Evaluation of Diarrhea

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Definition

- **Normal stooling frequency**: 3 per day, to 3 per week. Increased frequency may be diarrhea, or pseudodiarrhea.
- **Abnormal increase of stool liquidity, in excess of:**
  - **200 gm/day for US children and adults, or**
  - **10 gm/kg body-weight in infants, or**
  - **> 85% water content in either**

Classification
Duration

- **Acute**: less than 3 weeks
- **Chronic**: more than 3 weeks
- **Recurrent**: repetitive short episodes (less than 3 weeks each) that occur for several months

Normal Volumes and Compositions

Source	Contribution mL	TOTAL IN & OUT/day mL	Na mM/L	K mM/L	Ca, Mg, NH$_4$ mM/L	Cl mM/L	HCO$_3$ mM/L	Other Anions
PO	2,000	2,000 -0	variable	variable	variable	variable	variable	variable
Saliva	1,500	3,500 -0						
Gastric	2,500	6,000 -0						
Bile	500	6,500 -0						
Pancreas	1,500	8,000 -0						
Jejunum	1,000	9,000 -5,500	130	6	variable	90	30	0
Ileum	0	3,500 -2,000	140	8	10	60	70	0
Colon	0	1,500 -1,300						
Stool		200	40	90	20	15	30	80-180
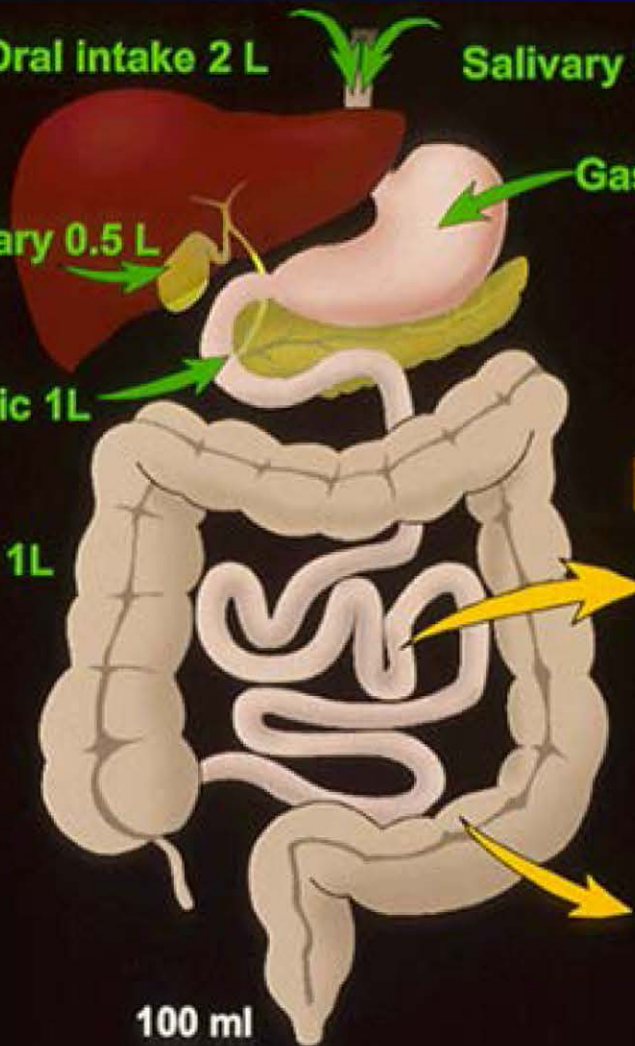
Fluid Absorption

- Absorption of water is passive; depends on the absorption of solutes.

- Neurotransmitters & enteric hormones can modify net water balance.

- Maximal absorptive capacity:
  - **Small bowel: 12 liters**
  - **Colon: 4-5 liters.**

- Theoretical Maximal Continuous "Oral Rehydration Solution" rate:
  - **375-400 mL/hour (9-10 L/d)**

Pathophysiologic Classification
Osmotic Diarrhea

- The human bowel can not keep osmotic gradients; Stool osmolarity is equal to plasma osmolarity (280-310 mOsm)

- If malabsorbed nutrients or non-absorbable solutes are ingested, fluid will enter the intestine to reach iso-osmolarity.

- Normally, most of the stool osmolarity comes from its electrolytes (Na, K, corresponding organic anions)

- **Osmolar gap = 290 - 2[Na + K]** ; Normal < 125 mOsm (usually < 50 mOsm)

Pathophysiologic Classification
Osmotic Diarrhea

- **Features of Osmotic Diarrhea:**
  - **Osmolar gap > 125 mOsm**
  - **Stool Na < 60 mM/L**
  - **Fasting (food & drugs) stool output < 200 g**
  - **Carbohydrate related: pH<5.3 ; reducing substances (+) [does not detect lactulose, sorbitol, mannitol, nor sucrose]**
- Examples:
  - **a) Osmolar load**: PEG, Mg salts, Na Phosphate, sorbitol, mannitol, lactulose, xylitol
  - **b) Malabsorption**: Mucosal damage (sprue, infections), disaccharidase deficiency, Olestra, bacterial overgrowth, pancreatic insufficiency, short bowel, IBD, lymphangiectasia, etc.

Pathophysiologic Classification
Osmotic Diarrhea

- In SO_4 or PO_4 diarrhea: they are > 10mmol/L
- In diarrhea due to Mg salts:
  - Mg concentration > 45 mM/L (usually > 100mM/L)
  - 24 hours stool Mg > 15 mmol; (7.3 g stool/ mmol Mg)
  - Stool output after 24 h fasting:
    - a) Innocent < 200 g/d;
    - b) Surreptitious: > 200 g/d & gap > 100 mOsm
- In diarrhea due to Na salts:
  - Stool Na > 90 mM/L
  - Osmotic gap < 50 mOsm
  - Stool Cl^- < 20 mM/L

Unusual Measured Stool Osmolalities

- If stool is stored for hours, even in deep freeze, Osm may exceed 350 due to degradation of carbohydrates: process immediately.
- **Stool Osm > 375 + Na > 150 mM/L**:
  - contamination with concentrated urine.
- **Stool Osm < 250**:
  - contaminated with diluted urine, or water was added.
- **Stool [Na] + [K] > 165 mM/L**:
  - concentrated urine in stool.

Pathophysiologic Classification
Secretory Diarrhea

- Due to:
  - Inhibition of ion (Na, K, Cl, HCO3) absorption,
  - Stimulation of ion secretion, or
  - Both.
- May affect small bowel, colon, or both;
  - in small bowel disease, the amount of fluid presented to the colon exceeds its maximal absorption capacity (5 L)

Pathophysiologic Classification
Secretory Diarrhea

- **Features of secretory diarrhea:**
  - Osmolar gap < 50 mOsm
  - Na concentration > 90 mM/L
  - 24 h fasting stool volume > 200 g
  - pH > 5.6; reducing substances (-)

Pathophysiologic Classification
Secretory Diarrhea

- **Classification:**

- **1) Exogenous:**
  - **a) Drugs**: Phenolphtalein, anthraquinones, bisacodyl, senna, aloe, ricinoleic acid, DOSS, furosemide, thiazides, theophylline, thyroid, misoprostol, 5-ASA, gold, colchicine, etc. (see PDR)
  - **b) Foods**: tea, coffee, cola, ethanol, MSG, seafood toxins (ciguatera, scombroid, paralytic or neurotoxic shellfish poisoning).
  - **c) Bacterial toxins**: S. aureus, C. perfringes, C. botulinum, B. cereus.
  - **d) Toxins**: Arsenic, Amanita phalloides, organophosphates,

Pathophysiologic Classification
Secretory Diarrhea

- **2) Endogenous:**
  - **a) Bacterial**: V. cholerae, Toxigenic E. coli, C. jejuni, Y. enterocolitica, K. pneumonia, C. difficile.
  - **b) Endogenous laxatives**: bile acids, long-chain fatty acids.
  - **c) Hormone-producing tumors**: VIPoma, ganglioneuromas, medullary carcinoma of thyroid, gastrinoma, carcinoid, glucagonoma, mastocytosis, villous adenoma.
  - **d) Congenital**: chloridorrhea, Na diarrhea, enterocyte heparan sulphate defic., microvillous inclusion disease.

Pathophysiologic Classification
Inflammatory Diarrhea

- Enterocyte damage or death, with minimal or severe inflammation; can cause malabsorption or secretion.
  - **Classification**:
- **1) Minimal to mild inflammation**:
  - **a) Infections**: enteroadherent or enteropathogenic E. coli, rotavirus, Norwalk, HIV, giardia, cryptosporidium, isospora, cyclospora, ascaris, trichinella, bacterial overgrowth, tropical sprue.
  - **b) Cytostatics**: chemotherapy, radiation.
  - **c) Hypersensitivity**: food allergy, nematodes.
  - **d) Autoimmune/ idiopathic**: microscopic colitis, collagenous colitis, Canada-Cronkhite, graft-vs-host.

Pathophysiologic Classification
Inflammatory Diarrhea

- **2) Moderate to severe inflammation with or without ulceration:**

  - **a) Destruction of enterocyte**: shigella, enteroinvasive E. coli, E. histolytica, hookworm.

  - **b) Penetration of mucosa**: salmonella, C. jejuni, Y. enterocolitica, M. avium complex, Whipple dz.

  - **c) Hypersensitivity**: Celiac sprue, milk or soybean hypersensitivity, eosinophilic gastroenteritis, gold, methyldopa, nematode infestation.

  - **d) Autoimmune/ idiopathic**: Ulcerative colitis, Crohn's disease, lymphoma

Pathophysiologic Classification
Deranged Motility

- Due to autonomic dysfunction, rapid small intestine transit, and/or colonic irritability.

- Examples:
  Sandhoff disease (hexosaminidase B deficiency), IBS.

Pathophysiologic Classification
Mixed

- Most diarrheal disorders have more than one pathophysiologic component.

Helpful Questions to the Patient with Diarrhea

- **Stool volume**:
  - a) Volume < 250 g + tenesmus, frequency, urgency, mucus or blood:
    - suggest recto-sigmoid involvement.
  - b) Volume > 400 g, watery, minimal urgency, no tenesmus, little mucus:
    - suggest SB or proximal colon origin, secretory diarrhea.
  - c) Volume > 400 g, foul smelling, greasy, minimal urgency, no tenesmus:
    - suggest SB origin with malabsorption.

Helpful Questions to the Patient with Diarrhea

- **Pain**:
  - a) Periumbilical or RUQ, crampy, with borborigmi:
    - Small bowel or asc. Colon.
  - b) Hypogastric, RLQ, or LLQ, aching, with tenesmus:
    - rectosigmoid
- **Blood**:
  - mucosal invasion (salmonella, campylobacter),
  - IBD,
  - neoplasia,
  - ischemia,
  - cytotoxin (enterohemorrhagic E. coli [EHEC], C. difficile, Shigella, Klebsiella oxytoca)
- **Effect of fasting (48-72h)**:
  - a) Stops: osmotic, or allergic.
  - b) Continues: secretory, or exudative /inflammatory.
- **Nocturnal Diarrhea**: suggest organicity

Helpful Questions to the Patient with Acute Diarrhea

- **Food ingestion**:
  - **Poultry**: salmonella, campylobacter, shigella.
  - **Ground beef, unpasteurized juice**: Entero-Hemorrhagic E. coli.
  - **Pork**: tapeworm.
  - **Seafood/shellfish**: v. cholerae, v. vulnificus, v. parahemolyticus, salmonella, anisakis, tapeworm.
  - **Cheese, milk**: listeria.
  - **Eggs**: salmonella.
  - **Mayonnaise & cream pies**: S. aureus & clostridium.
  - **Fried rice**: B. cereus.
  - **Fresh berries**: cyclospora.
  - **Canned foods**: clostridium
  - **Spring or contaminated water**: v. cholerae, Norwalk agent, giardia, cryptosporidium.

Helpful Questions to the Patient with Acute Diarrhea

- **Pet & livestock**: salmonella, giardia, campylobacter, cryptosporidium.
- **Day-care center**: shigella, campylobacter, cryptosporidium, giardia, c. difficile, virus.
- **Antibiotics, chemotherapy**: c. difficile, K. oxytoca (amoxicillin +/- clavunate), c. perfringes (plasmid cpe).
- **Swimming pool**: giardia, cryptosporidium.
- **Rectal intercourse**: N. gonorrhea, N. meningitides, Chlamydia, syphilis, CMV, HSV
- **Anilingus**: all enteric bacteria, virus, and parasites.

Infectious Doses of Enteric Pathogens

- Cryptosporidium parvum $1\text{-}10^3$
- Entamoeba histolytica $10\text{-}10^2$
- Giardia lamblia $10\text{-}10^2$
- Shigella $10\text{-}10^2$
- Campylobacter jejuni $10^2\text{-}10^6$
- Salmonella 10^5
- Escherichia coli 10^8
- Vibrio cholerae 10^8

Infectious Etiologies
Type & Site of Involvement

- **Noninflammatory**
  - *Watery diarrhea*
  - Proximal Small bowel
  - Enterotoxin/adherence/ superficial invasion
  - No fecal WBC
  - Minimal or no Lactoferrin
- **Inflammatory**
  - *Dysenteria*
  - Colon
  - Invasion/cytotoxin
  - (+) fecal WBC
  - High Lactoferrin
- **Penetrating**
  - Enteric fever
  - Distal small bowel
  - Penetration
  - Fecal mononuclear leukocytes

- **Distal Small Bowel (Penetrating)**

- **Salmonella typhi**
- **Yersinia enterocolitica**
- **Campylobacter fetus**

Infectious Etiologies
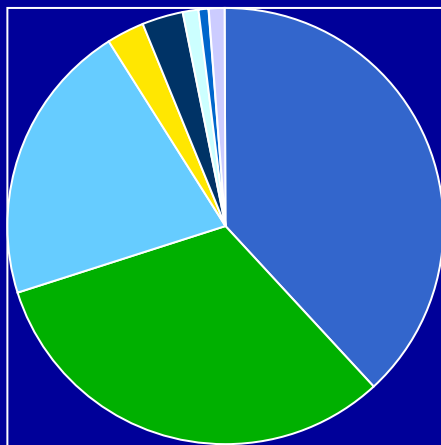# Site of Involvement

- **Proximal Small Bowel (Non-inflammatory)**
- **Salmonella (*)**
- **E. coli**
- **C. perfringes**
- **S. aureus**
- **Aeromonas hydrophila**
- **B. cereus**
- **V. cholerae**
- **Rotavirus**
- **Norwalk-like agents**
- **Cryptosporidium (*)**
- **Microsporidium (*)**
- **Giardia**
- **Cyclospora**
- **Isospora**

- **Colon (Inflammatory)**
- **Campylobacter (*)**
- **Shigella**
- **C. difficile (WBC(+) in 30%)**
- **Yersinia**
- **V. parahemolyticus**
- **Enteroinvasive E. coli**
- **Plesiomonas shigelloides**
- **Klebsiella oxytoca**
- **CMV (*)**
- **Adenovirus**
- **HSV**
- **Entamoeba histolytica (WBC absent b/o destruction)**
  - **(*) Dominant involvement**

Common Infectious Etiologies

WATERY DIARRHEA
6% of Stool studies (+)

BLOODY DIARRHEA
20-30% Stool studies (+)

- Salmonella
- Campylobacter
- Shigella
- EHEC
- Cryptosporidium
- Listeria
- Yersinia
- Vibrio

- EHEC
- Shigella
- Campylobacter
- Salmonella
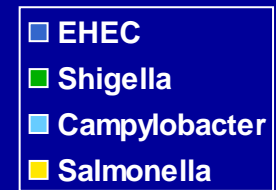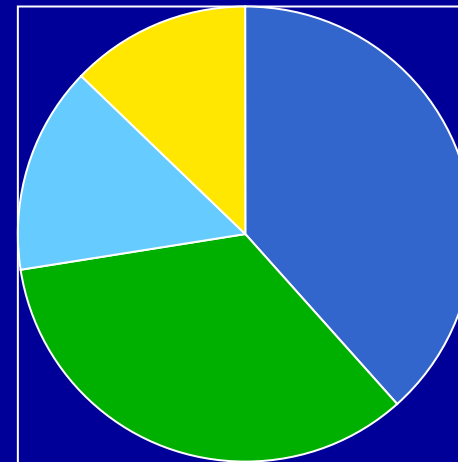
Complications & Extraintestinal Manifestations of Acute Infectious Diarrhea

- **V. cholerae, E. coli**: volume depletion, shock & death
- **B. cereus**: Fulminant liver failure
- **V. vulnificus, V. parahemolyticus**: shock & death in cirrhosis, Fe overload, or alcoholics.
- **C. difficile**: protein loosing enteropathy, toxic megacolon.
- **Enterohemorrhagic E. coli (EHEC)**: HUS & TTP
- **Salmonella**: sepsis, peritonitis, cholecystitis, pancreatitis, osteomyelitis, mycotic aneurism, intraabdominal abscess
- **Campylobacter**: Guillian-Barre syndrome
- **Shigella**: seizures and encephalopathy
- **Salmonella, shigella, campylobacter, yersinia**: Reiter syndrome
- **Yersinia**: Thyroiditis, pericarditis, glomerulonephritis, myocarditis, HUS, Guillian-Barre

Diagnostic Workup

Initial Diagnostic Tests
Acute Diarrhea

- **Patients with high priority for investigation**:
  - Severe volume depletion
  - Impaired host (immunodeficiency, age >70, malnutrition)
  - Bloody diarrhea, dysenteria.
  - Toxicity, or fever > 38.5 °C (101.3 °F)
  - Severe abdominal pain
  - Recent antibiotic use, or onset in the hospital (C. diff)
  - Inflammatory Bowel Disease
  - Duration > 3 days.
  - WBC's or Lactoferrin > 1:50 in stool (using these markers to guide further diagnostic studies has been proven to be imprecise and probably unnecessary)
  - Community outbreak, or food handlers.

Initial Diagnostic Tests

- **Calprotectin:** Elevated fecal calprotectin indicates the migration of neutrophils to the intestinal mucosa, which occurs during intestinal inflammation (In IBD: Sensitivity 93%; Specificity 96%)
  - Calprotectin is a 24 kDa dimer of calcium binding proteins S100A8 and S100A9. The complex accounts for up to 60% of the soluble protein content of the neutrophil cytosol.
  - Increased in inflammatory bowel diseases, celiac disease, infectious colitis, necrotizing enterocolitis, intestinal cystic fibrosis, use of NASAIDs and colorectal cancer.
- **Fecal Lactoferrin**: indicates inflammatory diarrhea (sensitivity=90%, specificity=95%); if (+); send stool culture.
  - C. difficile colitis, 64-77% are FL(+) @ titer >1:50. (Steiner et al. Clin Diag Lab Immun 1997,719-722)
  - Cryptosporidium: 7% adults & 70-83% malnourished children are LF(+) (Alcantara et al. Am J Trop Med Hyg 2003; 68:325-328)
  - Shigella, 95% are FL(+) @ titer > 1:200. (Guerrant et al. J Clin Microbiol, 1992; 30:1238-42)
- **Fecal Leukocytes**: indicates inflammatory diarrhea (sensitivity=42-73%, specificity=84%); if (+); send stool culture.
  - In C. difficile colitis, has sensitivity of 30% & specificity of 75% (Reddymasu et. al: Ann Clin Microbiol Antimicrob 2006, 5:9)

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- Diagnostic evaluation using **stool culture and culture-independent methods** if available should be used in situations where the individual patient is **at high risk of spreading disease** to others, and during **known or suspected outbreaks**. (Strong recommendation, low level of evidence)

- **Stool diagnostic studies** may be used if available in cases of **dysentery, moderate–severe disease, and symptoms lasting >7 days** to clarify the etiology of the patient's illness and enable specific directed therapy.(Strong recommendation, very low level of evidence)

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- Traditional methods of diagnosis (bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection.

- If available, the use of **FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct** to traditional methods. (Strong recommendation, low level of evidence)

Initial Diagnostic Tests

- **Molecular Stool Testing for Enteric Pathogens.**
  - If available is first line Test
  - May detect potential pathogens that are "not guilty".
- **Stool culture**: send only in **"high priority"** patients, or if stool lactoferrin, calprotectin or leukocytes is (+).
  - Stool should be fresh, and processed immediately.
  - Routine culture includes salmonella, shigella, and campylobacter; all other suspected pathogens should be "<u>ordered by name</u>".
  - In hospital acquired diarrhea, only c. difficile toxin A&B studies are cost effective.
  - If hemorrhagic: E. coli O157:H7 & O26:H11; also Klebsiella Oxytoca (post antibiotics)

FDA Approved Molecular Tests For Enteric Pathogens

Manufacturer	Test system	Platform	Pathogens detected		Detection time (h)
			Type	No.	
Luminex	GPP	xTAG	B, V, P	15	<5
Hologic/Gen-Probe	ProGastro SSCS	—	B	4	4
BD Diagnostics	EBP	BD MAX	B	4	3–4
Biofire Diagnostics	GI Panel	FilmArray	B, V, P	22	1–2
Nanosphere	EP	Verigene	B	6	2

can detect microbes at non-pathogenic levels

Molecular Diagnostic Testing
xTAG GPP (Luminex)

- **Bacteria & Toxins:**
  - Campylobacter
  - C. difficile toxin A/B
  - E coli 0157
  - Enterotoxigenic E coli L/T S/T (ETEC)
  - Shiga-like tixin producing E coli (STEC) stx1/stx2
  - Salmonella
  - Shigella

- **Parasites:**
  - Giardia lamblia
  - Cryptosporidium

- **Virus:**
  - Norovirus GI/GII
  - Rotavirus A

FilmArray Gastrointestinal (GI) Panel

Reverse transcription PCR with detection of 23 pathogens in a freeze-dried format in 1 hour

- **<u>Bacteria</u>**
  - Aeromonas
  - Campylobacter
  - Clostridium difficile (Toxin A/B)
  - Plesiomonas shigelloides
  - Salmonella
  - Yersinia enterocolitica
- Diarrheagenic E. coli/Shigella
  - Enteroaggregative E. coli (EAEC)
  - Enteropathogenic E. coli (EPEC)
  - Enterotoxigenic E. coli (ETEC) lt/st
  - Shiga-like toxin-producing E. coli (STEC) stx1/stx2
  - E. coli O157
  - Shigella/Enteroinvasive E. coli (EIEC)

- **<u>Vibrio</u>**
  - Vibrio cholerae
- **<u>Virus</u>**
  - Adenovirus F 40/41
  - Astrovirus
  - Norovirus GI/GII
  - Rotavirus A
  - Sapovirus
- **<u>Parasites</u>**
  - Cryptosporidium
  - Cyclospora cayetanensis
  - Entamoeba histolytica
  - Giardia lamblia

Detection of C. difficile

Toxin Assays

Test	Pro	Con
Cytotoxicity (Gold Standard; tests cytopathic effect)	Very sensitive (10 pg Toxin B) Very specific	Expensive Takes 2 days
EIA toxin A&B	Very specific (>95%) Cheap Takes < 24 h	Low sensitivity (60-90%) (100-1000 pg toxin B)
PCR (tests gene for toxin B)	Rapid (< 4h) Very sensitive Very specific (80-99%)	Expensive Does not differentiate colonization from infection

Bacteria Detection

Test	Pro	Con
GDH (common antigen testing for glutamate dehydrogenase)	High sensitivity Rapid Cheap	Intermediate specificity Does not differentiate colonization from infection
Stool culture (anaerobic stool culture)	Extremely sensitive	Turn over: 3 days Does not differentiate colonization from infection

Initial Diagnostic Tests

- **Stool for Ova & Parasites**:
  - Routine O&P *does not include* studies for cryptosporidium, isospora, cyclospora, nor microsporidium; giardia Ag is done in some labs. You should <u>order the test by name</u>.
  - O&P is not helpful in hospital acquired diarrhea.
  - Because of intermittent shedding, O&P studies should be done in stools of 3 different days.

Initial Diagnostic Tests

- Stool for Ova & Parasites:
  - **Indications:**
    - AIDS, man having sex with men
    - Immunodeficiency (post-transplant, IgA deficiency, common variable immunodeficiency, chemotherapy)
    - Persistent diarrhea (> 10 days).
    - Weight loss.
    - Community waterborne outbreak (from drinking water, or from swimming pool)
    - Bloody diarrhea with few or no leukocytes (ameba)
    - Exposure in day-care center
    - Ingestion of fresh berries
    - Practice of oral sex
    - Pets & farm animals.

Test done when Stool Test ordered

	O&P	Comprehensive O&P	C. Difficile toxin	Only on Special order
U of L	**Giardia Ag, Cryptosporidium immunoassay**	**Giardia Ag & Regular O&P**	**EIA (Toxin A & B) and GDH** **PCR (toxin B) for discrepancy** **Interval: 3/wk**	**Isospora** **Cyclospora** **Microsporidia**
VA	**Lactoferrin: (+) stool examined; (-) "negative"**		**PCR for toxin B** **Interval: 1/wk**	**Cryptosporidium** **Isospora** **Cyclospora** **Microsporidia**
Jewish	**Giardia Ag**	**Giardia Ag & Regular O&P**	**EIA (Toxin A&B)** **Interval: 1/day**	**Cryptosporidium** **Isospora** **Cyclospora** **Microsporidia**
Norton	**Regular O&P**		**EIA (Toxin A & B) and GDH** **PCR (toxin B) for discrepancy** **Interval: 1/wk**	**Cryptosporidium** **Isospora** **Cyclospora** **Microsporidia**

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of Travelers Diarrhea (TD) where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. (Strong recommendation, high level of evidence)

- Use of **antibiotics for community-acquired diarrhea should be discouraged** as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. (Strong recommendation, very low-level evidence)

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- In patients receiving **antibiotics for traveler's diarrhea**, adjunctive **loperamide therapy should be administered** to decrease duration of diarrhea and increase chance for a cure. (Strong recommendation, moderate level of evidence)

- The usage of **balanced electrolyte rehydration (ORS)** over other oral rehydration options in the **elderly with severe diarrhea** or any **traveler with cholera-like watery diarrhea** is recommended.

- Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers. (Strong recommendation, moderate level of evidence)

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- **Antibiotic sensitivity** testing for management of the individual with acute diarrheal infection is currently **not recommended**. (Strong recommendation, very low level of evidence)

- The use of **probiotics or prebiotics** for the treatment of acute diarrhea in adults is **not recommended**, except in cases of post-antibiotic-associated illness. (Strong recommendation, moderate level of evidence)

- **Bismuth subsalicylates** can be administered to control rates of passage of stool and may help **travelers** function better during bouts of **mild-to-moderate illness**. (Strong recommendation, high level of evidence)

ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- After the initial stool tests are done, Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. (Strong recommendation, very low level of evidence)

- Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. (Strong recommendation, very low level of evidence)
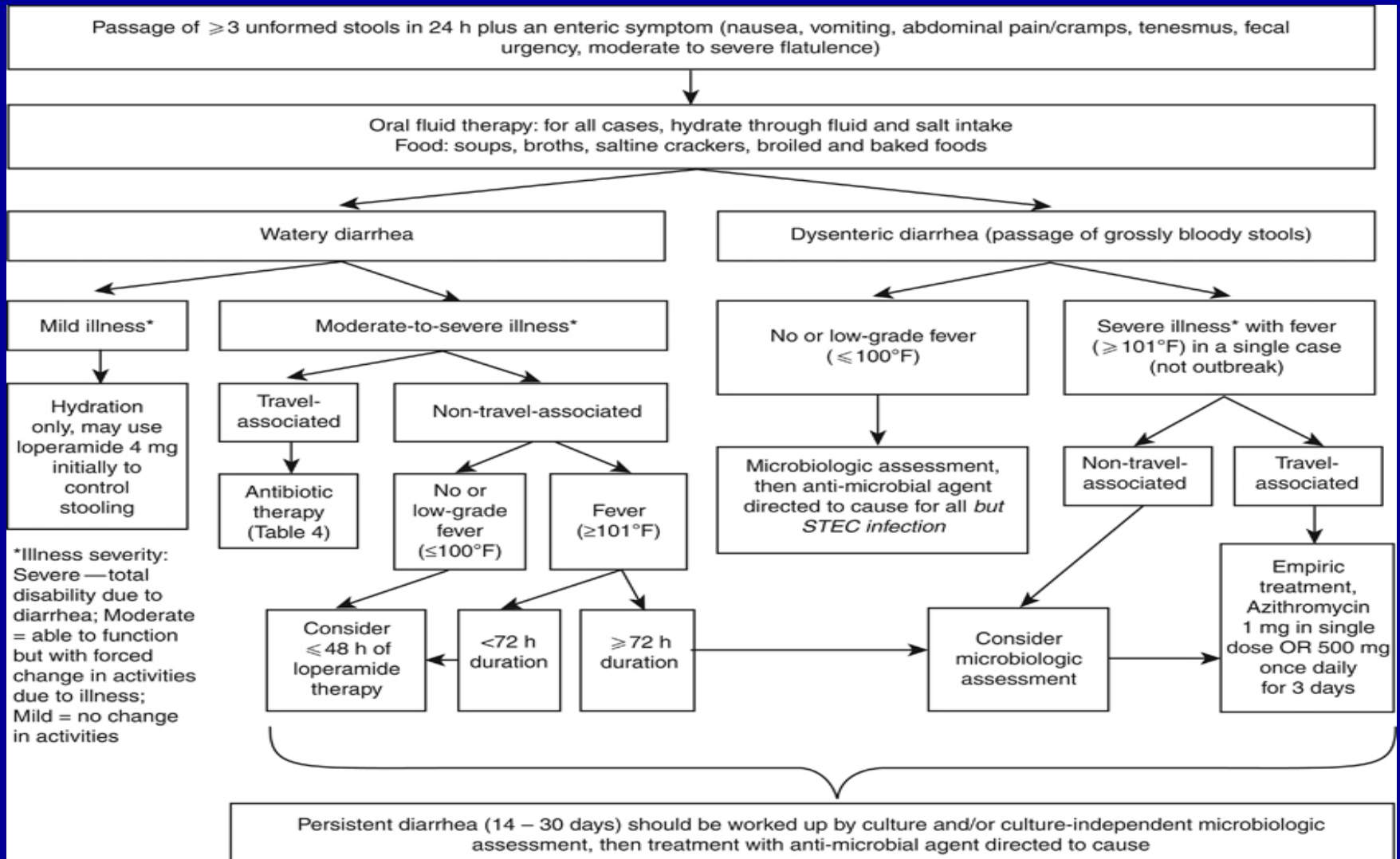
Preventive Interventions

- Individuals SHOULD undergo pre-travel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. (Conditional, very low level of evidence)

- Probiotics, prebiotics, and synbiotics are NOT recommended for prevention of TD. (Conditional recommendation, low level of evidence)

- Patient level counseling on prevention of acute enteric infection is NOT routinely recommended but:
  - may be considered in the individual or close contacts of the individual who is at high risk for complications. (Conditional, very low level of evidence)

Preventive Interventions

- Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but:
  - may be useful where low-dose pathogens are responsible for the illness as for an example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. (Conditional recommendation, low level of evidence)

- Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. (Strong recommendation, high level of evidence)

- Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use. (Strong recommendation, high level of evidence)

Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea
(suspect infectious etiology)

Passage of ≥3 unformed stools in 24 h plus an enteric symptom (nausea, vomiting, abdominal pain/cramps, tenesmus, fecal urgency, moderate to severe flatulence)

Oral fluid therapy: for all cases, hydrate through fluid and salt intake
Food: soups, broths, saltine crackers, broiled and baked foods

Watery diarrhea

Mild illness*

Hydration only, may use loperamide 4 mg initially to control stooling

*Illness severity: Severe —total disability due to diarrhea; Moderate = able to function but with forced change in activities due to illness; Mild = no change in activities

Moderate-to-severe illness*

Travel-associated → Antibiotic therapy (Table 4)

Non-travel-associated

No or low-grade fever (≤100°F)

Fever (≥101°F)

Consider ≤48 h of loperamide therapy

<72 h duration

≥72 h duration

Dysenteric diarrhea (passage of grossly bloody stools)

No or low-grade fever (≤100°F) → Microbiologic assessment, then anti-microbial agent directed to cause for all *but STEC infection*

Severe illness* with fever (≥101°F) in a single case (not outbreak)

Non-travel-associated

Travel-associated

Consider microbiologic assessment

Empiric treatment, Azithromycin 1 mg in single dose OR 500 mg once daily for 3 days

Persistent diarrhea (14 – 30 days) should be worked up by culture and/or culture-independent microbiologic assessment, then treatment with anti-microbial agent directed to cause

Second Line Diagnostic Tests

- **Flexible sigmoidoscopy**: Indicated in:
  - Dysenteria with negative stool studies.
  - History of rectal intercourse.
  - Suspect IBD
  - Immunocompromised patient when CMV, C. difficile, or opportunistic infections are suspected but stool studies are negative.
  - When ischemic colitis is suspected but radiology is equivocal.
  - Suspected pseudomembranous colitis with negative stool studies.
  - Persistent diarrhea with (-) stool studies

Second Line Diagnostic Tests

- **Special cultures**: with history of rectal intercourse, consider the following,
  - Rectal swab culture for N. gonorrhea, and N. meningitides.
  - Rectal swab for syphilis (dark field or immuno-fluorescence)
  - Rectal swab for chlamydia (culture & immuno-fluorescence)
  - Rectal/colonic Bx for CMV & HSV culture.

Studies for Acute Diarrhea Evolving to Chronic
(>/= 3 weeks)

Second Line Diagnostic Tests

- **EGD with SB Bx & Aspirate**:
  - Excellent for SB mucosal disease, but can have false (-) in patchy disease.
  - Fairly good for detection of giardia, cryptosporidium, isospora, cyclospora, microspora & strongyloides (patchy); aspirate & Bx.
  - Quantitative culture of > 10^5 colonies/mL is indicative of bacterial overgrowth.

Second Line Diagnostic Tests
EGD with Small Bowel Bx & Aspirate

- **Diagnostic Histology & Diffuse distribution**
- Whipple disease
- M. avium complex
- Abetalipoproteinemia
- Agammaglobulinemia

- **Diagnostic Histology but Patchy distribution**
- Lymphoma
- Lymphangiectasia
- Eosinophilic enteritis
- Mastocytosis
- Amyloidosis
- Crohn disease
- Giardia, coccidiosis, strongyloidasis

Second Line Diagnostic Tests
EGD with Small Bowel Bx & Aspirate

- **Abnormal Non-Diagnostic Histology & Diffuse distribution**

- Celiac & tropical sprue
- Viral enteritis
- Bacterial overgrowth
- Severe folate & B_{12} deficiency

- **Abnormal Non-Diagnostic Histology & Patchy distribution**

- Acute radiation enteritis
- Enteropathy of dermatitis herpetiformis

Second Line Diagnostic Tests

- **Serologic studies**:
  - Quantitative serum IgG, IgA, & IgM: to evaluate for "common variable immunodeficiency" & IgA deficiency; also for proper interpretation of Celiac Sprue serology
  - Anti-tissue transglutaminase (IgA & IgG), for Celiac Sprue.
  - Ameba serology
  - Anti-HIV serology

Second Line Diagnostic Tests

- **Stool Electrolytes:**
  - Na, K, Cl
  - Phosphorus, Magnesium, Sulphate, PEG.
  - pH and Reducing Substances.
- **Laxative analysis in stool & urine.**
  - Stool water can be tested for phenolphtalein, emetine (ipecac syrup), & bisacodyl.
  - Urine can be tested for anthraquinone.

Initial Treatment

- **Oral Rehydration Solution (ORS):**
  - Best way to treat fluid loss from diarrhea (unless vomiting)
  - WHO: 1 L water + 3.5 g NaCl (3/4 tsp)+ 2.5 g Na bicarbonate (1/2 tsp) + 1.5 g KCl (20 mEq) + [40 g sucrose (3 tbsp), or 20 g glucose, or 50-80 gm rice powder cooked x 3 minutes]. [Na=90 mEq, K=20 mEq, Cl=80 mEq, HCO_3=30 mEq, glucose=111 mMol]
  - WHO: Water 1 liter + ¾ tsp salt + ½ tsp baking soda + 1 cup orange juice + 4 Tbs of sugar.
  - Ceralyte-70 1 liter + ¼ tsp salt or 11 Zesta crackers
  - Pedialyte 1 liter + 1 Tbs sugar + ½ tsp salt, or 22 Zesta crackers
  - Gatorade 3 glasses + 1 glass orange juice + {[½ tsp salt + ½ tsp baking soda], or [37 Zesta crackers]}

½ tsp salt = 22 Zesta crackers   ½ tsp baking soda = 15 Zesta crackers

Initial Treatment

- **Racecadotril**: reduces output & duration of diarrhea in children and adults; is taken in addition to ORS

- **Zn supplements**: Decrease duration & need of antibiotics; taken in addition to ORS.

- **Crofelemer (Fulyzac):** 125 mg BID. For non-infectious diarrhea in HIV/AIDS.

Antisecretory Drugs

- **BSS** will reduce the stools passed by ~40%.
- **Crofelemer**:
  - cystic fibrosis transmembrane regulator chloride-channel blocker
  - Effective in some forms of diarrhea including TD and AIDS-associated diarrhea.
- **Zaldaride**:
  - calmodulin-inhibiting drug that has antisecretory properties related to intracellular concentrations of calcium.
- **Racecadotril**,
  - Specific enkephalinase inhibitor that prevents degradation of the endogenous antisecretory peptide neurotransmitter enkephalins that inhibit cyclic nucleotide secretory pathways
  - No effect on gut motility
  - Used successfully in pediatric diarrhea and in adults.
- **Loperamide** works through two mechanisms:
  - Primary effect is production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption.
  - Secondary effect appears to be inhibition of calmodulin leading to reduced mucosal secretion

Antibiotic Therapy in Diarrhea

- **Risk of Empiric antibiotic therapy**:
  - Increases risk of HUS in EHEC, and
  - Prolongs shedding of salmonella,
  - Do not give when you suspect:
    - c. difficile colitis (targeted therapy is OK), or
    - EHEC, or
    - salmonella
- **Consider antibiotics for:**
  - Travelers Diarrhea** with > 4 BM/d, fever, blood, pus in stool, or
  - Severe diarrhea (> 8 BM/d, or volume depletion), or
  - Diarrhea longer than 7 d, or
  - Diarrhea in immunocompromised

**In Traveler Diarrhea add Loperamide to Antibiotic Regimen

Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology)

Antibiotic[a]	Dose	Treatment duration
Levofloxacin	500 mg by mouth	Single dose[b] or 3-day course
Ciprofloxacin	750 mg by mouth or	Single dose[b]
	500 mg by mouth	3-day course
Ofloxacin	400 mg by mouth	Single dose[b] or 3-day course
Azithromycin[c,d]	1,000 mg by mouth or	Single dose[b]
	500 mg by mouth	3-day course[d]
Rifaximin[e]	200 mg by mouth three times daily	3-days

[a] Antibiotic regimens may be combined with loperamide, 4 mg first dose, and then 2 mg dose after each loose stool, not to exceed 16 mg in a 24-h period.
[b] If symptoms are not resolved after 24 h, complete a 3-day course of antibiotics.
[c] Use empirically as first line in Southeast Asia and India to cover fluoroquinolone-resistant *Campylobacter* or in other geographical areas if *Campylobacter* or resistant ETEC are suspected.
[d] Preferred regimen for dysentery or febrile diarrhea.
[e] Do not use if clinical suspicion for *Campylobacter*, *Salmonella*, *Shigella*, or other causes of invasive diarrhea.

Initial Treatment

- **Symptomatic therapy**: Loperamide, diphenoxylate, Pepto-Bismol
- May be used only in patients without fever nor bloody stool. Pepto-Bismol most helpful for nausea & vomiting.
- **Loperamide**: 4 mg, followed by 2 mg q BM, not to exceed 16 mg/d, x 2 days.
  - Used together with antibiotics in Traveler Diarrhea.
- **Diphenoxylate**: 4 mg QID x 2 days
- **Pepto-Bismol**: 2 tab, or 30 mL q 30 min. x 8 doses

Viral Foodborne Infections

Specific Causes of Foodborne Diarrhea - Viral
Norwalk & Norwalk-like Virus

- 40-60% of acute viral gastroenteritis epidemics in older children & adults
- Villous shortening, crypt hyperplasia, PMN & MN cells in lamina propria.
- **Spread**: person-to-person, contaminated food or water.
- **Incubation**: 12-48 hours
- **Duration**: 12-48 hours
- **Diagnosis**: Serology, or E/M for stool virus
- **Immunity**: weeks to months
- **Treatment**: ORS, supportive.

Specific Causes of Foodborne Diarrhea - Viral
Rotavirus

- 60% of diarrhea in children < 2 years-old
- Kills mature villous-tip cells
- **Spread**: fecal-oral
- **Season**: late-fall, winter, early-spring
- **Duration**: 3-10 days
- **Symptoms**: diarrhea, nausea, vomiting, cough, rhinitis, otitis. Subclinical in adults.
- **Diagnosis**: Stool antigen (Rotazyme for type A)
- **Treatment**: ORS, supportive.

Foodborne Bacterial Infections with Diarrhea due to Mucosal Invasion

Salmonella Gastroenteritis

- Causes 25-40% of food-borne infections in adults
- **Spread**: food-borne (food, flies, fingers, feces, fomites); meat, poultry, eggs, dairy products.
- **Incubation**: 8-48 hours
- **Duration**: usually 3-4 days (up to 3 weeks).
- **Symptoms**: nausea, vomiting, abdominal cramps, low grade fever < 102 ^{0}F, watery diarrhea; sometimes severe dysenteria. May cause osteomyelitis, septic or reactive arthritis, sepsis, peritonitis, cholecystitis, pancreatitis, mycotic aneurism, intraabdominal abscess.
- **Treatment**: ORS & support. Antibiotics prolong disease.
  - Treat only immunosupressed, age < 3 mo or > 50 y, hemolytic anemia, surgical prosthesis, valvular heart disease, severe atherosclerosis, cancer, uremia.
  - TMP-SMX DS p.o. BID x 7 days; 14 days if immunosupressed.

Campylobacter jejuni

- Most common cause of bacterial enteritis in many parts of the world.
- More frequent in young children, with secondary infections in household.
- **Spread**: fecal-oral, food-borne, water-borne.
- **Incubation**: 24-72 hours.
- **Duration**: usually 1 week
- **Symptoms**: prodrome of malaise, coryza, headache, and fever; then colicky periumbilical pain with profuse diarrhea, than improves and then worsens, with WBC's in stool.
- **Complications**: Endocarditis, meningitis, Guillian-Barre, cholecystitis, pancreatitis, septic abortion, glomerulonephritis, reactive arthritis (HLA-B27)
- **Treatment**: Erythromycin stearate 500 mg BID x 5 days

Specific Causes of Foodborne Diarrhea – Mucosal Invasion
Shigella

- **Spread**: person to person; most common in age 6 mo-10 y; adult infected from children. Well water contaminated with feces.
- **Incubation**: 36-72 hours.
- **Duration**: 1-30 days (1 week) without therapy
- **Symptoms**: biphasic illness: fever in 30-40%; cramps & voluminous watery diarrhea for 2-3 days, then dysenteria, with small bloody stool and tenesmus. Cough & meningismus in 40% of small children.
- **Complications**: Reiter syndrome, HUS, protein-loosing enteropathy, e. nodosum, keratoconjunctivitis, pneumonia, seizures, and encephalopathy.
- **Treatment**: Treat all patients. Ciprofloxacin 500 mg BID x 5 days, or TMP-SMX DS po BID x 5 days.

Yersinia Enterocolitica

- **Spread**: food-borne (undercooked meats & oysters) & contact with infected pets.
- **Children < 5y**: fever, abdominal cramps, diarrhea for 1 or more weeks.
- **Children > 5 y**: mesenteric adenitis, or ileitis; sometimes ileal perforation.
- **Adults**: acute diarrhea, followed 2-3 weeks later by arthritis, erythema nodosum, or erythema multiformis.
- **Post-infectious complications**: Reiter S., thyroiditis, myocarditis, pericarditis, glomerulopathy, ankylosing spondylitis, IBD, e. nodosum, e. multiformis, & HUS.
- **Treatment**: ORS & support. In septicemia: gentamicin 5 mg/kg iv; 50% mortality despite treatment.

Plesiomona shigelloides

- **Source**: contaminated water or shellfish. Common in Japan.
- **Symptoms**: variable; from watery diarrhea, with abdominal pain, vomiting and fever, to dysenteria and sepsis. Usually self-limited, but 30% have diarrhea > 3 weeks. Sepsis in cirrhosis and immunocompromised.
- **Complications**: Meningitis, osteomyelitis. Endophthalmitis.
- **Diagnosis**: Stool culture.
- **Treatment**: only in severe or prolonged disease; Ciprofloxacin 500 mg BID

Foodborne Bacterial Infections with Toxin Mediated Diarrhea

Specific Causes of Foodborne Diarrhea – Toxin Mediated
Cholera

- Endemic in the Gulf Coast (Lousiana & Texas)
- Vibrio colonizes small bowel and produces cytotonic toxin, activating adenylate cyclase, causing secretory diarrhea.
- **Spread**: Water or food contaminated with stools.
- **Incubation**: 18-40 hours
- **Symptoms**: vomiting and abdominal distension, followed by diarrhea of > 1 L/hour; dehydration & shock.
- **Diagnosis**: Stool culture neutralized by antisera. Stool PCR.
- **Treatment**: ORS; IV fluids only until ORS covers needs. Tetracycline 500 mg QID x 5 days.

Staphylococcus aureus

- After salmonella, second cause of food-borne diarrhea in USA
- **Spread**: contaminated food with preformed cytotoxic, heat-stable, enterotoxin A. No WBC in stool. Contamination most common in high salt & high sugar foods.
- **Incubation**: 1-6 hours
- **Duration**: 24-48 hours
- **Symptoms**: nausea, profuse vomiting, abdominal cramps followed by diarrhea.
- **Treatment**: Supportive.

Specific Causes of Foodborne Diarrhea – Toxin Mediated
Enterotoxigenic E. coli (ETEC)

- Major cause of Traveler's diarrhea, and of diarrhea in infants and toddlers in underdeveloped areas.
- Cytotonic toxins (one heat-labile, and two heat-stable), activate adenylate & guanilate cyclase.
- **Spread**: fecal-oral.
- **Symptoms**: Profuse watery diarrhea, with abdominal cramps and nausea. May have low-grade fever.
- **Duration**: 3-5 days
- **Diagnosis**: stool culture and serotype.
- **Treatment**: ORS. *Mild*: Pepto-Bismol 2 tab QID, or Loperamide. *Severe/dysenteria*: Bactrim DS 1 BID x 3d, Ciprofloxacine 500 mg BID x 3 days.

Specific Causes of Foodborne Diarrhea – Toxin Mediated
Enterohemorrhagic E. coli (EHEC)

- Serotypes E. coli O157:H7 (sorbitol negative), & O26:H11, with shiga-like verotoxin I & II; cytotoxic to endothelial cells and enterocyte. (After antibiotics, Klebsiella Oxytoca gives similar clinical picture).
- Sporadic and epidemic illness.
- **Spread**: ingestion of contaminated ground beef, unpasteurized milk or apple cider. Person-to-person.
- **Symptoms**: watery diarrhea with abdominal cramps and tenderness, followed by bloody stool with low-, or no fever.
- **Complications**: HUS or TTP in 7%.
- **Treatment**: support. Antibiotics increase risk of HUS or TTP

Specific Causes of Foodborne Diarrhea – Toxin Mediated
Clostridium perfringens

- Source: food poisoning due to meats cooked in bulk, with inadequate internal temperature to kill spores, and later inadequate cooling before reheating for consumption. [C. perfringes with **chromosomal** cpe]
- Heat-labile cytotoxic enterotoxin.
- **Incubation**: 8-24 hours.
- **Duration**: 24 hours.
- **Symptoms**: severe watery diarrhea, with intense abdominal cramps. Can cause antibiotic associated diarrhea without pseudomembranes (**plasmid** cpe).
- **Diagnosis**: c. perfringens enterotoxin in stool, by Latex agglutination.
- **Treatment**: a) Food poisoning: support, b) Antibiotic associated colitis: Flagyl 500 mg po TID x 10 days

Bacillus cereus - Diarrhea

- **Source**: foods cooked slowly at low temperature, permitting bacterial proliferation.
- B. cereus colonizes the small bowel and produces heat-labile cytotonic toxin.
- **Incubation**: 6-14 hours
- **Duration**: 20-36 hours
- **Symptoms**: diarrhea and generalized abdominal cramps; vomit is less frequent.
- **Diagnosis**: clinical features
- **Treatment**: ORS, support.

Bacillus cereus - Vomiting

- **Source**: cooked food that stays unrefrigerated for long time, and has short "final cooking", like "fried rice".
- Preformed heat-stable toxin
- **Incubation**: 2 hours
- **Duration**: few hours
- **Symptoms**: vomiting and abdominal cramps. Diarrhea is infrequent.
- **Complications**: Acute liver failure & lactic acidosis due to mitochondrial toxicity from cereulide.
- **Diagnosis**: clinical features
- **Treatment**: support.

Vibrio Parahaemolyticus

- **Source**: raw or poorly cooked fish or shellfish.
- **Pathogenesis**: variable; cytotonic and/or cytotoxic toxin, and/or mucosal invasion
- **Incubation**: 12-24 hours
- **Duration**: hours to 10 days
- **Symptoms**: explosive watery diarrhea, abdominal cramps, nausea, vomiting, headache; fever in 25%. Infrequent dysenteria/ bloody stool
- **Diagnosis**: stool culture in TCBS agar medium.
- **Treatment**: support. For prolonged illness: Tetracycline

Specific Causes of Foodborne Diarrhea – Toxin Mediated
Vibrio vulnificus & V. alginolyticus

- **Source**: contaminated seawater or seafood; oysters; Gulf of Mexico, East & West Coast
- **Incubation**: 3-7 days.
- **Symptoms**: diarrhea, otitis media, cellulitis with myonecrosis or fasciitis.
  Cirrhotic, immunocompromised host, Fe overload patient, diabetic, & alcoholic: Sepsis, with skin necrosis or bullae in 50-75%; 55% mortality.
- **Diagnosis**: culture from blood or necrotic tissue.
- **Treatment**: [Doxycicline 100 mg IV BID + ceftazidime 2 g IV q 8 h], or Ciprofloxacin 400 mg IV BID

Antibiotic Related Diarrhea

Enigmatic ARD

- **<u>Cause</u>**: antibiotic drug associated; probably carbohydrate and/or bile salt malabsorption due to altered bowel flora.

- **<u>Frequency</u>**: causes 80 % of ARD

- **<u>Symptoms</u>**: watery diarrhea. No pseudomembranes nor hemorrhage.

- **<u>Treatment</u>**: discontinue antibiotics, Zn suplementation, Probiotics (Culturelle – Lactobacillus GG); hydration, Loperamide up to 16 mg/d

Antibiotic Related Diarrhea (ARD)
Clostridium difficile

- Overgrowth of C. difficile during or up to 6 weeks after antibiotics, or MTX, cyclophosphamide, 5-FU. Causes 20% of ARD.
- Cytotoxic toxin A&B
- **Symptoms**: watery diarrhea (sometimes bloody), abdominal pain, fever, leukocytosis; may have hypoalbuminemia. (K. oxytoca gives severe hemorrhagic antibiotic-related diarrhea)
- **Diagnosis**:
  - Toxin B(+) in stool (EIA, PCR, or cytotoxicity);
  - Flex. Sigm. with typical findings +/- Bx.;
  - WBC in stool may be (-); Stool lactoferrin (+) in 64-77%.

Detection of C. difficile

Toxin Assays

Test	Pro	Con
Cytotoxicity (Gold Standard; tests cytopathic effect)	Very sensitive (10 pg Toxin B) Very specific	Expensive Takes 2 days
EIA toxin A&B	Very specific (>95%) Cheap Takes < 24 h	Low sensitivity (60-90%) (100-1000 pg toxin B)
PCR (tests gene for toxin B)	Rapid (< 4h) Very sensitive Very specific (80-99%)	Expensive Does not differentiate colonization from infection

Bacteria Detection

Test	Pro	Con
GDH (common antigen testing for glutamate dehydrogenase)	High sensitivity Rapid Cheap	Intermediate specificity Does not differentiate colonization from infection
Stool culture (anaerobic stool culture)	Extremely sensitive	Turn over: 3 days Does not differentiate colonization from infection

Antibiotic Related Diarrhea (ARD)
Clostridium difficile

- **<u>Complications</u>**: protein loosing enteropathy, ascites, toxic megacolon requiring colectomy; risk high in >64y/o, immunosupression & hospital acquisition.
- **<u>Risk Factors for complicated nosocomial PMC</u>**:
    - WBC > 20K,
    - Creat > 2 mg/dL
    - (Risk: 0=10%; 1=28%; 2=60%)
- Mortality due to "hypervirulent strain" PMC with "binary toxin" & "deletion in tcdC": 16% over expected by Dx.
- Mortality due to "Fulminant" PMC: 53% (most within initial 48h)

Antibiotic Related Diarrhea (ARD)
Clostridium difficile

- **Treatment**:
  - **Initial:**
    - **Severe disease or IBD:** Vancomycin 125 mg po or rectal QID x 14d (failure 4%, recurrence 20%, $600) , or
    - **Mild to Moderate disease:** Metronidazole 500 mg po QID x 14 d (failure 13%, recurrence 20%, $20)).
  - **First relapse**: treat as above
  - **Ileus or Fulminant Colitis**:
    - Vanco 500 mg po, or 500 mg in 100 mL 0.9% NaCl 1h-retention enema QID, **plus**
    - Metronidazol 500 mg IV q8h or 500 mg IV q6h.
  - **Critically ill**:
    - IVIG 400 mg/kg IV +/-
    - total colectomy if persistent hypotension, lack of response to medical therapy, megacolon or perforation.
  - **Multiple Relapses**: See Surawicz protocol later.

Updated Infectious Diseases Society of America guidelines for the treatment of CDI (2010)

Clinical classification	Clinical features	Recommended treatment
Mild or moderate disease	-Leukocytosis with a WBC count ≤15 × 10^9/l and -Serum creatinine level <1.5 times baseline level	Metronidazole administered orally at a dose of 500 mg three times daily for 14 days
Severe disease or with IBD	-Leukocytosis with a WBC count ≥15 × 10^9/l and/or -Serum creatinine level ≥1.5 times baseline level	Vancomycin administered orally at a dose of 125 mg four times daily for 14 days
Complicated disease	Hypotension, ileus, megacolon	-Vancomycin administered either orally or by nasogastric tube at a dose of 500 mg four times daily, plus - Metronidazole administered intravenously at a dose of 500 mg every 8 h. -If complete ileus is present, consider adding a rectal instillation of vancomycin (500 mg in 100mL of 0.9% NaCl, 1 hour retention enema) QID. -All treatments to be continued until the patient improves

# Treatment options for refractory and recurrent CDI

Table 1 | Treatment options for refractory and recurrent CDI

Type of therapy	Currently available agents	Agents under development
Antimicrobial agents	Vancomycin, metronidazole, nitazoxanide*, tigecycline*	Fidaxomicin, ramoplanin, CB-183315
Nonantimicrobial agents	*Saccharomyces boulardii*, *Lactobacillus plantarum*	NA
Biotherapeutic agents	Fecal microbiota transplant	Nontoxigenic *Clostridium difficile*
Intraluminal toxin-neutralizing agents	NA	Bovine whey protein, tolevamer
Systemic antibody approaches	Intravenous immunoglobulin	Monoclonal antibodies, active vaccines

Data obtained from Gerding & Johnson (2010).[103] *The efficacy of these drugs in the treatment of refractory CDI has been shown in case reports. Abbreviations: CDI, *Clostridium difficile* infection; NA, not applicable.

Treatment algorithm for **recurrent** *Clostridium difficile* infection
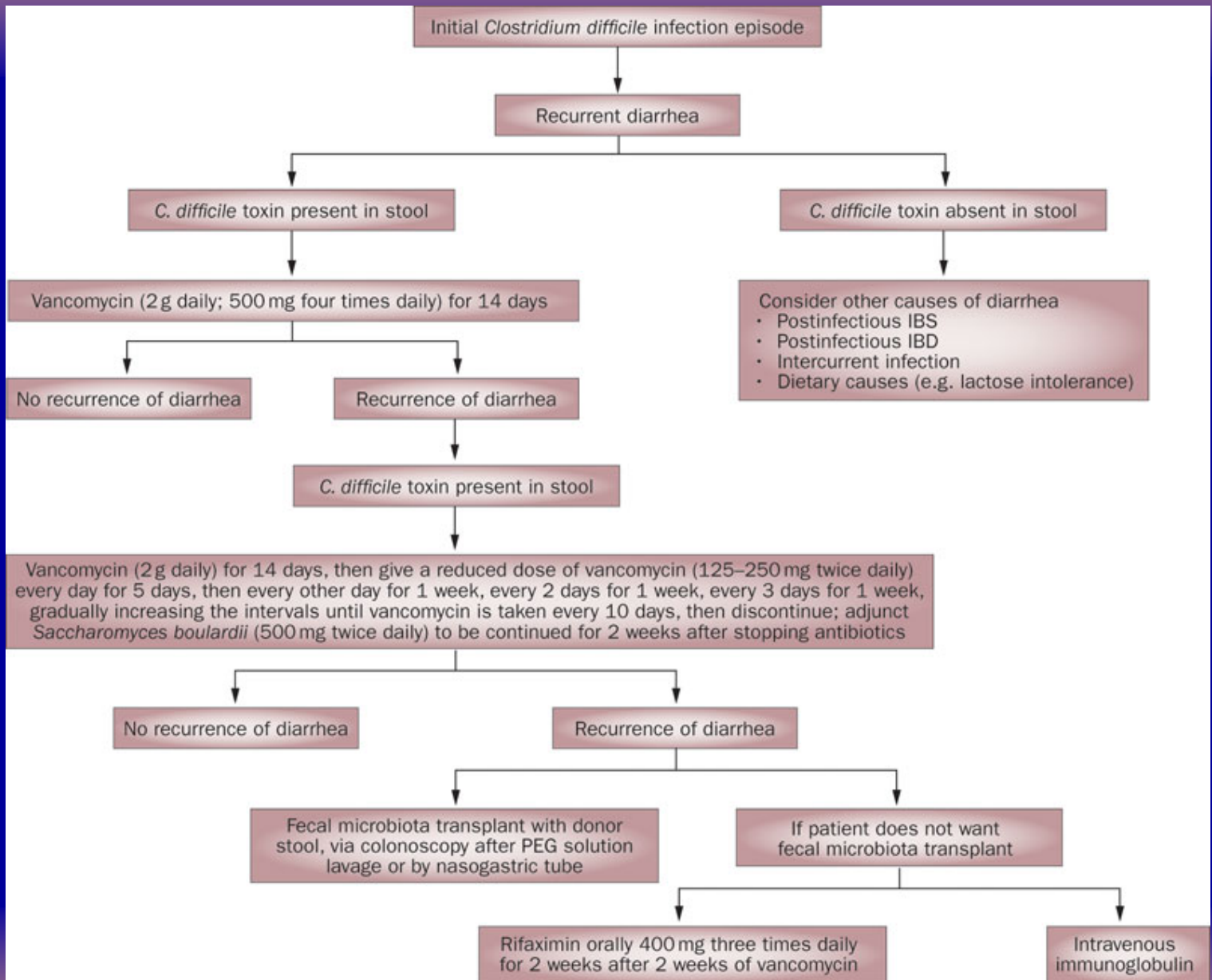
Fecal Flora Reconstitution (FFR) or Fecal Microbiota Transplant

- **Donors:**
  - **Inclusion** in this order;
    - 1. intimate domestic partners,
    - 2. family members or those living in the same household,
    - 3. close friends
  - **Exclusion** of donors:
    - recent antibiotic use,
    - current or recent diarrheal illness,
    - hospital or health care worker, and
    - at-risk sexual behaviors
  - **Screening for illness**:
    - Donor stool screened for C. difficile, and enteric pathogens;
    - Serology for HIV and viral hepatitis.
  - Stool is spontaneously passed or prompted with an small dose of Mg Citrate.

Fecal Flora Reconstitution (FFR)

Rohlke, F., Surawicz, C. M. & Stollman, N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J. Clin. Gastroenterol.* **44**, 567–570 (2010)

- **Preparation of recipient:**
  - Informed consent
  - The patients' prior treatment regimens (generally vancomycin) is stopped 1 to 3 days before the FFR procedure.
  - Patient is prepped for the FFR with a standard 4.0 liter polyethelyne glycol purge taken the evening before their procedure

Fecal Flora Reconstitution (FFR)

- **Preparation and delivery of donated stool:**
  - In a room separate from the procedure area donated stool is suspended in 350 mL of **nonbacteriostatic saline**, with manual shaking in a large suction canister.
  - To prevent clogging of the colonoscope channel, the suspension is then poured once or twice through a filter. The filter is made of multiple 4×4 gauze sheets opened up, and draped over another suction canister, and then held in place by rubber bands. This process presumably does not significantly affect the bacterial content.
  - Stool is infused through the colonoscope channel into the TI or cecum, with the help of 60 cc syringes.
  - Immodium 2 tablets after procedure and 2 tablets 6 hours later.
  - Recipients are instructed to remain at bed rest for several hours after the colonoscopy, or the remainder of the day of infusion, as much as possible.
  - A bland diet is advanced slowly.

NIH Recommended Testing

Donor

Stool Testing

- *C. difficile* toxin,
- Enteric bacterial pathogens (including specifically *Listeria monocytogenes*, *Vibrio cholera* and *Vibrio parahemolyticus*),
- Parasites such as Giardia (Giardia antigen test) Cryptosporidium (Cryptosporidium antigen test), and Isospora (acid-fast stain),
- Rotavirus;
- H. Pylori stool Ag

Donor & Recipient

Blood Testing

- **Donor blood** must be screened for hepatitis A (IgM), B (HBsAg, anti-HBc (IgG and IgM), and anti-HBsAg) and C (HCV antibody) viruses, HIV types 1 and 2, and syphilis.
- **Recipients blood** is tested for HIV 1 and 2, Hepatitis A, C, and syphilis.

RePOOPulate

- Synthetic stool made with 33 of 62 bacterial isolates from the stool of a healthy 41 years old woman.

- Isolates were chosen because they were "commensal", susceptible to multiple antibiotics, and easy to culture.

- Bacterial ratios were derived from those observed in healthy population.

- Presentation: 100 ml pre-reduced sterile 0.9% normal saline with an estimated concentration of 3.5×10^9 colony-forming units/ml. The bacterial suspension was placed in a reduced atmosphere in a double-sealed container at 4° C, and used within 24 hours

Antibiotic Related Diarrhea (ARD)
Clostridium perfringes Type A

- Proliferation of C. perfringes type A after antibiotics
- Causes 5-15% of cases of pseudomembranous colitis.
- **Symptoms**: watery diarrhea after antibiotics, abdominal pain. May give fever & leukocytosis.
- **Dx**: culture of c. perfringes in stool (plasmid cpe (+)); have to order specifically.
- **Treatment**: discontinue antibiotics.

Antibiotic Related Diarrhea (ARD)
Klebsiella Oxytoca

- Proliferation of K. oxytoca in the colon (downstream from cecum) after antibiotics (usually penicillin derivate +/- clavulanate); toxin mediated.
- **Symptoms**: sudden onset of hemorrhagic diarrhea 3 to 7 days after antibiotics; abdominal cramps, leukocytosis and high CRP.
- **Diagnosis**: culture of K. oxytoca (have to order specifically)
- **Colonoscopy**: segmental hemorrhagic colitis (edema + petechiae +/- erosions or linear ulcers; no pseudomembranes), more severe in right side of colon, with rectal sparing.
- **Treatment**: discontinue antibiotics and NSAIDs; resolution in 4 days.

Antibiotic Related Diarrhea (ARD)
Others

- *Salmonella species*: treat with cipro 500 mg po QID x 5-7 days

- *Staphyloccocus aureus: treat with Vancomycin 500 mg po QID x 10 days. (Need to give specific order to culture for S. aureus).*

Diarrhea due to Protozoa

Giardia lamblia

- **Prevalence**: healthy adults < 2%; homosexuals 4-18%.
- **Symptoms**: intermittent bloating and abdominal cramps, with watery and low grade steatorrhea; "sulfuric belching". Rare fever.
- **Diagnosis**: giardia Ag in stool; Duodenal aspirate, string-test, or Bx.
- **Treatment**: Metronidazole 250 mg po TID x 5-7 days; Quinacrine 100 mg TID x 5 days. Patients with IgA or IgM deficiency need 6-8 weeks of therapy. Nitazoxanide (Alinia) 500 mg TID x 3 days.

Cryptosporidium parvum

- **Transmission**: usually person-to-person; domestic animal reservoir.
- Causes 4% of acute diarrhea in small children; frequent in AIDS.
- **Symptoms**:
  - a) Immunocompetent host: explosive, profuse watery diarrhea, with abdominal cramps; lasts 5-11 days.
  - b) Immunocompromised host: extremely severe diarrhea (up to 17 L/day), which may persist for months. Fever in 30%.
- **Diagnosis**: AFB stain or fluorescent Ab in stool; small bowel Bx.
- **Treatment**:
  - a) Immunocompetent: Nitazoxanide (Alinia) 500 mg TID x 3 days
  - b) Immunosupressed: Paramomycin 500 mg with food, TID x 2-4 weeks + HAART

Amebiasis

- **Prevalence**: 1-5% of US population; 20-30% in male homosexuals. Only Zymodemes II & XI are invasive.
- **Symptoms**: usually asymptomatic. Bloody diarrhea, fever, abdominal cramps, malaise, and tenesmus. Cecal involvement more common than rectal disease. Infrequent toxic megacolon or perforation.
- **Diagnosis**: Stool Ag. O&P x 4-6 samples. Colonoscopy or Flex. Sigm with Bx (non-specific colitis). Serology (+) in 88% of colitis (99% in liver abscess). Stool WBC usually (-) due to destruction.
- **Treatment**: {Metronidazole 750 mg TID x 5-10 d, or Tinidazole 2 gm/d x 3 d} + {Diloxanide 500 mg TID x 10 d, or Iodoquinol 650 mg TID x 20 d or Paramomycin 25-35 mg/k per day, divided TID, x 7 days}

Balantidium coli

- **Source**: ingestion of contaminated short stalk vegetables

- **Symptoms**: frequently asymptomatic; mild to moderate, acute or chronic recurrent diarrhea.

- **Treatment**: Tetracycline 500 mg QID x 10 days

Isospora belli

- **Transmission**: fecal-oral
- More common in children and male homosexuals.
- **Symptoms**: fever, headache, abdominal cramps, diarrhea with mild malabsorption. In normal host lasts a few weeks; lasts months to years in immunocompromised host.
- **Diagnosis**: duodenal aspirate & Bx. Stool incubated at room temperature x 2 days; then Zn sulfate flotation & AFB stain.
- **Treatment**: Bactrim

Cyclospora cayetanensis

- **Source:** contaminated fresh berries or water
- **Symptoms**: abrupt onset of watery diarrhea; fever in 30%. Diarrhea improves in 3-4 days, and then relapses. Anorexia, fatigue, nausea, malabsorption with 5-10% weight loss.
- **Duration**: 2-12 weeks, with abrupt end.
- **Pathology**: Acute & chronic inflammation in distal duodenum, with villous atrophy, and/or crypt hyperplasia.
- **Diagnosis**: spherical 9-10 micron with red stain in AFB. Duodenal aspirate (+) in 25%
- **Treatment**: Bactrim DS BID x 7-10 days.

Microsporidiosis

Enterocytozoan bienusi & Encephalitozoon intestinalis

- **Symptoms**: self limited diarrhea in immunocompetent.
  In immunocompromised gives chronic diarrhea for months.

- **Treatment**:
  - a) Enterocytozoan bienusi: fumagillin 60 mg/d x 14 days.
  - b) Encephalitozoon intestinalis: albendazole 400 mg BID x 3-4 weeks.

Diarrhea due to Fish & Shellfish associated Toxins

Ciguatera

- Ciguatoxin accumulates in large-fish muscles after eating smaller fish; is heat-stable
- Common in fish from Hawaii & Florida
- **Associated fish**: Barracuda, red-snapper, amberjack, grouper, and goatfish.
- **Onset**: minutes to 30 hours
- **Duration**: 1-9 days; sensory disturbance for months.
- **Symptoms**: nausea, vomiting, cramps, diarrhea, malaise, myalgia, arthralgia, blurred vision, pain in teeth, reversal of hot-cold sensation, sharp pain in extremities, bradycardia; respiratory paralysis in severe cases.
- **Treatment**: Mannitol 20% solution; 1 g/kg IV over 45 min. Atropine for bradycardia. Gastric lavage and cathartics. May need respiratory support. Amitryptiline for chronic neuropathy.

Scombroid

- Formation of histamine & saurine in flesh of fish by action of marine bacteria
- Fish tastes sharp and peppery.
- Fish from Hawaii & California.
- **Associated fish**: tuna, mackerel, albacore, bonito, skip jack, mahi-mahi.
- **Onset**: minutes to 2 hours
- **Duration**: 4-10 hours.
- **Symptoms**: flushing, headache, dizziness, burning in mouth, abdominal cramps, nausea, vomiting, diarrhea & bronchospasm.
- **Treatment**: anti-histamines + H-2 blockers, bronchodilators; cathartics & gastric lavage.

Paralytic Shellfish Poisoning

- Heat-stable saxitoxins concentrated by bivalved mollusks, after ingestion of dinoflagellates; worse in "red tide".
- New England, West Coast, Alaska.
- Outbreaks in summer.
- **Onset**: 30 minutes - 3 hours; may be fatal in hours.
- **Duration**: hours to few days.
- **Symptoms**: paresthesias in lips, mouth, face and extremities; nausea, vomiting, diarrhea, dysphonia, dysphagia, weakness, paralysis and respiratory insufficiency.
- **Treatment**: respiratory support; gastric lavage and cathartics.

Neurotoxic Shellfish Poisoning

- Dinoflagellate with brevotoxin, concentrated by mollusks. Associated to "red tide".
- Heat-stable toxin
- Gulf Coast, North Carolina, and Florida
- **Onset**: few hours
- **Duration**: hours to days.
- **Symptoms**: paresthesias, reversal of hot-cold sensation, nausea, vomiting, diarrhea, ataxia. Respiratory symptoms after aerolization.
- **Treatment**: symptomatic

Diarrheic Shellfish Poisoning

- From eating mussels, scallops, or clams who have okadaic acid or dinophysistoxin-1
- Described in Japan & Europe; the organism has been found in U.S. coast.
- **Onset**: few hours
- **Duration**: hours to days.
- **Symptoms**: nausea, vomiting, abdominal pain & diarrhea.
- **Treatment**: symptomatic

Amnestic Shellfish Poisoning

- From eating shellfish (Razor clams, Dungeness crabs), and anchovies who have domoic acid.
- Described in Canada; toxin-producing blooms found in Maine & Texas
- **Onset**: few hours
- **Duration**: hours to days.
- **Symptoms**: nausea, vomiting, abdominal cramps, headache, diarrhea, and loss of short-term memory. Anterograde memory deficits may persist for months; neuronal necrosis in hippocampus and amygdala.
- **Treatment**: symptomatic

Specific Causes of Acute Diarrhea - Viral
Other Virus

- HSV & CMV: may cause proctitis and diarrhea after anal sex. Colitis and diarrhea in immunocompromised patients.

- Adenovirus, coronavirus, astrovirus, and calicivirus.

Common Infectious Etiologies

- **WATERY DIARRHEA**
- *6% of stool studies (+):*
- Salmonella 38%
- Campylobacter 32%
- Shigella 21%
- E. coli O157:H7 3%
- Cryptosporidium 3%
- Listeria 1%
- Yersinia 1%
- Vibrio 1%

- **BLOODY DIARRHEA**
- *20-30% of stool studies (+):*
- E. coli O157:H7 39%
- Shigella 35%
- Campylobacter 15%
- Salmonella 13%
- K. oxytoca

Second Line Diagnostic Tests

Tests suggestive of Malabsorption

- **Decreased**:
  - Hemoglobin,
  - RBC folate,
  - Vitamin B_{12},
  - Transferrin saturation,
  - Ferritin,
  - carotene,
  - albumin,
  - cholesterol,
  - Mg,
  - Ca

- **Elevated**:
  - Urine oxalate,
  - Prothrombin time

Second Line Diagnostic Tests

- **Qualitative fecal fat** (while in >/= 100 gm/d fat diet):
  - 90% sensitive & 90% specific.
  - Neutral fat (dietary triglycerides) detected with alcohol + sudan stain.
  - Fatty acids (endogenous phospholipids & cholesterol) detected with glacial acetic acid + sudan.
  - False (+) with suppositories & mineral oil use.

Second Line Diagnostic Tests

- **72 hours stool fat**: (with food intake diary)
  - Start 100 gm/d fat diet at least 2 days before stool collection.
  - Values of 7-14 g/24 h can be seen in secretory, malabsorption, or osmotic diarrhea.
  - Values > 14 g/24 h, indicate malabsorption or maldigestion.
  - Values =/> 9.5 g fat/100g of stool suggest pancreatic insuficiency, or biliary steatorrhea.
  - Values < 9.5 g fat/100 g of stool suggest mucosal disease.

Second Line Diagnostic Tests

- **Bile Acid Malabsorption assay:**
  - 7α-hydroxy-4-cholesten-3-one (7C4) in serum (Prometheus Lab)
  - Fibroblast growth factor 19 serum level
- **D-Xylose absorption test**:
  - Useful for patchy mucosal disease.
  - Overnight fast, then give 25 g of D-xylose and 1 liter of water; immediately after collect 5 hour-urine; obtain blood sample 1 hour after D-xylose ingestion.
  - Normal: >/= 5g D-xylose in 5-hour urine & >/= 20 mg/dl D-Xylose in serum (1.3 mmol/L/1.73m^2)
  - False (+) & false (-) in 30%.
  - False (+) in: portal HNT, ascites, decreased GFR, use of NSAID's
- **Alpha-1-antitrypsin stool clearance**:
  - Serum sample + random stool sample from 24 h stool
  - Excellent test for protein loosing enteropathy; false (-) in Menetrier's disease.

Second Line Diagnostic Tests

- **Peptides & Hormones**:
  - **24 hour urine collection for**:
    - 5-HIAA (carcinoid),
    - VMA + metanephrine (pheochromocytoma),
    - histamine.
  - **Serum for**:
    - Cortisol, TSH, Free T4 and T3.
    - VIP (if secretory diarrhea > 1 L/d),
    - fasting Gastrin (Z-E syndrome),
    - Calcitonin (medullary Ca. of thyroid),
    - Glucagon (glucagonoma),
    - Chromogranin A (carcinoid & neuroendocrine tumors),
    - Tryptase (mast cell disease & foregut carcinoids).
  - **Imaging**: Octreotide scan

24 hours 5-HIAA
## (Normal: 2-8 mg/day) (Most Carcinoids > 50 mg/d)

- Falsely high values (up to 30 mg/day):
  - Tryptophan-rich foods: avocados, pineapples, bananas, kiwi fruit, plums, eggplants, walnuts, hickory nuts, pecans, tomatoes, plantains
  - Drugs: acetaminophen, coumaric acid, guaifenisin, mephenisin, phenobarbital, reserpine, acetanilid, ephedrine, methamphetamine, nicotine, phentolamine, phenmetrazine, caffeine, flourouracil, melphalan, methocarbamol, phenacetin, mesalamine*
- Falsely low values:
  - Drugs: corticotrophin, ethanol, imiprimine, levodopa, MAO inhibitors, phenothiazines, aspirin, isoniazid, gentisic acid, methenamine, streptozotocin, heparin, methyldopa

Second Line Diagnostic Tests

- **Test used less often**:
  - Lactose Breath Test (25 g) vs. milk removal test, for milk intolerance.
  - Glucose Breath Test (50-100 g) vs. quantitative SB fluid culture, for bacterial overgrowth.
  - Schilling-II Test (radiolabeled B_{12} + IF) vs. Bx of terminal ileum, for TI disease.
  - Radiolabeled bile acid Test (75Se-HCAT) vs. Cholestiramine trial, for bile malabsorption
  - Pancreatic enzyme/bicarbonate Secretin Test vs. pancreas CT scan or EUS + pancreas enzyme trial
  - Fecal Elastase 1: low in pancreatic insufficiency causing steatorrhea.

EVALUATION OF CHRONIC DIARRHEA

LR Schiller
AJG May 2018
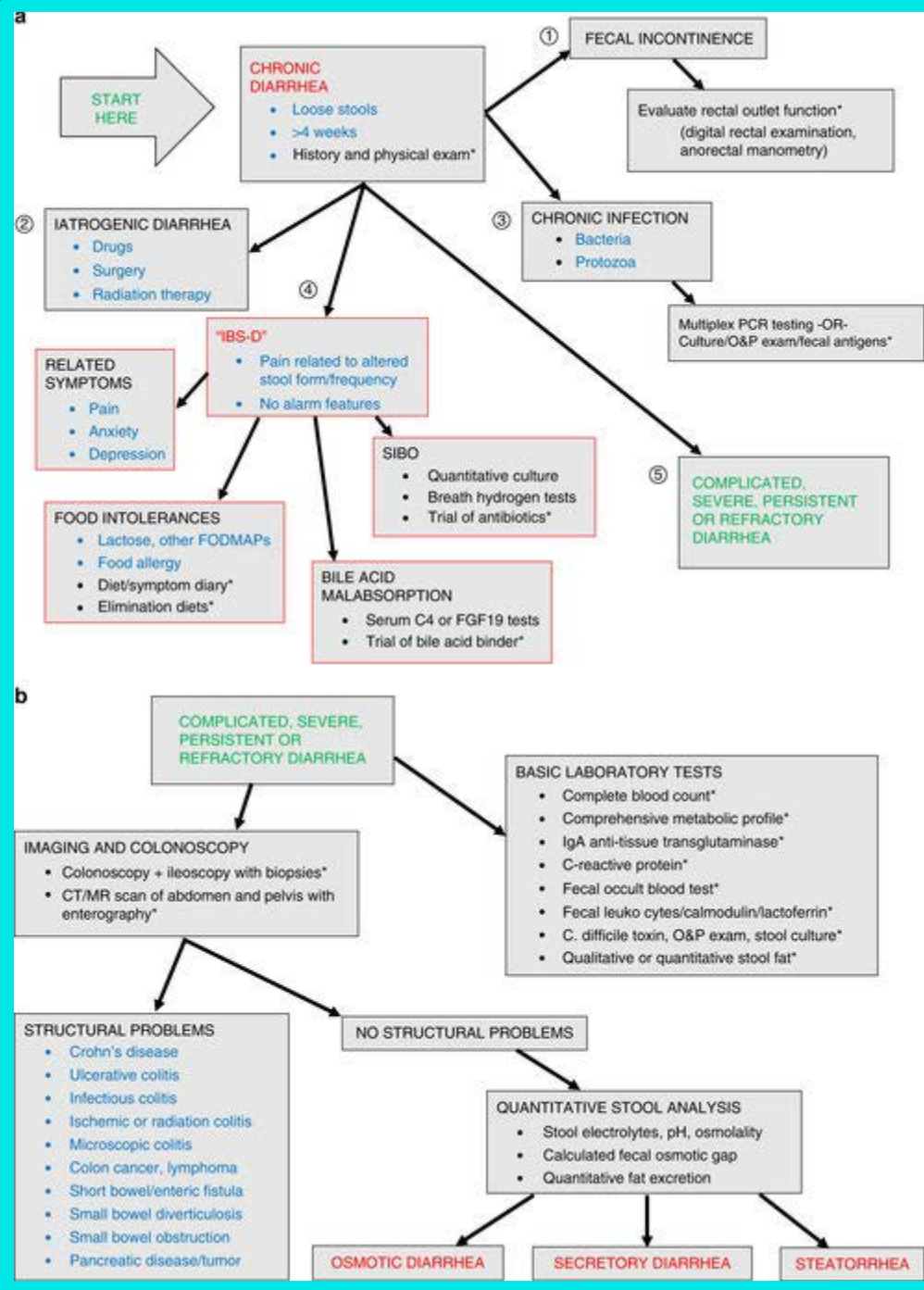
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OSMOTIC DIARRHEA

- Carbohydrate/sugar alcohol malabsorption
- Magnesium, sulfate, phosphate ingestion
- Use of PEG-containing laxatives

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- Review stool pH, fecal fat*
- Review medication list*
  - Prescription, OTC, and herbal drugs
- Stool magnesium, sulfate, phosphate, and PEG assays*
- Diet/symptom diary*
- Elimination diets*

SECRETORY DIARRHEA

- Microscopic colitis
- Medications, stimulant laxatives
- Bile salt malabsorption
- Celiac disease
- SIBO
- Chronic infections
- Endocrine diarrhea (systemic and tumor syndromes)
- Idiopathic secretory diarrhea

↓

- Review previous studies*
  - Imaging, biopsies
- Review medication list*
- Serum C4/FGF19 test
- Trial of bile acid binder*
- Endoscopy with small bowel biopsy*
- Small bowel aspirate for quantitative culture
- Breath hydrogen testing
- Stool culture/O&P exam/fecal antigens*
- Serum cortisol, TSH, and thyroxine levels
- Serum gastrin, VIP, calcitonin levels

STEATORRHEA

- Maldigestion
  - Exocrine pancreatic insufficiency
  - Duodenal bile acid deficiency
  - Classical SIBO
- Malabsorption
  - Mucosal disease (e.g., celiac disease)
  - Short bowel syndrome
  - Chronic bowel ischemia
  - Lymphatic obstruction

↓

- Endoscopy with small bowel biopsy*
- Small bowel aspirate for quantitative culture
- Breath hydrogen testing
- CCK-secretin test for exocrine pancreatic insufficiency
- Fecal elastase-1 or chymotrypsin test
- Therapeutic trial of pancreatic enzymes*
- Serum C4/FGF19 test

Physical Finding Clues in Chronic Diarrhea

Findings	Potential implications
Orthostasis, hypotension	Dehydration, neuropathy
Muscle wasting, edema	Malnutrition
Urticaria pigmentosa, dermatographism	Mast cell disease (mastocytosis)
Pinch purpura, macroglossia	Amyloidosis
Hyperpigmentation	Addison's disease
Migratory necrotizing erythema	Glucagonoma
Flushing	Carcinoid syndrome
Malignant atrophic papulosis	Kohlmeier–Degos disease
Dermatitis herpetiformis	Celiac disease
Thyroid nodule, lymphadenopathy	Medullary carcinoma of the thyroid
Tremor, lid lag	Hyperthyroidism
Right-sided heart murmur, wheezing	Carcinoid syndrome
Hepatomegaly	Endocrine tumor, amyloidosis
Arthritis	Inflammatory bowel disease, yersinosis
Lymphadenopathy	HIV, lymphoma, cancer
Abdominal bruit	Chronic mesenteric ischemia
Anal sphincter weakness, perianal dermatitis	Fecal incontinence

Patterns of stool composition in chronic diarrhea

Stool Weight < 200 g/day

Features	Possible Diagnosis
No objective evidence of diarrhea	Change in stool frequency, intermittent diarrhea, fecal incontinence, treatment with antidiarrheal drugs during collection
Hyperdefecation (increased frequency without excess volume)	Possible IBS, proctitis, abnormal rectal reservoir function
Abnormal consistency (unformed-runny stools)	Possible IBS
Elevated fecal osmotic gap	Presumed mild carbohydrate malabsorption or excess Mg intake from supplements
Steatorrhea	Malabsorption or maldigestion

Stool Weight > 200 g/day

Features	Possible Diagnosis
Secretory diarrhea without steatorrhea	Microscopic colitis or other cause of secretory diarrhea Carbohydrate malabsorption without steatorrhea
High fecal osmotic gap	Ingestion of poorly absorbed carbohydrates, malabsorption
Steatorrhea with or without carbohydrate malabsorption	Small bowel mucosal disease, small intestinal bacterial overgrowth, bile acid deficiency, pancreatic exocrine insufficiency
Osmotic diarrhea	Ingestion of poorly absorbed ions (e.g., magnesium, phosphate, sulfate) or osmotically active polymers (e.g., polyethylene glycol)
Unclassified	Blood or pus suggests inflammatory causes of diarrhea

Differential diagnosis of chronic watery diarrhea

Osmotic

Cause	Examples
Medications	Osmotic laxatives (Mg, SO_4, PO_4)
Unabsorbed sugars/sugar alcohols	Diet foods/drinks/gum (sorbitol, mannitol, others)
	Enzyme dysfunction (e.g., lactase, sucrase)

Secretory

Cause	Examples
Medications	Stimulant laxatives, antibiotics, many others
Small intestinal bacterial overgrowth	
Microscopic colitis	
Endocrine	
Tumors	Carcinoid, gastrinoma, medullary thyroid cancer, VIPoma
Systemic	Adrenal insufficiency, hyperthyroidism
Bile salt malabsorption	Ileal resection, postcholecystectomy, idiopathic
Non-invasive infections	Giardiasis, cryptosporidiosis

Differential diagnosis of chronic fatty and secretory diarrhea

Fatty Diarrhea

Cause	Examples
Maldigestion	Decreased duodenal bile salt concentration (cirrhosis, bile duct obstruction, ileal resection)
	Pancreatic dysfunction (chronic pancreatitis, cystic fibrosis, duct obstruction)
Malabsorption	Mucosal disease (celiac sprue, tropical sprue, giardiasis, Whipple's disease, chronic mesenteric ischemia)
	Short bowel syndrome
	Small intestinal bacterial overgrowth (diabetes mellitus, scleroderma, prior bowel surgery)
	Lymphatic obstruction

Secretory Diarrhea

Cause	Examples
Inflammatory bowel disease	Ulcerative colitis, Crohn's disease
Malignancy	Colon cancer, lymphoma
Radiation colitis/enteritis	
Mastocytosis	
Invasive or inflammatory infections	*Clostridium difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis
Ischemia	

Differential diagnosis of IBS-D and diagnostic strategies

Diagnosis	Estimated prevalence in IBS-D	Diagnostic strategy
Food intolerances	20–67%	Diet and symptom diary→exclusion diet
Bile acid malabsorption	10–40%	SeCHAT retention, C4 or FGF-19 assay; trial of bile acid sequestrant
Small intestinal bacterial overgrowth	23–45%	Quantitative culture of small intestinal aspirate, breath hydrogen testing; trial of antibiotic therapy
Post-infectious IBS	28–58%	Anti-cytolethal distending toxin B and anti-vinculin antibody assays
Microscopic colitis	5–10%	Colon biopsies (from above rectum)
Celiac disease	0.4–4%	IgA anti-tissue transglutaminase antibody and total IgA assays; duodenal biopsy
Pancreatic exocrine insufficiency	unknown	Fecal elastase-1 concentration; trial of pancreatic enzyme replacement
Rapid or slow intestinal transit	unknown	Scintigraphic or capsule-based transit study