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:
  – 9.4 million episodes of diarrheal illness,
  – 55,961 hospitalizations, and
  – 1,351 deaths.

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

• 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.
  – **Seafood/shellfish:** v. cholerae, v. vulnificus, v. parahemolyticus, salmonella, anisakis, tapeworm.
  – **Cheese, milk:** listeria.
  – **Eggs:** salmonella.
  – **Mayonnaise & cream pies:** S. aureus & clostridium.
  – **Fried rice:** B. cereus.
  – **Fresh berries:** cyclospora.
  – **Canned foods:** clostridium
  – **Spring or contaminated water:** v. cholerae, Norwalk agent, giardia, cryptosporidium.
Helpful Questions to the Patient with 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. 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: $10^8$
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

- **Site:** Colon
- **Mechanism:**
  - Invasion and/or cytotoxin
- **Features:**
  - **Clinical:** dysenteria
  - **Laboratory Features:**
    - (+) fecal WBC
    - High Lactoferrin

**Pathogens (Colon)**
- 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: Colon
Common Infectious Etiologies

**WATERY DIARRHEA**
6% of Stool studies (+)

**BLOODY DIARRHEA**
20-30% Stool studies (+)
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 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)
• Traditional methods of diagnosis (bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection.

  – 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).
# 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>
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<tbody>
<tr>
<td>Luminex</td>
<td>GPP</td>
<td>xTAG</td>
<td>B, V, P</td>
<td>15</td>
</tr>
<tr>
<td>Hologic/Gen-Probe</td>
<td>ProGastro SSCS</td>
<td>—</td>
<td>B</td>
<td>4</td>
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<tr>
<td>BD Diagnostics</td>
<td>EBP</td>
<td>BD MAX</td>
<td>B</td>
<td>4</td>
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<tr>
<td>Biofire Diagnostics</td>
<td>GI Panel</td>
<td>FilmArray</td>
<td>B, V, P</td>
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<tr>
<td>Nanosphere</td>
<td>EP</td>
<td>Verigene</td>
<td>B</td>
<td>6</td>
</tr>
</tbody>
</table>

- can detect microbes at non-pathogenic levels
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
**FilmArray Gastrointestinal (GI) Panel**

Reverse transcription PCR with detection of 22 pathogens in a freeze-dried format in 1 hour

<table>
<thead>
<tr>
<th><strong>Bacteria</strong></th>
<th><strong>Vibrio</strong></th>
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</thead>
<tbody>
<tr>
<td>Aeromonas</td>
<td>Vibrio cholerae</td>
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<tr>
<td>Campylobacter</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile (Toxin A/B)</td>
<td>Adenovirus F 40/41</td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td>Astrovirus</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Norovirus GI/GII</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>Rotavirus A</td>
</tr>
<tr>
<td><strong>Diarrheagenic E. coli/Shigella</strong></td>
<td>Sapovirus</td>
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<tr>
<td>Enteroaggregative E. coli (EAEC)</td>
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<tr>
<td>Enteropathogenic E. coli (EPEC)</td>
<td><strong>Virus</strong></td>
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<tr>
<td>Enterotoxigenic E. coli (ETEC) lt/st</td>
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<tr>
<td>Shiga-like toxin-producing E. coli (STEC) stx1/stx2</td>
<td>Adenovirus F 40/41</td>
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<td>E. coli O157</td>
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<tr>
<td>Shigella/Enteroinvasive E. coli (EIEC)</td>
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<tr>
<td><strong>Parasites</strong></td>
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<tr>
<td>Cryptosporidium</td>
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<tr>
<td>Cyclospora cayetanensis</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td></td>
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<tr>
<td>Giardia lamblia</td>
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</tbody>
</table>
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

• **Antibiotic sensitivity testing is not recommended.**
  – (Strong recommendation, very low level of evidence)

• **Balanced electrolyte rehydration (ORS) (Normalyte, Trioral) in preference** over other oral rehydration options is recommended in:
  – the elderly with severe diarrhea or
  – any traveler with cholera-like watery diarrhea.
  – 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)**
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- **Probiotics or prebiotics** in adults is **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)

- In patients receiving **antibiotics for traveler’s diarrhea**:
  - adjunctive **loperamide therapy should be administered** to decrease duration of diarrhea and increase chance for a cure.
  - Level: (Strong recommendation, moderate level of evidence)
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- **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)
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

• In patients with persistent symptoms (between 14 and 30 days):
  – Recommend: Obtain stool culture and/or culture independent microbiologic studies (if not already done after 7 days of diarrhea)
  – Not recommended: Serological and clinical lab testing.
  – Not recommended: Endoscopic evaluation for cases with negative stool work-up.
  – Level: (Strong recommendation, very low level of evidence)

• 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)
ACG Guidelines for Acute Diarrheal Infections in Adults 2016

• **For Prevention of 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 a cruise ship outbreak of norovirus infection, in an institutional outbreak, or in endemic diarrhea prevention.
    
    • Level: (Conditional recommendation, low level of evidence)
For Prevention of Travelers Diarrhea:

- **Probiotics, prebiotics, and synbiotics** are not recommended.
  - Level: (Conditional recommendation, low level of evidence)

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

- **Antibiotic chemoprophylaxis** has moderate to good effectiveness: may be considered in high-risk groups for short-term use.
  - Level: (Strong recommendation, high level of evidence)
Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology)

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

**Oral Fluid Therapy**: For all cases, hydrate through fluid and salt intake. Food: soups, broths, saltine crackers, broiled and baked foods.

**Watery Diarrhea**
- **Mild Illness**
  - Hydration only, may use loperamide 4 mg initially to control stooling

**Moderate-to-severe Illness**
- **Travel-associated**
  - Antibiotic therapy (Table 4)
- **Non-travel-associated**
  - No or low-grade fever (≤100°F)
  - Fever (≥101°F)

**Dysenteric Diarrhea** (passage of grossly bloody stools)
- **No or low-grade fever** (≤100°F)
- **Severe illness** with fever (≥101°F) in a single case (not outbreak)

**Microbiologic Assessment**
- No or low-grade fever (≤100°F)
- Fever (≥101°F)
- Microbiologic assessment, then anti-microbial agent directed to cause for all but STEC infection

**Empiric Treatment**
- Azithromycin 1 mg in single dose OR 500 mg once daily for 3 days

**Consideration**
- Consider <48 h of loperamide therapy
- <72 h duration
- ≥72 h duration

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

**STEC = VTEC = EHEC = Shiga-like or Verocytotoxin-producing E. coli stx1/stx2**
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 500 mg by mouth</td>
<td>Single dose(^b)</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 500 mg by mouth</td>
<td>Single dose(^b)</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.
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, or
  – Severe community diarrhea (> 8 BM/d, or volume depletion), or
  – Diarrhea longer than 7 d, or > 3 days + fever > 101 °F
  – Diarrhea in immunocompromised
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
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 \textbf{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**: immunosupressed, age < 3 mo or > 50 y, hemolytic anemia, surgical prosthesis, valvular heart disease, severe atherosclerosis, cancer, uremia.
  - TMP-SMX DS p.o. BID x 7 days; 14 days if immunosupressed.
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, Guillain-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.**
- **Cytotoxic toxins** (one heat-labile, and two heat-stable), activate adenylate cyclase & guanyl 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 to 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%.
## 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)</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Very specific</td>
<td>Takes 2 days</td>
</tr>
<tr>
<td><strong>EIA toxin A&amp;B</strong></td>
<td>Very specific (&gt;95%)</td>
<td>Low sensitivity (60-90%) (100-1000 pg toxin B)</td>
</tr>
<tr>
<td></td>
<td>Cheap</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Takes &lt; 24 h</td>
<td></td>
</tr>
<tr>
<td><strong>PCR (tests gene for toxin B)</strong></td>
<td>Rapid (&lt; 4h)</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Very sensitive</td>
<td>Does not differentiate colonization from infection</td>
</tr>
<tr>
<td></td>
<td>Very specific (80-99%)</td>
<td></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</td>
<td>Intermediate specificity</td>
</tr>
<tr>
<td><strong>Stool culture</strong> (anaerobic stool culture)</td>
<td>Rapid</td>
<td>Does not differentiate colonization from infection</td>
</tr>
<tr>
<td><strong>PCR</strong> (tests gene for toxin B)**</td>
<td>Extremely sensitive</td>
<td>Turn over: 3 days</td>
</tr>
<tr>
<td><strong>PCR</strong> (tests gene for toxin B)**</td>
<td></td>
<td>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, 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 due to “hypervirulent strain” PMC with “binary toxin” & “deletion in tcdC”.
- Mortality due to “Fulminant” PMC: 53% (most within initial 48h)
### Updated Infectious Diseases Society of America guidelines for the treatment of CDI (2013)

<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>- Diarrhea without evidence of Severe nor Complicated CDI</td>
<td>- Metronidazole administered orally at a dose of 500 mg three times daily for 10-14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no improvement in 5-7 days, change to</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vancomycin 125 mg four times a day x 10 days</td>
</tr>
<tr>
<td>Severe disease or with IBD</td>
<td>- Serum albumin &lt; 3 g/dL and - Leukocytosis with a WBC count ≥15 × 10⁹/l, or - Abdominal tenderness</td>
<td>- Vancomycin administered orally at a dose of 125 mg four times daily for 10-14 days</td>
</tr>
<tr>
<td>Complicated disease</td>
<td>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 &lt;2,000 cells/mm³ - Serum lactate levels &gt;2.2 mmol/l - End organ failure (mechanical ventilation, renal failure, etc.)</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 hours, plus - Vancomycin per rectum (vancomycin 500 mg in 500 ml saline as enema) four times a day - Surgical Consultation - All treatments to be continued until the patient improves</td>
</tr>
</tbody>
</table>
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)

- **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
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/)
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. perfringens 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 derivative +/- 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

• *Staphyloccocus 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.
  – Amitryptyline, gabapentin for chronic neuropathy.
  – Amitryptyline 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.