Infectious & Toxin-Mediated Diarrhea

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Scope of the Problem

• 47.8 million foodborne-related illnesses occur annually (one out of every six persons) in the United States.

• Each year 31 major pathogens acquired in the United States caused 20% of the episodes:
  – 9.4 million episodes of diarrheal illness,
  – 55,961 hospitalizations, and
  – 1,351 deaths.

• Each year other unspecified agents resulted in 80% of the episodes:
  – ~38.4 million episodes of domestically acquired foodborne illnesses.
  – 71,878 hospitalizations and
  – 1,686 deaths,
Scope of the Problem

• Over 44 million US residents traveled abroad to non-Canadian and non-European destinations in 2014, resulting in:
  – 4 to 17 million cases of traveler’s diarrhea (TD) based on 10–40% attack rates

• The cost of acute and chronic illness attributable to these infections is estimated to be upwards of US $145 billion to the US economy.
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 Exposure

- **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. perfringens (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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium parvum</td>
<td>$1-10^3$</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>$10-10^2$</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>$10-10^2$</td>
</tr>
<tr>
<td>Shigella</td>
<td>$10-10^2$</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>$10^2-10^6$</td>
</tr>
<tr>
<td>Salmonella</td>
<td>$10^5$</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>$10^8$</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>$10^8$</td>
</tr>
</tbody>
</table>
Types of Diarrhea

- Non-Inflammatory
- Mucosal Penetrating
  - Inflammatory
Non-Inflammatory Diarrhea
Site, Mechanism, Features, & Pathogens

• **Site:**
  – Proximal Small Bowel

• **Mechanism:**
  – Enterotoxin/adherence/superficial invasion

• **Features:**
  – *Clinical: Watery diarrhea*
  – *Laboratory:*
    • No fecal WBC
    • Minimal or no Lactoferrin

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

(*) Dominant involvement: Proximal small bowel
Mucosal Penetrating Diarrhea
Site, Mechanism, Features, & Pathogens

• **Site:**
  – Distal small bowel

• **Mechanism:**
  – Mucosal penetration

• **Features:**
  – **Clinical:** Enteric fever
  – **Laboratory Features:**
    • Fecal mononuclear leukocytes

• **Pathogens (Distal Small Bowel):**
  – Salmonella typhi
  – Yersinia enterocolitica
  – Campylobacter fetus
# Inflammatory Diarrhea

**Site, Mechanism, Features, & Pathogens**

<table>
<thead>
<tr>
<th>Site:</th>
<th>Pathogens (Colon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Campylobacter (*)</td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
</tr>
<tr>
<td>Mechanism:</td>
<td>C. difficile (WBC(+) in 30%)</td>
</tr>
<tr>
<td>Invasion and/or</td>
<td>Yersinia</td>
</tr>
<tr>
<td>cytotoxin</td>
<td>V. parahemolyticus</td>
</tr>
<tr>
<td>Features:</td>
<td>Enteroinvasive E. coli</td>
</tr>
<tr>
<td>Clinical: dysenteria</td>
<td>Plesiomonas shigelloides</td>
</tr>
<tr>
<td>Laboratory Features:</td>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td>(+) fecal WBC</td>
<td>CMV (*)</td>
</tr>
<tr>
<td>High Lactoferrin</td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td>HSV</td>
</tr>
<tr>
<td></td>
<td>Entamoeba histolytica (WBC absent b/o destruction)</td>
</tr>
</tbody>
</table>

(*) Dominant involvement: Colon
Common Infectious Etiologies

**WATERY DIARRHEA**

6% of Stool studies (+)

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

**BLOODY DIARRHEA**

20-30% Stool studies (+)

- EHEC
- Shigella
- Campylobacter
- 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 loosing enteropathy, toxic megacolon.
- **Enterohemorrhagic E. coli (EHEC)**: HUS & TTP
- **Salmonella**: sepsis, peritonitis, cholecystitis, pancreatitis, osteomyelitis, mycotic aneurism, intraabdominal abscess, Reiter S.
- **Campylobacter**: Guillian-Barre syndrome, Reiter S
- **Shigella**: seizures and encephalopathy, Reiter S.
- **Yersinia**: Thyroiditis, pericarditis, glomerulonephritis, myocarditis, HUS, Guillian-Barre, Reiter S.
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

Stool Testing

• **Stool culture and culture-independent methods** if available should be used in:
  – individual patient at high risk of spreading disease to others, and
  – known or suspected outbreaks.
  – Level: (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.
  – Level: (Strong recommendation, very low level of evidence)
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

Stool Testing

- **Sensitivity of Stool Test:**
  - 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 (80%) of cases of acute diarrheal infection.
  - FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods.
    - Level: (Strong recommendation, low level of evidence).

- **Antibiotic sensitivity testing is not recommended.**
  - (Strong recommendation, very low level of evidence)
### FDA Approved Molecular Tests For Enteric Pathogens

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Test system</th>
<th>Platform</th>
<th>Pathogens detected</th>
<th>Detection time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofire Diagnostics</td>
<td>GI Panel</td>
<td>FilmArray</td>
<td>B, V, P</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1–2</td>
</tr>
<tr>
<td>Luminex</td>
<td>GPP</td>
<td>xTAG</td>
<td>B, V, P</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;5</td>
</tr>
<tr>
<td>Nanosphere</td>
<td>EP</td>
<td>Verigene</td>
<td>B</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hologic/Gen-Probe</td>
<td>ProGastroSSCS</td>
<td>—</td>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>BD Diagnostics</td>
<td>EBP</td>
<td>BD MAX</td>
<td>B</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3–4</td>
</tr>
</tbody>
</table>

can detect microbes at non-pathogenic levels
FilmArray Gastrointestinal (GI) Panel
Reverse transcription PCR with detection of 22 pathogens in a freeze-dried format in 1 hour

- **Bacteria**
  - 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)

- **Vibrio**
  - Vibrio cholerae

- **Virus**
  - Adenovirus F 40/41
  - Astrovirus
  - Norovirus GI/GII
  - Rotavirus A
  - Sapovirus

- **Parasites**
  - Cryptosporidium
  - Cyclospora cayetanensis
  - Entamoeba histolytica
  - Giardia lamblia
Molecular Diagnostic Testing

xTAG GPP (Luminex)

can detect microbes at non-pathogenic levels

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

• **Parasites:**
  – Giardia lamblia
  – Cryptosporidium

• **Virus:**
  – Norovirus GI/GII (Norwalk virus)
  – Rotavirus A
Oral Hydration

- 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.
  - Level: (Strong recommendation, moderate level of evidence)
- Balanced electrolyte rehydration (ORS) *(Normalyte, Trioral)* in preferred in:
  - 1. Elderly with severe diarrhea or
  - 2. Traveler with cholera-like watery diarrhea.
Symptomatic & Empiric Therapy

- **Probiotics or prebiotics** in adults are not recommended, except in cases of postantibiotic-associated illness.
  - Level: (Strong recommendation, moderate level of evidence)

- **Bismuth subsalicylates** to control rates of passage of stool in:
  - travelers during bouts of **mild-to-moderate illness**.
  - Level: (Strong recommendation, high level of evidence)

- If receiving **antibiotics for traveler’s diarrhea**:
  - adjunctive **loperamide therapy should be administered** to decrease duration of diarrhea and increase chance for a cure.
  - Level: (Strong recommendation, moderate level of evidence)
Empiric Antibiotic Therapy

• **Do not give empiric anti-microbial therapy** for routine acute diarrheal infection, except in:
  - cases of TD where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics.
  - **Level:** *(Strong recommendation, high level of evidence)*

• **Use of antibiotics for community-acquired diarrhea should be discouraged** because:
  - Most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and
  - Diarrhea is not shortened by the use of antibiotics.
  - **Level:** *(Strong recommendation, very low-level evidence)*
evaluation of persistent diarrhea

- in patients with persistent symptoms (between 14 and 30 days):
  - recommended:
    - stool culture and/or culture independent microbiologic studies (if not already done after 7 days of diarrhea)
  - not recommended:
    - serological and clinical lab testing.
    - endoscopic evaluation for cases with negative stool work-up.
  - level: (strong recommendation, very low level of evidence)
• **Community Acquired Diarrhea**
  
  – Patient level counseling on prevention of acute enteric infection is not routinely recommended.
    
    • May be considered in the individual or close contacts of the individual who is at high risk for complications.
  
  – **Level: (Conditional, very low level of evidence)**
Travelers Diarrhea:

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

- Frequent and effective hand washing and alcohol-based **hand sanitizers** are of limited value but may be useful where low-dose pathogens are expected, as during:
  
  - cruise ship outbreak of norovirus infection,
  - institutional outbreak, or
  - endemic diarrhea prevention.
  
  - Level: (Conditional recommendation, low level of evidence)
Prevention and Counseling

• **Drugs for Prevention of Travelers Diarrhea:**
  
  – **Bismuth subsalicylates** (moderate effectiveness): for travelers without contraindications to its use and who can adhere to the frequent dosing. (Pepto-Bismol 2 tab QID; 50% protection)
    • Level: (Strong recommendation, high level of evidence)
  
  – **Antibiotic chemoprophylaxis** (moderate to good effectiveness): in high-risk groups for short-term use. (Rifaximin 200 mg TID x 14 days; 60% protection)
    • Level: (Strong recommendation, high level of evidence)

  – **Not Recommended:** Probiotics, prebiotics, and synbiotics.
    • Level: (Conditional recommendation, low level of evidence)
Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology)

STEC = VTEC = EHEC = Shiga-like or Verocytotoxin-producing E. coli stx1/stx2
Antibiotic Therapy in Diarrhea

• **Risk of Empiric antibiotic therapy:**
  – Increases risk of HUS in EHEC (STEC, VTEC), and
  – Prolongs shedding of salmonella,
  – Do not give when you suspect:
    • C. difficile colitis (targeted therapy is OK), or
    • EHEC, or
    • Salmonella (except in special cases; see later)

• **Consider antibiotics for:**
  – Travelers diarrhea with > 4 BM/d, or with fever, blood, pus in stool,
  – Diarrhea in immunocompromised
  – Diarrhea longer than 7 d (after microbiology studies are sent),
  – Diarrhea > 3 days + fever > 101 °F (after microbiology studies are sent)
  – Dysentery (bloody diarrhea) with fever > 101 °F (after microbiology studies are sent)
Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>500 mg by mouth</td>
<td>Single dose(^b) or 3-day course</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750 mg by mouth or</td>
<td>Single dose(^b)</td>
</tr>
<tr>
<td></td>
<td>500 mg by mouth</td>
<td>3-day course</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg by mouth</td>
<td>Single dose(^b) or 3-day course</td>
</tr>
<tr>
<td>Azithromycin(^c,d)</td>
<td>1,000 mg by mouth or</td>
<td>Single dose(^b)</td>
</tr>
<tr>
<td></td>
<td>500 mg by mouth</td>
<td>3-day course(^d)</td>
</tr>
<tr>
<td>Rifaximin(^e)</td>
<td>200 mg by mouth three times daily</td>
<td>3-days</td>
</tr>
</tbody>
</table>

\(^a\) 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.
Antisecretory Drugs

- **Bismuth SS** will reduce the stools passed by ~40%.
- **Crofelemer (FULYZAQ):**
  - 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 (Hidrasec):**
  - 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: production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption.
  - Secondary: inhibition of calmodulin leading to reduced mucosal secretion
  - 4 mg first dose, and then 2 mg dose after each loose stool, not to exceed 16 mg / 24-h period
Viral Foodborne Infections
Specific Causes of Foodborne Diarrhea - Viral

Norovirus / Norwalk Virus

- 40-60% of acute viral gastroenteritis epidemics in older children & adults
- **Pathology**: 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
- **Symptoms**: nausea, vomiting, diarrhea, abdominal pain, muscle aches, headache, tiredness and low-grade fever.
- **Diagnosis**: Serology, stool PCR or E/M for stool virus
- **Immunity**: lasts only weeks to 4 months
- **Treatment**:
  - ORS, supportive.
Specific Causes of Foodborne Diarrhea - Viral

Rotavirus

• 60% of diarrhea in children < 2 years-old
• **Pathology:** 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), PCR
• **Treatment:**
  – ORS, supportive.
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, sapovirus.
Foodborne Bacterial Infections with diarrhea due to Mucosal Invasion
Specific Causes of Foodborne Diarrhea – **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 dysenteria.
- **Complications:**
  - osteomyelitis, septic or reactive arthritis, sepsis, peritonitis, cholecystitis, pancreatitis, mycotic aneurism, intraabdominal abscess, Reiter S.
- **Treatment:** ORS & support. Antibiotics prolong the disease.
  - Treat with antibiotics only in: 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, that improves and then worsens, with WBC’s in stool.
- **Complications**:
  - Endocarditis, meningitis, Guillian-Barre, cholecystitis, pancreatitis, septic abortion, glomerulonephritis, reactive arthritis (HLA-B27), Reiter S.
- **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.
Specific Causes of Foodborne Diarrhea – Mucosal Invasion

Yersinia Enterocolitica

• **Spread:** food-borne (undercooked meats & oysters) & contact with infected pets.

• **Symptoms Children < 5y:**
  – fever, abdominal cramps, diarrhea for 1 or more weeks.

• **Symptoms Children > 5 y:**
  – mesenteric adenitis, or ileitis; sometimes ileal perforation.

• **Symptoms 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 or PCR.
- **Treatment:**
  - Treat only in severe (> 8 BM/d) or prolonged disease (> 7 days);
  - 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 Liter/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

- Second cause of food-borne diarrhea in USA (after salmonella).

- **Spread:**
  - Contaminated food with preformed cytotoxic, heat-stable, enterotoxin A.
  - 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.
  - No WBC in stool.

- **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 (3: one heat-labile, and two heat-stable), activate adenylate cyclase & 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; Stool PCR.
- **Treatment**: ORS.
  - **Mild**: Pepto-Bismol 2 tab QID, or Loperamide.
  - **Severe/dysenteria**: Bactrim DS 1 BID x 3d; Ciprofloxacin 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**,  
- Has shiga-like verocytotoxin I & II; (STEC or VTEC)  
  – cytotoxic to endothelial cells and enterocyte.
- Sporadic and epidemic illness.

**Spread:**
- Ingestion of contaminated ground beef, unpasteurized milk or apple cider. Lives in the intestine of ruminants.  
- 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. perfringens with *chromosomal* enterotoxin gene (cpe)]
  - C. perfringens can also cause antibiotic associated diarrhea without pseudomembranes (*plasmid* cpe gene).
  - Heat-labile cytotoxic enterotoxin.

- **Incubation:** 8-24 hours.
- **Duration:** 24 hours.
- **Symptoms:**
  - severe watery diarrhea, with intense abdominal cramps.
- **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; cytotoxic 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 supplementation,
  – 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.
  – 500,000 cases/y with 30,000 deaths/y;
  – 5 billion excess cost/y.
  – Cytotoxic toxin A&B

• **Symptoms:**
  – watery diarrhea (sometimes bloody), abdominal pain, fever, leukocytosis;
  – may have hypoalbuminemia (protein loosing enteropathy).

• **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%.
Healthcare vs Community Associated CDI
Site of Onset

- Community Onset
- Nursing Home Onset
- Hospital Onset

Estimated No. of CDI Cases

- CO-HCA
- NHO
- HO
Detection of C. difficile

<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 toxin A&amp;B</strong></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 (tests gene for toxin B)</strong></td>
<td>Rapid (&lt; 4h) Very sensitive Very specific (80-99%)</td>
<td>Expensive Does not differentiate colonization from infection</td>
</tr>
</tbody>
</table>

Use stool toxin test as part of a **multistep algorithm** rather than NAAT alone:
- Glutamate dehydrogenase [GDH] plus toxin (EIA);
- GDH plus toxin (EIA), arbitrated by nucleic acid amplification test [NAAT] ;
- NAAT plus toxin (EIA)

<table>
<thead>
<tr>
<th>Test</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GDH (common antigen testing for glutamate dehydrogenase)</strong></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 > 64 y/o, immunosupression & hospital acquisition.

• **Risk Factors for complicated nosocomial PMC:**
  – WBC > 15 K,
  – Creat > 2 mg/dL (> 1.5 times baseline)
  – (Risk: 0=10%; 1=28%; 2=60%)

• Mortality 16% over expected, due to “hypervirulent strain” PMC with “binary toxin” & “deletion in tcdC”.

• 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, or Fidaxomicin 200 mg BID x 10d (superior to Vanco for 1st CD recurrence).
  - **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:**
    - Sub-total colectomy or diverting loop ileostomy + warmed PEG/Vanco colon lavage for persistent hypotension, lack of response to medical therapy, megacolon or perforation. Consider FMT.
    - IVIG 400 mg/kg IV +/- (specially in hypogammaglobulinemia).
  - **Multiple Relapses:** See Surawicz protocol later.
<table>
<thead>
<tr>
<th>Clinical classification</th>
<th>Clinical features</th>
<th>Recommended treatment</th>
</tr>
</thead>
</table>
| Mild or moderate disease| -Diarrhea without evidence of Severe nor Complicated CDI | -Vancomycin 125 mg four times a day x 10 days  
-FDX 200 mg given twice daily for 10 days  
-Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days |
| Severe disease or with IBD| -Creatinine > 1.5 mg/dL, or  
-Leukocytosis with a WBC count ≥15 × 10⁹/l, or  
-Abdominal tenderness | -Vancomycin administered orally at a dose of 125 mg four times daily for 10-14 days  
-FDX 200 mg given twice daily for 10 days |
| Complicated disease | Any of the following attributable to CDI:  
-Admission to ICU for CDI  
-Hypotension +/- vasopressors  
-Fever ≥38.5 °C  
-Ileus or significant abdominal distention  
-Mental status changes  
-WBC ≥35,000 cells/mm³ or <2,000 cells/mm³  
-Serum lactate levels >2.2 mmol/l  
-End organ failure (mechanical ventilation, renal failure, etc.) | -VAN, 500 mg 4 times per day by mouth or by nasogastric tube.  
-If ileus, consider adding rectal instillation of VAN (500 mg in 100 mL of 0.9% NaCl QID).  
-Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN (500 mg in 100 mL of 0.9% NaCl QID), particularly if ileus is present |
Surgical Management for Severe CDI

• If surgical management is necessary for severely ill patients:
  – Subtotal colectomy with preservation of the rectum (Strong recommendation, moderate quality of evidence).
  – Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes (Weak recommendation, low quality of evidence).
## Treatment of Recurrent CDI

<table>
<thead>
<tr>
<th>Recurrence Number</th>
<th>Regimen</th>
</tr>
</thead>
</table>
| **First Recurrence**               | - VAN 125 mg given 4 times daily for 10 days, if metronidazole was used for the initial episode.  
- Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR  
- FDX 200 mg given twice daily for 10 days, if VAN was used for the initial episode |
| **Second, or Subsequent Recurrence** | - VAN in a tapered and pulsed regimen, OR  
- VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR  
- FDX 200 mg given twice daily for 10 days, OR  
- Fecal microbiota transplantation |
### 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><em>Saccharomyces boulardii</em>, <em>Lactobacillus plantarum</em></td>
<td>NA</td>
</tr>
<tr>
<td>Biotherapeutic agents</td>
<td>Fecal microbiota transplant</td>
<td>Nontoxigenic <em>Clostridium difficile</em></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 Gerdig & Johnson (2010). 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.

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## The CDI Non-FMT Therapy Pipeline

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Date</th>
<th>Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin</td>
<td>FDA approved 5/2011</td>
<td>Macro cyclic antibiotic</td>
<td>Limited-spectrum antibiotic; does not promote sporulation; reduced recurrence</td>
</tr>
</tbody>
</table>
| Bezlotoxumab   | FDA approved 10/2016 | Monoclonal Ab (anti-TcdB)         | • First in class IgG1 kappa antibody  
• ARR 24.2%-15% = 9.2%  
• Adjunctive to standard antibiotic therapy |
| NTCD-M3        | Phase 2        | Non-toxigenic C. difficile strain competitive exclusion | • 30%-11% = 19% ARR in dose-ranging trial1  
• Colonization with drug strain in only 69% of patients  
• Transfer of toxin genes to NTCD-M3 known to occur in vitro |
| Surotomycin    | Phase 3        | Bactericidal cyclic lipopeptide    | Limited-spectrum antibiotic                                           |
| Cadazolid      | Phase 3        | Oxazolidinone antibiotic           | Limited-spectrum antibiotic                                           |
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
              - Intravenous immunoglobulin
VANCOMYCIN TAPPER FOR RELAPSING C. DIFFICILE COLITIS

- Vancomycin 500 mg QID x 14 days, then
- Vancomycin Pulse therapy: 125 mg, PO, every 3 days for 10 doses (1 month)
- Florestor 500 mg BID, PO, during vancomycin of 2 g a day therapy and pulse therapy, plus for 2 additional weeks?
  - No in patients in ICU or with central lines
- If patient Relapses again (3rd relapse) after Vanco (+/- Probiotic) tapper, consider:
  - FMT or
  - Fidaxomicin 200 mg BID x 10 days
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
  - 4. Volunteer Donor pool tested every 4 months

- **Exclusion** of donors:
  - recent antibiotic use (3 months),
  - current or recent diarrheal illness,
  - hospital or health care worker, and
  - at-risk sexual behaviors

- **Screening for illness**: see next slide.

- Stool is spontaneously passed or prompted with an small dose of Mg Citrate.

- **CPT 44705 = 1.42 RVU (MEDICARE G0455 = 0.97 RVU):** Preparation of fecal microbiota for instillation, including assessment of donor specimen (G0455 includes also INSTILLATION).
Donor Absolute Contraindications

**FMT**

**Risk of infectious agent**
- Known HIV, hepatitis B or C infections
- Known exposure to HIV or viral hepatitis (within the previous 12 months)
- High-risk sexual behaviors
- Use of illicit drugs
- Tattoo or body piercing within six months
- Incarceration or history of incarceration
- Known current communicable disease (eg, upper respiratory tract infection)
- Risk factors for variant Creutzfeldt-Jakob disease
- Travel (within the last six months) to areas of the world where diarrheal illnesses are endemic or risk of traveler's diarrhea is high

**Gastrointestinal comorbidities**
- History of inflammatory bowel disease
- History of IBS, idiopathic chronic constipation, or chronic diarrhea
- History of gastrointestinal malignancy or known polyposis

**Factors that can or do affect the composition of the intestinal microbiota**
- Antibiotics within the preceding three months
- Major immunosuppressive medications (eg, calcineurin inhibitors, exogenous glucocorticoids, biological agents, etc)
- Systemic antineoplastic agents

**Additional recipient-specific considerations**
- Recent ingestion of a potential allergen (eg, nuts) where recipient has a known allergy to this (these) agent(s)
Donor Relative Contraindications

FMT

- History of major gastrointestinal surgery (e.g., gastric bypass)
- Metabolic syndrome
- Systemic autoimmunity (e.g., multiple sclerosis, connective tissue disease)
- Atopic diseases including asthma and eczema, eosinophilic disorders of the gastrointestinal tract
- Chronic pain syndromes (e.g., chronic fatigue syndrome, fibromyalgia)
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.
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 polyethylene 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 (> 50 gm) is suspended in 350 mL of nonbacteriostatic saline, with manual shaking in a large suction canister or using a blender.
  - 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 (350 mL) is infused through the colonoscope channel into the TI or cecum, with the help of 60 cc syringes, or given by NGT or EGD (if cannot tolerate NGT)
  - 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.
  - **CPT 44799** = unlisted procedure; No RVU: For fecal instillation by oro-nasogastric tube or enema. For Medicare **G0455 includes Preparation + Instillation**.
Commercial Fecal Microbiota

- **Vendor**: OpenBiome
- **Cost**: $250/each
- **Recommend purchase**: 5 doses to decrease shipping cost
- **Shipping**: 5 days
- **Storage**: stored in a -20°C (-4°F) freezer, and should only be thawed immediately before treatment
- [http://www.openbiome.org/work-with-us/](http://www.openbiome.org/work-with-us/)
RePOOPulate
Petrof EO et al. *Microbiome* 2013, 1:3

- 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 $3.5 \times 10^9$ colony-forming units/ml. The bacterial suspension was placed in a reduced atmosphere in a double-sealed container at $4^\circ C$, and used within 24 hours.
Antibiotic Related Diarrhea (ARD)

**Clostridium perfringens Type A**

- Proliferation of C. perfringens type A with **plasmid cpe gene**, 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)
  - Suggested in colonoscopy by: 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

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

- **Salmonella species**:  
  - treat with cipro 500 mg po QID x 5-7 days
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; stool PCR
  - Duodenal aspirate, string-test, or Bx.

- **Treatment:**
  - Metronidazole 250 mg po TID x 5-7 days; Quinacrine 100 mg TID x 5 days; Nitazoxanide (Alinia) 500 mg TID x 3 days.
  - Patients with IgA or IgM deficiency need 6-8 weeks of therapy.
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; Stool PCR
  - 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
Entamoeba histolytica

• **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. - Stool PCR.
  – 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, **PLUS**
  – 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. - Stool PCR.
  – 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:**
  – Enterocytozoan bienusi:
    • fumagillin 60 mg/d x 14 days.
  – Encephalitozoon intestinalis:
    • albendazole 400 mg BID x 3-4 weeks.
Foodborne Diarrhea due to Fish & Shellfish associated Toxins
Specific Causes of Foodborne Diarrhea – Toxin Mediated

Ciguatera

- **Cause:** heat-stable Ciguatoxin accumulated in large-fish muscles after eating smaller fish.
- **Geography:** 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.
  - Gastric lavage and cathartics.
  - Atropine for bradycardia. May need respiratory support.
  - Amitryptiline, gabapentin for chronic neuropathy.
  - Amitryptiline or Fluoxetine for depression and fatigue.
  - Symptoms may recur after eating fish, nuts, caffeine or alcohol.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

**Scombroid**

- **Cause:** histamine & saurine in flesh of fish by action of marine bacteria
  - Fish tastes sharp and peppery.
- **Geography:** 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 & epinephrine for bronchospasm;
  - cathartics & gastric lavage.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

**Paralytic Shellfish Poisoning**

- **Cause:** heat-stable saxitoxins, from dinoflagellates, concentrated in
  - bivalved mollusks,
  - worse in “red tide”.
  - outbreaks in summer.

- **Geography:** New England, West Coast, Alaska.

- **Onset:** 30 minutes - 3 hours; may be fatal in hours.

- **Duration:** hours to few days.

- **Symptoms:**
  - nausea, vomiting, diarrhea,
  - paresthesias in lips, mouth, face and extremities;
  - dysphonia, dysphagia, weakness, paralysis and respiratory insufficiency.

- **Treatment:**
  - respiratory support;
  - gastric lavage and cathartics.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

Neurotoxic Shellfish Poisoning

- **Cause:** heat-stable *brevotoxin*, from dinoflagellates, concentrated in
  - Mollusks.
    - Associated to "red tide".
- **Geography:** Gulf Coast, North Carolina, and Florida
- **Onset:** few hours
- **Duration:** hours to days.
- **Symptoms:**
  - Nausea, vomiting, diarrhea,
  - Paresthesias, reversal of hot-cold sensation, ataxia.
  - Respiratory symptoms after aerolization.
- **Treatment:**
  - Symptomatic; IV fluids, cathartics, bronchodilators.
Specific Causes of Foodborne Diarrhea – Toxin Mediated

Diarrheic Shellfish Poisoning

- **Cause:** okadaic acid or dinophysistoxin-1 in
  - mussels, scallops, or clams.
- **Geography:** 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

- **Cause:** domoic acid concentrated in
  - shellfish (Razor clams, Dungeness crabs), and
  - anchovies.
- **Geography:**
  - 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; cathartics; benzodiazepines for seizures.