Enteric Infections
VCU SOM
M2 Medical Microbiology

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Case

• 20 year old homosexual man presents with a 3 day history of bloody diarrhea, tenesmus, crampy lower abdominal pain, chills and fever to 39.5C

• He admits to having multiple sexual partners but has never been tested for HIV

Cunha, Burke. *Infectious Diseases Pearls.* Hanley & Belfus Inc, 1999
Definition

• Diarrhea
  – Increased frequency defined as more than 3 bowel movements per day
    • Or
  – Increased volume of stool
    • > 2—mL/day
Important Host Defense Systems

• Barrier
  – Gastric acidity
  – Mucosal integrity

• Intestinal Motility
  – Peristalsis

• Intestinal Immunity
  – Phagocytic
  – Cellular
  – Humoral
Important Virulence Factors

- Inoculum size
- Invasiveness
- Toxins
  - Enterotoxin
  - Cytotoxins
  - Neurotoxins
Case

- T 39.6°C, P 126, R 24
- Cachectic, lethargic and dehydrated
- Tongue coated, thrush on buccal mucosa
- Chest clear
- Heart no murmurs
- Abdomen: mildly distended with bilateral lower quadrant tenderness and hyperactive bowel sounds, no hepatosplenomegaly
- Rectal exam: blood-tinged mucous; stool has currant jelly appearance
Currant Jelly
Case

- Stool cultures grew
  - *S. flexernii*
- Patient tested positive for HIV
  - CD4 count <20
- The patient died 4 days after admission

http://www.textbookofbacteriology.net/Shigella.gif
## Major foodborne microbes by the principal presenting gastrointestinal symptom

<table>
<thead>
<tr>
<th>Major presenting symptom</th>
<th>Likely microbes</th>
<th>Incubation period</th>
<th>Likely food sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>S. aureus</td>
<td>1 to 6 hours</td>
<td>Prepared food, eg, salads, dairy, meat</td>
</tr>
<tr>
<td></td>
<td>B. cereus</td>
<td>1 to 6 hours</td>
<td>Rice, meat</td>
</tr>
<tr>
<td></td>
<td>Norwalk-like viruses</td>
<td>24 to 48 hours</td>
<td>Shellfish, prepared foods, salads, sandwiches, fruit</td>
</tr>
<tr>
<td>Watery diarrhea</td>
<td>C. perfringens</td>
<td>8 to 16 hours</td>
<td>Meat, poultry, gravy</td>
</tr>
<tr>
<td></td>
<td>Enterotoxigenic E. coli</td>
<td>1 to 3 days</td>
<td>Fecally contaminated food or water</td>
</tr>
<tr>
<td></td>
<td>Enteric viruses</td>
<td>10 to 72 hours</td>
<td>Fecally contaminated food or water</td>
</tr>
<tr>
<td></td>
<td>C. parvum</td>
<td>2 to 28 days</td>
<td>Vegetables, fruit, unpasteurized milk, water</td>
</tr>
<tr>
<td></td>
<td>C. cayetanensis</td>
<td>1 to 11 days</td>
<td>Imported berries, basil</td>
</tr>
<tr>
<td>Inflammatory diarrhea</td>
<td>Campylobacter spp</td>
<td>2 to 5 days</td>
<td>Poultry, unpasteurized milk, water</td>
</tr>
<tr>
<td></td>
<td>Non-typhoidal salmonella</td>
<td>1 to 3 days</td>
<td>Eggs, poultry, meat, unpasteurized milk or juice, fresh produce</td>
</tr>
<tr>
<td></td>
<td>Shiga toxin-producing E. coli</td>
<td>1 to 8 days</td>
<td>Ground beef, unpasteurized milk and juice, raw vegetables, water</td>
</tr>
<tr>
<td></td>
<td>Shigella spp</td>
<td>1 to 3 days</td>
<td>Fecal contamination of food and water</td>
</tr>
<tr>
<td></td>
<td>V. parahemolyticus</td>
<td>2 to 48 hours</td>
<td>Raw shellfish</td>
</tr>
</tbody>
</table>
Dysentery

– An infection of the digestive system that results in severe diarrhea containing mucus and blood in the feces.
– Dysentery is typically the result
– There are two major types of dysentery due to micro-organisms:
  • amoebic dysentery
  • bacillary dysentery
Dysentery

• Amebic dysentery
  – *Entamoeba histolytica*

• Bacillary dysentery
  – Shigellosis is caused by one of several types of *Shigella* bacteria
  – Campylobacteriosis caused by any of the dozen species of *Campylobacter*
  – Salmonellosis caused by *Salmonella enterica* (serovar *Typhimurium*)
Shigella

- Gram negative
- Rod shaped
- Non-spore forming
- Aerobic
- Classic agent of dysentery
Shigella

- The most commonly affected group is children aged 6 months to 10 years
- Shigella species are human pathogens, transmitted from person to person by the fecal-oral route
  - Crowded unsanitary conditions
  - Contaminated food and water
  - Male homosexuals are known reservoirs
  - Immunocompromised patients are predisposed to greater severity of illness and increased mortality
**Shigella**

- Four species of *Shigella* cause disease in humans
  - *S. dysenteriae* and *S. flexnerii* - cause most severe illness and are associated with epidemics of dysentery and high mortality
  - *S. sonnei*, and *S. boydii*
    - Cause a self limited, watery diarrhea, less severe
    - *S. sonnei* is the most commonly isolated species of shigella both in the USA and in the industrialized world.
**Shigella**

- Infection with *Shigella* spp occurs after ingestion of contaminated food or water
- Ingestion of as few as 10 to 100 organisms has been shown to cause disease in volunteers
  - Low inoculum
- *Shigella* are relatively resistant to killing by stomach acid.
  - Ingested bacteria pass into the small intestine where they multiply, so that several logs more bacteria pass into the colon
Shigella

- Shigella produces disease first by invading the intestinal mucosa of the colon and rectum.
- Invasion is superficial, rarely penetrating beyond the mucosa.
  - Blood cultures will rarely be positive.
- Once the organisms are intracellular, they multiply in the cytoplasm and move from cell to cell via an actin-mediated mechanism.
Shigella Virulence

- Invasiveness is the primary virulence factor
- Toxin production
  - (Shiga toxin- *S. dysenteriae*)
- Invasion +toxins results in local, destruction and inflammation of the colon
- Microabscesses and abscess formation
Fecal leukocytes

• The presence of fecal leukocytes suggest an inflammatory process
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Shigella</th>
<th>Amebic Dysentery</th>
<th>Salmonella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious/Abrupt</td>
<td>Subacute</td>
</tr>
<tr>
<td>Incubation</td>
<td>&lt;24hrs</td>
<td>20-90 days</td>
<td>8-48 hours</td>
</tr>
<tr>
<td>Vomiting/Nausea</td>
<td>Absent</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Shaking Chills</td>
<td>Multiple</td>
<td>None</td>
<td>Single initial chill</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>Common/Severe</td>
<td>Uncommon/mild</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Severe and maximal over RLQ</td>
<td>Cecal tenderness</td>
<td>Generalized</td>
</tr>
</tbody>
</table>
Dysentery Treatment

- If untreated, bacillary dysentery lasts for about 1 week
  - Symptoms can persist for a month
- Antibiotic treatment decreases the duration of symptoms and decreases fecal shedding of organisms
  - TMP-SMX or fluoroquinolone
  - IV antibiotics and fluids may be needed in severely ill patients with dehydration
Picnics and Illness
Case

• 41 year old Caucasian woman attends a picnic during mid-day
• 8 hours later, she reports nausea, vomiting, abdominal cramps and several loose stools
• Her husband, who also attended the picnic, is ill with similar symptoms
Case

- T 38.2°C, P 88, R 24
- Well nourished, not in distress
- Oral mucosa moist, no lesions
- Chest clear
- Heart no murmurs
- Abdomen: Not distended, bowel sounds hyperactive, not tender no hepatosplenomagaly
- Rectal exam: brown stool, heme test negative
Interstate Common-Source Outbreaks of Staphylococcal Food Poisoning -- North Carolina, Pennsylvania

From July 21 to August 4, 1982, three outbreaks of acute gastroenteritis associated with a single Pennsylvania caterer and caused by Staphylococcus aureus phage type 53 were reported to CDC. Two outbreaks were linked to a specialty ham product, which had been produced in Brooklyn, New York, and distributed to five states, and one was associated with a stuffed chicken-breast product.

North Carolina: On July 21, 14 cases of acute gastrointestinal illness occurred among 41 persons traveling by bus from Allegheny County, Pennsylvania, through Iredell County, North Carolina. Box lunches, containing ham-and-cheese sandwiches prepared by an Allegheny County caterer, had been served to the passengers after more than 5 hours without refrigeration. Symptoms included vomiting (86%), abdominal cramps (86%), nausea (79%), diarrhea (69%), dizziness or weakness (69%), and fever (14%). The incubation period was 2-5 hours (mean 3 hours). All affected persons sought medical aid at a hospital in Iredell County; nine were hospitalized.

Food histories obtained from 39 passengers implicated the ham-and-cheese sandwiches as the vehicle of transmission. Fourteen (38%) of 37 persons who ate the sandwiches became ill, and none (0%) of those who had not eaten them became ill, (p < 0.05). Stool cultures from four of nine hospitalized persons were positive for S. aureus phage type 53, which was also isolated from the ham-and-cheese sandwiches; enterotoxin tests of the sandwiches revealed preformed enterotoxin type A.
• **Staphylococcus aureus** is a common bacterium found on the skin and in the noses of up to 25% of healthy people and animals.

• **Staphylococcus aureus** has the ability to make different toxins that are frequently responsible for food poisoning.
Staphylococcal Food Poisoning

- Staphylococcal food poisoning is a gastrointestinal illness caused by eating foods contaminated with toxins produced by *Staphylococcus aureus*.
- Contamination with *Staphylococcus* occurs through contact with food workers who carry the bacteria or through contaminated milk and cheeses.
- *Staphylococcus* is salt tolerant and can grow in salty foods like ham. As the germ multiplies in food, it produces toxins that can cause illness.
- Staphylococcal toxins are resistant to heat and cannot be destroyed by cooking.
Staphylococcal Food Poisoning

- High risk foods for *S. aureus* contamination and subsequent toxin production are those that are made by hand and require no cooking.

Examples of foods associated with staphylococcal food poisoning are sliced meat, puddings, potato salads, coleslaw and some pastries and sandwiches.
Staphylococcal Food Poisoning

• Staphylococcal toxins are fast acting
  – Illness can ensue in as little as 30-60 minutes.
  – Symptoms usually develop within one to six hours after eating contaminated food.

• Patients typically experience several of the following:
  – nausea, vomiting, stomach cramps, and diarrhea.

• The illness is usually mild and most patients recover after one to three days
Staphylococcal Food Poisoning

- Classic toxin of Staphylococcus food poisoning
- Water soluble, heat stable (100°C), can survive in freeze dried state for up to one year
- Organisms that make a toxin in the food before the food is consumed
- Consumption of the toxin-contaminated food will usually lead to the rapid onset of symptoms (6 to 12 hours) that are predominantly upper intestinal
  - *Staphylococcus aureus*
  - *Bacillus cereus and botulism.*
Staphylococcal Food Poisoning

- Staphylococcal food poisoning will cause a brief, self-limited illness.
- Treatments is rest, fluids, and anti-emetics.
- Elderly or debilitated patients with dehydration may require intravenous hydration therapy and care in a hospital.
- Antibiotics are not useful in treating this illness. The toxin is not affected by antibiotics.
<table>
<thead>
<tr>
<th>Disease or agent</th>
<th>Estimated total cases</th>
<th>Percent foodborne transmission</th>
<th>Percentage of deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwalk-like viruses</td>
<td>23,000,000</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Campylobacter spp</td>
<td>2,500,000</td>
<td>80</td>
<td>5</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>2,000,000</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>Salmonella</td>
<td>1,400,000</td>
<td>95</td>
<td>31</td>
</tr>
<tr>
<td>Shigella</td>
<td>450,000</td>
<td>20</td>
<td>0.8</td>
</tr>
<tr>
<td>Cryptosporidium parvum</td>
<td>300,000</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>Clostridium spp</td>
<td>250,000</td>
<td>100</td>
<td>0.4</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>225,000</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Staphylococcal food poisoning</td>
<td>185,000</td>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>Shiga toxin producing E. coli</td>
<td>110,000</td>
<td>85</td>
<td>1.4</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>100,000</td>
<td>90</td>
<td>0.1</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>27,000</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
<td>16,000</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>2,500</td>
<td>99</td>
<td>28</td>
</tr>
</tbody>
</table>

* Expressed as a percentage of the number of deaths related to foodborne pathogens.

Case

- 24 year old Caucasian woman, medical student
- Travels to Honduras to participate in the VCU HOMBRE program
- On day 6 of the trip, she experiences nausea, no vomiting, but 3-5 loose bowel movements, lasting 2-3 days
- No fever, tenesmus or abdominal pain or cramping are reported
Case

- T 38.2°C, P 75, R 17
- Well nourished, not in distress
- Oral mucosa moist, no lesions
- Chest clear
- Heart no murmurs
- Abdomen: Not distended, bowel sounds normal, not tender no hepatosplenomegaly
- Rectal exam: not done
Traveler’s Diarrhea

• Traveler's diarrhea is the most common illness in persons traveling from resource-rich to resource-poor regions of the world.
• 40 to 60 percent of travelers to these countries may develop diarrhea.
• Episodes of travelers' diarrhea (TD) are nearly always benign and self-limited.
  – Dehydration can complicate an episode and this may be severe and pose a greater health hazard than the illness itself.
Traveler’s Diarrhea

• Classic
  – Passage of three or more unformed stools in a 24 hour period
  – Plus at least one of these other symptoms:
    • Nausea
    • Vomiting
    • Abdominal pain or cramps
    • Fever
    • Blood in stools (uncommon)
Traveler’s Diarrhea

- Diarrheal disease in travelers may be caused by a variety of bacterial, viral, and parasitic organisms, which are most often transmitted by food and water.
- More than 90 percent of illnesses in most geographic areas are caused by bacteria; the most common organism is enterotoxigenic *Escherichia coli* (ETEC).
Traveler’s Diarrhea

- **Enterotoxigenic E. coli**
  - Produces heat labile and stable toxins:
    - Toxins act by stimulating adenylate cyclase and increasing intracellular cyclic AMP/GMP, which results in secretion of chloride from intestinal crypt cells and inhibition of absorption of sodium chloride at the villus tips
      - Small Bowel involvement
    - The secretion of free water follows these changes
    - The result is a watery diarrhea
### Clinical syndromes associated with diarrheagenic Escherichia coli

<table>
<thead>
<tr>
<th>Strain</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>Watery diarrhea</td>
</tr>
<tr>
<td>Enteropathogenic E. coli (EPEC)</td>
<td>Infantile diarrhea</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli (EHEC)</td>
<td>Hemorrhagic colitis and hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Enteroinvasive E. coli (EIEC)</td>
<td>Dysentery</td>
</tr>
<tr>
<td>Enteroaggregative E. coli (EAEC)</td>
<td>Persistent diarrhea in children and patients infected with HIV</td>
</tr>
</tbody>
</table>
The Causes of Traveler’s Diarrhea are Multiple

<table>
<thead>
<tr>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic Escherichia coli</td>
</tr>
<tr>
<td>Enteroaggregative E. coli</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
</tr>
<tr>
<td>Salmonella species</td>
</tr>
<tr>
<td><strong>Shigella species</strong></td>
</tr>
<tr>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus (V. cholerae less common)</td>
</tr>
<tr>
<td>Aeromonas hydrophilia</td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td>Viruses</td>
</tr>
<tr>
<td>Rotavirus</td>
</tr>
<tr>
<td>Enteric adenovirus</td>
</tr>
<tr>
<td>Parasites</td>
</tr>
<tr>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Cryptosporidium parvum</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
</tr>
</tbody>
</table>
Case

- A 51-year-old woman was brought to the hospital after a close friend found her semiconscious, obtunded, and listless.
- On Sunday, she appeared healthy, alert, and talkative. The next morning, she began to experience episodic chills lasting 30 to 40 minutes.
- As the day progressed, her appetite waned as she became weaker. That evening, her lethargy was pronounced.
- The patient had a medical history of chronic active hepatitis B virus (HBV) infection.

http://www.residentandstaff.com/article.cfm?ID=281
Case

• In the ED, she was lethargic and diaphoretic
• She was tachypneic (25-32 breaths/min) & mildly tachycardic (95-105 beats/min), temperature was 103°F and systolic blood pressure between 90 and 100 mm Hg.
• Her sclera were icteric, skin was jaundiced with mild generalized edema.
• Auscultation of her abdomen revealed decreased bowel sounds.
• Palpation of the abdomen revealed diffuse tenderness, and a liver edge was noted 2 to 3 cm below the costodiaphragmatic angle

http://www.residentandstaff.com/article.cfm?ID=281
Case

- Edema of the legs was noted, with the right being more swollen than the left.
- The right leg was erythematous and exquisitely tender.
- Two prominent blisters, approximately 4 and 6 cm in diameter, soft and compressible and filled with serous fluid.

http://www.residentandstaff.com/article.cfm?ID=281
Case

- On the third day, debridement of the right leg was necessary.
- The surgical specimen taken from the right ankle grew a bacillus species later identified as *Vibrio vulnificus*.
- *It was discovered that she had purchased and eaten raw oysters.*
Vibrio vulnificus

June 04, 1993 / 42(21);405-407

July 26, 1996 / 45(29);621-624
Vibrio vulnificus Infections Associated with Eating Raw Oysters -- Los Angeles, 1996
Vibrio vulnificus causes wound infections, gastroenteritis or a serious syndrome known as "primary septicema."
# Vibrio vulnificus

<table>
<thead>
<tr>
<th>Mode of Transmission</th>
<th>Clinical Manifestations</th>
<th>Dermatologic Manifestations</th>
</tr>
</thead>
</table>
| Transmitted to humans through open wounds in contact with seawater or through consumption of certain improperly cooked or raw shellfish. | - Gastroenteritis: usually develops within 16 hours of eating the contaminated food.  
- Sepsis: 60% case fatality  
Over 70 percent of infected individuals have distinctive bullous skin lesions. | From hematogenous spread or from direct inoculation  
Bullous skin lesions |

Avoid raw clams and oysters!
Vibrio vulnificus
Vibrio vulnificus

• High Risk Conditions Predisposing to Vibrio vulnificus infection:
  – Liver disease, either from excessive alcohol intake, viral hepatitis or other causes
  – Hemochromatosis
  – Diabetes mellitus
  – Stomach problems, including previous stomach surgery and low stomach acid (for example, from antacid use)
  – Immune disorders, including HIV infection
  – Long-term steroid use (as for asthma and arthritis).
**Vibrio vulnificus**

<table>
<thead>
<tr>
<th>Diagnostic Pearls</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>- A physician should suspect <em>V. vulnificus</em> if a patient has watery diarrhea and has eaten raw or undercooked oysters or when a wound infection occurs after exposure to seawater</td>
<td>Vibrio organisms can be isolated from cultures of stool, wound, or blood the laboratory should be notified as a special growth medium is preferred</td>
</tr>
</tbody>
</table>

**RX:**
Doxycycline or a third-generation cephalosporin (e.g., ceftazidime)
Case

- 50 year old woman presents to the office with a 3 day history of watery diarrhea accompanied by crampy abdominal pain
- She is having 10-12 bowel movements in a 24 hour period and is awakened from sleep to use the bathroom
- She has low grade fever, but denies nausea, vomiting and blood in the stool
- Two weeks ago she was treated with a course of ampicillin for an *E.coli* infection of the urinary tract
Case

- T 38, P 92, RR 12, BP 122/80
- General: well nourished
- HEENT: dry mucous membranes
- Cardiac- normal
- Chest- clear
- Abdomen- soft, diffuse, mild tenderness to the right and left lower quadrants; bowel sounds hyperactive
- Rectal: trace heme positive stools
- Extremity and skin: no edema, no rashes
Case

- WBC 16,200/uL
  - 90% Neutrophils
  - 8% Bands
  - 2% Lymphocytes
- Bun 40 mg/dL
- Creat 1.2 mg/dL
- Sigmodoscopy:
Clostridium difficile

- *Clostridium difficile* is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of antibiotic-associated diarrhea and colitis.
Epidemiology

• *C. difficile* cultured from the stool of 3% of healthy adults and up to 80% of healthy newborns and infants.

• Stool carriage of *C. difficile* reaches 16–35% among hospital inpatients.

• *C. difficile* persists in the stools of 10–40% of patients with CDAD regardless of antibiotic treatment.

• Contaminated environmental surfaces, other patients with CDAD and hand carriage on the part of healthcare personnel are important reservoirs for cross transmission.


Risk Factors and Pathophysiology

• *C. difficile* is more likely to cause clinical disease in patients who are newly exposed

• Patients who are already colonized with *C. difficile* typically remain asymptomatic during their hospital stay

Risk Factors and Pathophysiology

• The association of developing *C. difficile* infection following exposure to antibiotic is well defined
  – The probability of CDAD is greatest with Clindamycin and Ampicillin
  – Fluoroquinolones are now increasingly associated with CDAD

## Antibiotics and CDAD

<table>
<thead>
<tr>
<th>Highly associated</th>
<th>Moderately Associated</th>
<th>Rarely Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Other Beta-lactam antibiotics</td>
<td>Parenteral Aminoglycosides</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Sulfonamides</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Erythromycin</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Trimethoprim</td>
<td>Metronidazole</td>
</tr>
<tr>
<td></td>
<td>Quinolones</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>
Toxins

- **Enterotoxin A**
  - Causes fluid accumulation in the bowel
- **Cytotoxin B**
  - Cytopathic toxin
    - Promotes cell lysis and death

*C. difficile endospores*
Pathophysiology

• *C. difficile* toxins A and B are large proteins
  (308 kDa and 275 kDa)
• Both toxins adhere to receptors on the human colonocyte brush border and cause:
  • Necrosis
  • Shedding of cells into the GI lumen
Risk Factors and Pathophysiology

1. Receipt of antibiotics
2. Disruption of microflora in colon
3. Exposure and colonization by *C. difficile*
4. Release of toxins A and B with resultant mucosal injury
Carrier State

• Once infected, 2/3 of infected hospitalized patients remain asymptomatic
  – Carriers are reservoirs of toxigenic organisms

• Routine treatment of carriers is not recommended
  – The carrier state can be eliminated by use of vancomycin, however, culture positivity returns upon cessation of the antibiotic
  – Treatment of carriers may be employed during hospital outbreaks
    • Elimination of the organism from the hospital environment


Antibiotic Associated Diarrhea Without Colitis

- Common in hospitalized patients
- Diarrhea is mild
  - 3-4 loose watery stools per day
  - Cramping
- Physical examination is normal with only minimal lower abdominal tenderness
- Fever, leukocytosis, and dehydration are mild or absent
- *C. difficile* toxins present in stool
- Sigmoidoscopic examination is normal
Antibiotic Associated Colitis Without Pseudomembrane Formation

- Abdominal pain, nausea, anorexia
- Profuse watery diarrhea of 5 to 15 watery bowel movements per day
- Left or right lower quadrant abdominal pain and cramps
- Fever and dehydration
- Sigmoidoscopic examination may reveal a nonspecific diffuse or patchy erythematous colitis without pseudomembranes
Pseudomembranous Colitis

• Appears as raised yellow or off-white plaques ranging up to 1 cm in diameter scattered over the colorectal mucosa

• Similar clinical symptoms of diarrhea, fever, leukocytosis and abdominal pain
Histopathology of pseudomembranous colitis

- The pseudomembrane membrane is composed of fibrin.
- Adheres to the damaged colon surface and blocks the absorptive surface layer further adding to diarrhea.

http://www.pathguy.com/~tdemark/0075.htm
Pseudomembranous colitis

Axial CT images show distention and significant colonic wall thickening of the transverse and sigmoid colon
Fulminant Colitis and Toxic Megacolon

- 2 or 3 percent of patients
- Marked leukocytosis (>30,000 to 40,000 WBC/microL)
- Fever, chills, dehydration and metabolic (lactic) acidosis
- Diarrhea is prominent
  - However, diarrhea is less prominent in patients with ileus and secondary pooling of secretions in the dilated, adynamic colon
Toxic Megacolon

- Diagnosis based upon the finding of an enlarged dilated colon
  - >7 cm in its greatest diameter
- Accompanied by severe systemic toxicity

http://www.cfpc.ca/cfp/2004/Nov/_images/Fig0376_104_A.jpg
Hospital-acquired *Clostridium difficile*-associated disease in the intensive care unit setting: epidemiology, clinical course and outcome

- Historical cohort study on 58 adults with CDAD occurring in intensive care units at VCUMC.
- In ICU patients with CDAD, advanced age and increased severity of illness at the onset of infection were independent predictors of death.
- The in-hospital mortality was 27.6%.

Marra A, Edmond MD, Wenzel RP and Bearman G. *BMC Infectious Diseases* 2007, 7:42
ELISA for Toxin Detection

- Rapid assays with comparable sensitivity (70 to 90 percent) and specificity (99 percent)
- Some detect Toxin A only
  - Toxin A variant strains (toxin A-negative, toxin B-positive strains) relatively infrequent
    - (1-2% of all isolates)

# Treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Mild CDAD                        | • Discontinue offending antibiotic  
                                       • Oral Metronidazole                                                      |
| Moderate to severe               | • Oral vancomycin  
                                       • Oral metronidazole  
                                       • IV metronidazole (ileus) + oral vancomycin via NG tube  
                                       • Antibiotics + IVIG                                                      |
| Recurrences                      | • Repeat metronidazole therapy  
                                       • Repeat Vancomycin therapy  
                                       • Nitazoxanide                                                            |
| Severe ileus, toxic megacolon    | • Surgical evaluation for complete colectomy                              |
• “An Anchorage woman reported that she and her husband had become ill about one-half hour after consuming a meal of marinated raw salmon. Illness consisted of generalized hives, a brassy taste, flushing, abdominal cramps, nausea, and vomiting without diarrhea. Symptoms persisted for four hours.”
August 12th, a Valdez physician informed our office that three days previous she had treated nine Japanese sailors for an illness which began one hour after eating a meal of mixed raw cod, flounder and salmon.

Illness was said to have affected most of the 23 man crew, but only nine were seen by the doctor.

She found tachycardia in two, hives in four, nausea in eight, and vomiting in two. No respiratory difficulty was noted. Treatment included emetics, antihistamines, and epinephrine.

Symptoms resolved by morning and the crew left for Japan with a cargo of refrigerated raw fish.
Is this an allergic reaction to fish?
Scombroid

- Scombroid fish poisoning is a food-related illness typically associated with the consumption of fish.
  - Scombroidea fish
    - Large dark meat marine tuna, Albacore, mackerel, skipjack, bonito, marlin Mahi-Mahi
Scombroid

Symptoms are related to the ingestion of biogenic amines, especially histamine. Serum histamine levels and urinary histamine excretion are elevated in humans with acute illness.

The result is a massive histamine like reaction

Cooking does not inactivate the toxin!
# Scombroid

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Dermatologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The onset of symptoms is 10-30 minutes after ingestion the fish, which is said to have a characteristic <strong>peppery bitter</strong> taste.</td>
<td>Nonspecific: diffuse, macular, blanching erythema and hives</td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Nausea and Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Sense of anxiety</td>
<td></td>
</tr>
<tr>
<td>Prostration or loss of vision (rare)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia and wheezing</td>
<td></td>
</tr>
<tr>
<td>Hypotension or hypertension</td>
<td></td>
</tr>
</tbody>
</table>
## Scombroid

<table>
<thead>
<tr>
<th>Diagnostic Pearls</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease of acute onset and short duration</td>
<td>• ECG, IV access, oxygen, and cardiac monitoring as needed.</td>
</tr>
<tr>
<td>• Diagnosis is clinical; no laboratory tests are necessary.</td>
<td>• Treat bronchospasm as needed</td>
</tr>
<tr>
<td>• If the diagnosis requires confirmation, histamine levels can be measured in a the suspect frozen fish</td>
<td>• Treat with antihistamines: H1- and H2-blockers.</td>
</tr>
<tr>
<td></td>
<td>• Consider use of activated charcoal only if presentation is very early and a large amount of fish was ingested.</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Incubation Period</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Histamine (scombroid)</td>
<td>5 min–1 h</td>
</tr>
<tr>
<td>Ciguatera</td>
<td>1–6 h</td>
</tr>
<tr>
<td>Neurotoxic shellfish poisoning</td>
<td>5 min–4 h</td>
</tr>
<tr>
<td>Paralytic shellfish poisoning</td>
<td>5 min–4 h</td>
</tr>
<tr>
<td>Domoic acid</td>
<td>15 min–38 h</td>
</tr>
<tr>
<td>Haff disease</td>
<td></td>
</tr>
</tbody>
</table>
Enteric Infections