Microsporidia

Breath test for bacterial overgrowth

Calculate the osmotic gap





# Difficult Cases: Osmotic

## Laxative screen

- Inadvertent or surreptitious laxative use
  - Melanosis coli
- Anthraquinones (eg. Senna, cascara, aloe), bisacodyl and phenolphthalein (eg. ExLax) in urine
- magnesium and phosphate in stool.

## Stool pH < 5.3

- Carbohydrate malabsorption (e.g. lactulose, sorbitol)



# Difficult Cases: Secretory

24 hour urine collection: 5-HIAA (carcinoid)

Plasma peptides:

- VIP, gastrin, glucagon (NETs), calcitonin (thyroid), tryptase

Imaging:

Dotatate PET scan: Good for NETs

VIPomas, gastrinomas, glucagonomas are typically located in the pancreas or duodenum

Carcinoid tumors: Most often small intestine but can occur throughout the GI tract, including the appendix and rectum.

Endoscopic Ultrasound: Particularly sensitive for small pancreatic NETs



# Difficult Cases: Inflammatory and Fatty

## Fecal fat assessment

- Stool sudan stain

## Suspect pancreatic insufficiency

- Pancreatic imaging: Chronic pancreatitis
  - MRI/MRCP
- Stool: Fecal elastase
  - Reliable only in moderate to severe insufficiency
- Urine collection: Pancreolauryl test
- Trial of pancreatic enzymes

## Small bowel follow through, MR enterography

- Rule-out IBD

## Small bowel biopsies for sprue, Whipple's

## Breath test for SIBO

- Trial of antibiotics



# SYMPTOMATIC THERAPY

## Therapeutic Options:

- Opiates: most effective
- Empiric trial of antimicrobial therapy
- Cholestyramine and colestipol
- Octreotide



# Summary and MOC Reflections: Acute Diarrhea

- Infections: Most common cause of acute diarrhea
  - Viral more common than bacterial etiology
  - 90% self-limited, require no further evaluation
- Further evaluation with stool studies
  - Multiplex diagnostic panel: Supplanting stool culture
    - Very sick (blood/fever), immunocompromised, hospitalized, outbreak detection
    - Higher sensitivity, faster turnaround, and broader pathogen detection.
  - Standard culture: Outpatients, antimicrobial susceptibility testing is needed, public health reporting, outbreak tracking
  - Antibiotic exposure, hospitalized → C. Diff. Toxin
- Empiric Antibiotics: Severely ill, immunocompromised
  - Quinolone
  - Second line: Azithromycin or erythromycin
  - Vancomycin: C. difficile suspected
- Avoid antibiotics: E. coli 0157:H7



# Summary and MOC Reflections: Chronic Diarrhea

- Broad differential diagnosis

Categorize the diarrhea:

- Watery, Inflammatory or Fatty

Initial testing: Include

- Fecal calprotectin: Screen for IBD
- Stool: Giardia
- TTG IgA and total IgA level: Celiac disease
- Future: Fasting serum C4 level: Elevated in bile acid diarrhea
- Keep in mind possibility of fecal incontinence
- Many patients with chronic diarrhea require endoscopic evaluation
- Acute and chronic diarrhea:
  - Supportive measures: Rehydration, antidiarrheal agents



## Question 1

Which is a hallmark of watery secretory diarrhea?

- A) Diarrhea improves with fasting
- B) Stool osmotic gap  $>125$  mOsm/kg
- C) Nocturnal diarrhea
- D) Steatorrhea
- E) Symptoms triggered by lactose-containing foods



## Question 1: Answer C

The correct answer is **Nocturnal diarrhea**.

Secretory diarrhea: Large volume, watery stools that persist during fasting and often occur at night. Bile acid diarrhea is an example.

Osmotic diarrhea typically abates with fasting and is associated with a high stool osmotic gap ( $>125\text{mosm/kg}$ ). Lactose intolerance falls into this category.

Steatorrhea/fatty diarrhea, is distinguished from watery diarrhea. Presence of excess fat in the stool, typically due to malabsorption or maldigestion of lipids, as seen in conditions such as exocrine pancreatic insufficiency or celiac disease.





## Question 2:

In patients with acute diarrhea, empiric antibiotic therapy should be avoided in one of the following contexts:

- a. Fever and bloody diarrhea
- b. Moderate to severe travelers diarrhea
- c. Known or suspected *E. coli* O157: H7
- d. Elderly and immunocompromised
- e. Hospitalization under consideration



## Question 2: Answer C

Known or suspected E. coli 0157: H7

Most common EHEC infection

- Avoid antibiotics:
  - Increases production of shiga toxin
  - Increases risk of Hemolytic-uremic Syndrome (HUS)
    - Acute renal failure
    - Microangiopathic hemolytic anemia
    - Thrombocytopenia



# Commercial/Faculty Disclosures

None



# References

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