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

<table>
<thead>
<tr>
<th>Source</th>
<th>Contribution mL</th>
<th>TOTAL IN &amp; OUT/day mL</th>
<th>Na mM/L</th>
<th>K mM/L</th>
<th>Ca, Mg, NH₄ mM/L</th>
<th>Cl mM/L</th>
<th>HCO₃ mM/L</th>
<th>Other Anions</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>2,000</td>
<td>2,000</td>
<td>variable</td>
<td>variable</td>
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<tr>
<td>Saliva</td>
<td>1,500</td>
<td>3,500</td>
<td>-0</td>
<td>variable</td>
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<tr>
<td>Gastric</td>
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<td>6,000</td>
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<td>variable</td>
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<tr>
<td>Bile</td>
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<td>-0</td>
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<td></td>
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<tr>
<td>Pancreas</td>
<td>1,500</td>
<td>8,000</td>
<td>-0</td>
<td></td>
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<tr>
<td>Jejunum</td>
<td>1,000</td>
<td>9,000</td>
<td>130</td>
<td>6</td>
<td>variable</td>
<td>90</td>
<td>30</td>
<td>0</td>
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<tr>
<td>Ileum</td>
<td>0</td>
<td>3,500</td>
<td>140</td>
<td>8</td>
<td>10</td>
<td>60</td>
<td>70</td>
<td>0</td>
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<tr>
<td>Colon</td>
<td>0</td>
<td>1,500</td>
<td>-1,300</td>
<td>10</td>
<td></td>
<td>70</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Stool</td>
<td>200</td>
<td>40</td>
<td>90</td>
<td>20</td>
<td>15</td>
<td>30</td>
<td>80-180</td>
<td></td>
</tr>
</tbody>
</table>
Fluid Entering (per day)

- Oral intake 2 L
- Salivary 1.5 L
- Biliary 0.5 L
- Gastric 2.5 L
- Pancreatic 1 L
- Intestinal 1 L

Fluid Reabsorbed

- Small intestine 7.0 L (max 12 L)
- Large intestine 1.4 L (max 5 L)

100 ml
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 SO₄ or PO₄ 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: Phenolphthalein, 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:
  – c) Hormone-producing tumors: VIPoma, ganglioneuromas, medullary carcinoma of thyroid, gastrinoma, carcinoid, glucagonoma, mastocytosis, villous adenoma.
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.
  
  
  – 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 Diarrhea

• Food ingestion:
  – **Poultry**: salmonella, campylobacter, shigella.
  – **Ground beef, unpasteurized juice**: Entero-Hemorrhagic E. coli.
  – **Pork**: 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 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: $1-10^3$
- Entamoeba histolytica: $10-10^2$
- Giardia lamblia: $10-10^2$
- Shigella: $10-10^2$
- Campylobacter jejuni: $10^2-10^6$
- Salmonella: $10^5$
- Escherichia coli: $10^8$
- Vibrio cholerae: $10^8$
Diagnostic Workup
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 (+)

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

BLOODY DIARRHEA
20-30% Stool studies (+)

- Salmonella
- Campylobacter
- Shigella
- EHEC
- Cryptosporidium
- Listeria
- Yersinia
- Vibrio
- EHEC
- Shigella
- Campylobacter
- Vibrio
- Salmonella
Complications & Extraintestinal Manifestations of 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 losing 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
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
  – Community outbreak, or food handlers.
Initial Diagnostic Tests

- **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)
- **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)
  - Shigella, 95% are FL(+) @ titer > 1:200. (Guerrant et al. J Clin Microbiol, 1992; 30:1238-42)
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
## Detection of C. difficile

### Toxin Assays

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

### Bacteria Detection

<table>
<thead>
<tr>
<th>Test</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GDH</strong> (common antigen testing for glutamate dehydrogenase)</td>
<td>High sensitivity Rapid Cheap</td>
<td>Intermediate specificity Does not differentiate colonization from infection</td>
</tr>
<tr>
<td><strong>Stool culture</strong> (anaerobic stool culture)</td>
<td>Extremely sensitive</td>
<td>Turn over: 3 days Does not differentiate colonization from infection</td>
</tr>
</tbody>
</table>
Initial Diagnostic Tests

- **Stool culture**: send only in “high priority” patients, or if stool leukocytes, or lactoferrin is (+).
  - Stool should be fresh, and processed immediately.
  - Routine culture includes salmonella, shigella, and campylobacter; all other suspected pathogens should be “ordered by name”.
  - 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)
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 order the test by name.
  - 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 Test ordered

<table>
<thead>
<tr>
<th></th>
<th>O&amp;P</th>
<th>Comprehensive O&amp;P</th>
<th>C. Difficile toxin</th>
<th>Only on Special order</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U of L</strong></td>
<td>Giardia Ag, Cryptosporidium immunoassay</td>
<td>Giardia Ag &amp; Regular O&amp;P</td>
<td>EIA (Toxin A &amp; B) and GDH PCR (toxin B) for discrepancy Interval: 3/wk</td>
<td>Isospora Cyclospora Microsporidia</td>
</tr>
<tr>
<td><strong>VA</strong></td>
<td>Lactoferrin: (+) stool examined; (-) “negative”</td>
<td></td>
<td>PCR for toxin B Interval: 1/wk</td>
<td>Cryptosporidium Isospora Cyclospora Microsporidia</td>
</tr>
<tr>
<td><strong>Jewish</strong></td>
<td>Giardia Ag</td>
<td>Giardia Ag &amp; Regular O&amp;P</td>
<td>EIA (Toxin A&amp;B) Interval: 1/day</td>
<td>Cryptosporidium Isospora Cyclospora Microsporidia</td>
</tr>
<tr>
<td><strong>Norton</strong></td>
<td>Regular O&amp;P</td>
<td></td>
<td>EIA (Toxin A &amp; B) and GDH PCR (toxin B) for discrepancy Interval: 1/wk</td>
<td>Cryptosporidium Isospora Cyclospora Microsporidia</td>
</tr>
</tbody>
</table>
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

- **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 & strongyloidies (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, strongyloidiasis
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

- **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 immunofluorescence)
  - Rectal swab for chlamydia (culture & immunofluorescence)
  - Rectal/colonic Bx for CMV & HSV culture.
Second Line Diagnostic Tests

- Laxative analysis in stool & urine.
  - Stool water can be tested for phenolphthalein, emetine (ipecac syrup), & bisacodyl.
  - Urine can be tested for anthraquinone.
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

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 \( \geq 100 \) 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 insufficiency, or biliary steatorrhea.
  – Values < 9.5 g fat/100 g of stool suggest mucosal disease.
Second Line Diagnostic Tests

• **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: \( \geq 5 \text{g D-xylose in 5-hour urine} \) & \( \geq 20 \text{mg/dl D-Xylose in serum (1.3 mmol/L/1.73m}^2) \)
  – 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:**
    • 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, phenolamine, phenmetrazine, caffeine, fluorouracil, 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
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, HCO₃=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; 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.
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

• **Empiric Antibiotic Regimens:**
  – fluoroquinolone x 3 days,
  – azithromycin x 1 day, or
  – erythromycin for 3 to 5 days.
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.

• **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°F, watery diarrhea; sometimes severe dysentery. May cause osteomyelitis, septic or reactive arthritis, sepsis, peritonitis, cholecystitis, pancreatitis, mycotic aneurism, intraabdominal abscess.
- **Treatment**: ORS & support. Antibiotics prolong disease.
  - Treat only immunosuppressed, 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 immunosuppressed.
Specific Causes of Foodborne Diarrhea – Mucosal Invasion

**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 dysentery, 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.
Specific Causes of Foodborne Diarrhea – Mucosal Invasion

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.
Specific Causes of Foodborne Diarrhea – Mucosal Invasion

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 (Louisiana & Texas)
- Vibrio colonizes small bowel and produces cytotoxic 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.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

**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.
Enterotoxigenic E. coli (ETEC)

- Major cause of Traveler’s diarrhea, and of diarrhea in infants and toddlers in underdeveloped areas.
- Cytotoxins (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
Specific Causes of Foodborne Diarrhea – Toxin Mediated

**Bacillus cereus - Diarrhea**

- **Source:** foods cooked slowly at low temperature, permitting bacterial proliferation.
- B. cereus colonizes the small bowel and produces heat-labile cytotoxic 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.
Specific Causes of Foodborne Illness – Toxin Mediated

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.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

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**: [Doxycycline 100 mg IV BID + ceftazidime 2 g IV q 8 h], or Ciprofloxacin 400 mg IV BID
Antibiotic Related Diarrhea
Antibiotic Related Diarrhea (ARD)

Enigmatic ARD

- **Cause**: antibiotic drug associated; probably carbohydrate and/or bile salt malabsorption due to altered bowel flora.
- **Frequency**: causes 80% of ARD
- **Symptoms**: watery diarrhea. No pseudomembranes nor hemorrhage.
- **Treatment**: discontinue antibiotics, Zn suppletionation, 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, cyclophosphamidate, 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

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

### Bacteria Detection

<table>
<thead>
<tr>
<th>Test</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GDH</strong> (common antigen testing for glutamate dehydrogenase)</td>
<td>High sensitivity Rapid Cheap</td>
<td>Intermediate specificity Does not differentiate colonization from infection</td>
</tr>
<tr>
<td><strong>Stool culture</strong> (anaerobic stool culture)</td>
<td>Extremely sensitive</td>
<td>Turn over: 3 days Does not differentiate colonization from infection</td>
</tr>
</tbody>
</table>
Antibiotic Related Diarrhea (ARD)

Clostridium difficile

- **Complications**: protein loosing enteropathy, ascites, toxic megacolon requiring colectomy; risk high in >64y/o, immunosuppression & hospital acquisition.
- **Risk Factors for complicated nosocomial PMC**:
  - 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 14d (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.
<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>Clinical features</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate disease</td>
<td>Leukocytosis with a WBC count $\leq 15 \times 10^9/l$ and Serum creatinine level $&lt;1.5$ times baseline level</td>
<td>Metronidazole administered orally at a dose of 500 mg three times daily for 14 days</td>
</tr>
<tr>
<td>Severe disease or with IBD</td>
<td>Leukocytosis with a WBC count $\geq 15 \times 10^9/l$ and/or Serum creatinine level $\geq 1.5$ times baseline level</td>
<td>Vancomycin administered orally at a dose of 125 mg four times daily for 14 days</td>
</tr>
<tr>
<td>Complicated disease</td>
<td>Hypotension, ileus, megacolon</td>
<td>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</td>
</tr>
</tbody>
</table>
Treatment options for refractory and recurrent CDI

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

Data obtained from Gerdling & 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.

Surawicz, C. M. & Alexander, J. (2011) Treatment of refractory and recurrent Clostridium difficile infection
Treatment algorithm for **recurrent** *Clostridium difficile* infection

**Initial *Clostridium difficile* infection episode**

- **Recurrent diarrhea**
  - **C. difficile** toxin present in stool
    - Vancomycin (2 g daily; 500 mg four times daily) for 14 days
      - No recurrence of diarrhea
      - Recurrence of diarrhea
        - **C. difficile** toxin present in stool
          - Vancomycin (2 g daily) for 14 days, then give a reduced dose of vancomycin (125–250 mg twice daily) every day for 5 days, then every other day for 1 week, every 2 days for 1 week, every 3 days for 1 week, gradually increasing the intervals until vancomycin is taken every 10 days, then discontinue; adjunct *Saccharomyces boulardii* (500 mg twice daily) to be continued for 2 weeks after stopping antibiotics
            - No recurrence of diarrhea
            - Recurrence of diarrhea
              - Fecal microbiota transplant with donor stool, via colonoscopy after PEG solution lavage or by nasogastric tube
                - If patient does not want fecal microbiota transplant
                  - Rifaximin orally 400 mg three times daily for 2 weeks after 2 weeks of vancomycin
        - **C. difficile** toxin absent in stool
          - Consider other causes of diarrhea
            - Postinfectious IBS
            - Postinfectious IBD
            - Intercurrent infection
            - Dietary causes (e.g. lactose intolerance)

Surawicz, C. M. & Alexander, J. (2011) Treatment of refractory and 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)

- **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.
Antibiotic Related Diarrhea (ARD)

**Clostridium perfringens Type A**

- Proliferation of C. perfringens 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) Immunosuppressed: 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
Specific Causes of Foodborne Diarrhea – Toxin Mediated

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. Amitriptyline for chronic neuropathy.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

**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.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

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
Specific Causes of Foodborne Diarrhea – Toxin Mediated

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
Specific Causes of Foodborne Diarrhea – Toxin Mediated

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. oxytocca