• Chapter 57, Digestive System
• Chapter 16, Enteric Bacteria, Secretory Diarrhea
• Chapter 17, Invasive and Tissue-damaging enteric Bacteria
• Chapter 37, Rotavirus and other viral agents of gastroenteritis
• Chapter 51, Intestinal Protozoa
• Chapter 73, Food-borne diseases
I. Diarrhea, definition:
- Implies a change in bowel habits
- Production of up to 3 loose stools per day without abdominal or systemic symptom (mild).
- Production of 4 or more loose stools per day, often associated with local symptoms such as abdominal cramps, nausea, vomiting or tenesmus, or systemic symptoms, such as fever, malaise or dehydration (moderate to severe).

II. Diarrhea, worldwide impact:
- Second only to acute respiratory infections as leading cause of death (3.1 million deaths in 1995)
- Major toll in children
Other major killers worldwide in 1995:

- acute respiratory infections 4.4 million
- tuberculosis 3.1 million
- malaria 2.1 million
- AIDS > 1 million
- measles > 1 million
- hepatitis B 1.1 million
- neonatal tetanus 0.5 million
- whooping cough 0.4 million
III. Infectious causes of gastrointestinal disease, classification systems:

A. By organism

1. Bacteria
   - Shigella
   - Salmonella
   - Escherichia coli
   - Campylobacter
   - Yersinia
   - Vibrio cholera
   - Clostridium difficile
   - Aeromonas hydrophila
   - Bacillus cereus
2. Protozoa
   - Giardia lamblia
   - Cryptosporidia
   - Entamoeba histolytica
   - Isospora belli
   - Cyclospora
   - Microsporidia

3. Virus
   - Rotavirus
   - Adenovirus, serotypes 40, 41
   - Calicivirus (includes Norwalk and other small round structured virus)
   - Astrovirus

4. Fungus
   - Candida ??
B. By mechanism of disease production
   1. Non-inflammatory
      - Majority of diarrhea disease
      - Usually involves upper small bowel
      - Often result from production of an enterotoxin
        a) Vibro cholera
        b) Enterotoxigenic E. coli
        c) Bacillus cereus
        d) Clostridium perfringens
      - May result from other processes which alter absorptive function of villus tip
        a) Enteropathogenic E. coli
        b) Cryptosporidium
        c) Giardia
        d) Rotavirus
        e) Norwalk virus
2. Inflammatory
- Often involves invasion of GI mucosa and/or production of cytotoxin
- Usually involves colon
  a) Shigella
  b) Salmonella
  c) Campylobacter
  d) Clostridium difficile (cytotoxin)
  e) Entamoeba histolytica

3. Bacteremia and systemic infection
   a) Enteric fevers (typhoid)
   b) Non-typhoid salmonella bacteremia
   c) Less common, shigella, campylobacter
C. By clinical presentation

1. Emphasis on nausea, vomiting rather than diarrhea, and absent or low grade fever, upper abdominal symptoms
   a) Staphylococcus aureus, preformed enterotoxin in food
   b) Bacillus cereus (emetic), preformed enterotoxin in food
   c) Heavy metal food poisoning

2. Emphasis on nausea, vomiting, large volume watery stools, absent or low grade fever (<102°F)
   a) Vibrio cholera
   b) Enterotoxigenic E. coli
   c) Bacillus cereus (diarrheal)
   d) Clostridium perfringens
   e) Giardia lamblia
   f) Rotavirus, Norwalk
   g) Cryptosporidium
3. Emphasis on lower intestinal (colon) symptoms with smaller volume frequent stools, tenesmus, fever, abdominal cramps, bloody stools, leukocytes in stools.
   a) Shigella
   b) Salmonella (colonic form)
   c) Campylobacter
   d) Non-cholera vibrios (e.g. V. parahemolyticus)
   e) Enteroinvasive E. coli
   f) Entamoeba histolytica

4. Emphasis on systemic illness with toxicity, prostration, high fever; diarrhea may be absent
   a) Enteric fever (typhoid)
   b) Non-typhoid salmonella bacteremias

D. By social setting or underlying immune status of host
1. Hospital acquired (nosocomial)
   a) Clostridium difficile
   b) Salmonella
   c) Rotavirus
   d) Candida ?
2. Day-care centers
   a) Shigella
   b) Rotavirus
   c) Giardia
   d) Cryptosporidium

3. Traveler’s diarrhea
   a) Enterotoxigenic E. coli
   b) Giardia lamblia
   c) Salmonella
   d) Shigella

4. Food-borne and water-borne disease
   (See Appendix)
   a) 90% of food poisoning in USA caused by Salmonella, Shigella, Clostridium perfringens, Staphylococcus aureus and Campylobacter
   b) Most outbreaks of water-borne disease in USA involves Giardia, Cryptosporidium, Shigella, Salmonella, Campylobacter and Norwalk virus

5. Patients with AIDS
   (See Appendix)
IV. Workup and Management of Patients with Diarrhea  
(See Appendix)  
V. Notes on specific pathogens  

A. Enteropathogenic E. coli  
- Specific serotypes (0111:H-4, 055:H-5 examples)  
- Epidemic infantile diarrhea, hospital nursery outbreaks, especially in developing countries  
- Adhere to and efface the brush border of small intestine  
- In-vitro, adhere to Hep-2 cells in focal manner  
- Diagnosis not available in routine lab
B. Enterohemorrhagic E. coli

- Recently described outbreaks and sporadic cases
- Undercooked ground beef most frequently documented food
- A rare serotype, 0157:H7, most common cause
- A shiga-like toxin or verotoxin, toxic to epithelial and endothelial cells is elaborated
- Patients may present with severe abdominal cramps, grossly bloody stools, copious diarrhea without fecal leukocytes or fever
- Diagnosis facilitated by finding sorbitol negative organisms on Mac-conkey-sorbitol agar
- Antibiotics not shown to be effective; may promote HVS
- Associated with hemolytic uremic syndrome
C. Enterotoxigenic E. coli

- Most common bacterial cause of acute bacterial diarrhea worldwide, especially as traveler’s diarrhea and diarrhea of children less than age 2 years
- Most commonly spread through contaminated food
- Humans only known source
- Plasmid mediated enterotoxin, heat liable and heat stable, result in large volume watery diarrhea
- Heat labile enterotoxin, immunologically similar to cholera toxin activates adenylate cyclase, increases cellular CAMP, resulting in chloride and water secretion
- Diagnosis not available in routine lab
- Treatment for “traveler’s diarrhea” using trimethoprim-sulfra or ciprofloxacin
D. Enteroinvasive E. coli
- Uncommon outbreaks of dysentery in adults, often transmitted by food
- Clinically and pathologically similar to Shigella
- As in Shigella, a large 140 MD plasmid codes for invasiveness
- Diagnosis not available in routine lab

E. Entroaggregative E. coli
- Identified by typical aggregative, “stacked brick” pattern of adherence to Hep-2 cells
- Recently identified as cause for traveler’s diarrhea, persistent childhood diarrhea in developing countries, and chronic diarrhea in patients with AIDS
F. Salmonella
- Taxonomy/classification is confusing. S. enteritidis and S. typhimurium most common in United States. S. choleraesuis frequently causes bacteremia
- Non-typhi salmonella widely distributed in animal kingdom (zoonosis). S. typhi have humans as their only host
- In both instances organisms often spread through contaminated food and water
- Three basic clinical presentations: gastroenteritis, enteric fever and extra intestinal infection
- Diagnosis made in most labs by culture of stool or blood
- Antibiotics necessary for enteric fever and extra intestinal infection; usually not given for gastroenteritis (except extremes of age, immunocompromised, AIDS, sickle cell)

G. Shigella
- S. dysenteriae, boydii, flexneri and sonnei.
- S. sonnei, most common in United States. S. flexneri most common in patients with AIDS
- As true for salmonella, isolation rates highest from children under 5 years
- Classic cause of dysentery
- Shiga toxin, a potent cytotoxin, produced by S. dysenteriae, type 1; role in pathogenesis not clear
- Complications, especially with S. dysenteriae, include HUS, toxic megacolon, encephalopathy, seizures, reactive arthritis
- Diagnosis made in most labs by stool culture (bacteremia is rare)
- Treatment with antibiotics provided for patients with moderate to severe illness (probably shortens course and reduces transmission).

H. Cholera

- Epidemic cholera caused by Vibrio cholera 01 and recently (India, 1992) 0139 - possibly 8th cholera pandemic
- Usually transmitted to humans by contaminated water (or food) or poorly cooked shellfish
- Classic non-inflammatory diarrhea mediated by enterotoxin (choleragen)
- Patients die from dehydration and electrolyte loss (hypokalemia and hyperchloremic acidosis)
- Diagnosis made in most labs by stool culture
- Treatment consists of aggressive rehydration and tetracycline (which helps to shorten the illness).

I. Campylobacter
- C. jejuni is the most frequent bacterial cause of enteritis in developed countries
- Incidence peaks in children less than 1 year and adults 15-29 years
- Widely dispersed in animal kingdom; handling and consuming poultry are most important risk factors in United States
- Diarrhea is often accompanied by severe cramping abdominal pain
- Sequelae may include reactive arthritis and Guillain-Barre
- Diagnosis made in most labs using microaerophilic atmosphere and 42°C temperature for stool culture
- Treatment using erythromycin given to those with marked symptoms and/or immunocompromised host.
J.  Clostridium difficile
- A common (perhaps most common) infectious cause of hospital-acquired diarrhea.
- Preceding antibiotic use (almost all classes of antibiotics) predispose to its overgrowth in the colon.
- Overgrowth with this organism can result in elaboration of cytotoxin(s) which mediate an inflammatory colitis and diarrhea.
- Severe colitis may be present with pseudomembranes seen on colonoscopy or sigmoidoscopy.
- Diagnosis can be established by performing tissue-culture assay or EIA on the patient’s stool sample.
- Effective treatment is available using oral metronidazole or vancomycin.

K. - Norwalk virus
- 27 nanometer single-stranded RNA
- Epidemic outbreaks in children and adults
- Disease can occur throughout the year
- “Classic” cause of winter vomiting disease in adults
- Transmitted by contaminated water and poorly cooked shellfish, and person to person (fecal/oral)
Illness, usually lasts 1-2 days with vomiting and diarrhea

Diagnosis made using immune electron microscopy, RIA, EIA, PCR; available only in reference labs such as CDC

L. Rotavirus

- 70 nanometer double-standard RNA

- Most common cause of severe diarrhea in children both in developed and under developed countries

- Especially common in children age 6-24 months. Adults less commonly symptomatic

- Tends to infect community in the winter and be sporadic rather than epidemic

- Transmitted primarily person to person (fecal/oral) and not by common sources (food, water) outbreak

- Recently developed vaccine has been removed from clinical use because associated with intussusception
- Illness, usually lasts 4-8 days with vomiting and diarrhea
- Diagnosis made using immune electron microscopy, or (in most labs) using ELISA, on stool samples.

M. Giardia lamblia
- Giardiasis is the most commonly reported parasitic disease in the United States
- Infection occurs by direct fecal-oral transmission and through contaminated water or food
- Inhabits upper small bowel; does not invade mucosa
- Incubation period is 1-3 weeks and symptoms usually last 5-7 days
- Giardia well known to cause prolonged illness and diarrhea
- Diagnosis made by stool exam for cysts (may require multiple samples), small bowel biopsy, “string test” or detection of stool antigen using ELISA
- Treatment is with metronidazole, furazolidone or quinacrine
<table>
<thead>
<tr>
<th>Cause</th>
<th>Outbreaks</th>
<th>Percent Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non typhoidal salmonella</td>
<td>342</td>
<td>57.3</td>
</tr>
<tr>
<td>Shigella</td>
<td>44</td>
<td>18</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>47</td>
<td>5.8</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>24</td>
<td>5.0</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>28</td>
<td>1.3</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>(EHEC &gt; ETEC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Listeria</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>3</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichinella spiralis</td>
<td>33</td>
<td>0.3</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norwalk</td>
<td>10</td>
<td>2.1</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>29</td>
<td>2.0</td>
</tr>
</tbody>
</table>
## Common Causes of Food Poisoning in the United States*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Outbreaks</th>
<th>Percent Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infectious/Chemical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciguatoxin</td>
<td>87</td>
<td>0.6</td>
</tr>
<tr>
<td>Scrombrotoxin</td>
<td>83</td>
<td>0.6</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>13</td>
<td>0.3</td>
</tr>
<tr>
<td>Mushrooms</td>
<td>14</td>
<td>0.1</td>
</tr>
<tr>
<td>Paralytic shellfish</td>
<td></td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Neurotic shellfish</td>
<td></td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

* Data from CDC, 1983-87
Food Poisoning in the United States

Important Points to Remember

1. From 1988 through 1991, 58 percent of outbreaks and 56 percent of cases never had a specific etiology found.

2. In the last 5-10 years, there has been increasing recognition of the following organisms as important causes of food poisoning in the United States:

   - **Enterohemorrhagic E. coli**: Since 1993, more than 100 documented outbreaks of E. coli 0157 H7
   - **Cryptosporidium***: Recent outbreak in Maine, freshly pressed apple cider
   - **Cyclospora**: Highly publicized outbreaks 1996, 1997; Guatemalan raspberries
   - **Listeria**: Contaminated milk and cheese and hotdog; pregnant women and immunocompromised patients may be at high risk for severe invasive disease
   - **Campylobacter jejuni**: The most common cause of bacterial gastroenteritis in developed countries, and most cases result from contaminated poultry products

*1993: 400,000 persons were infected in Milwaukee from contaminated tap water
## Foods Associated with Some Foodborne Diseases

<table>
<thead>
<tr>
<th>Food</th>
<th>Associated Organisms and Diseases</th>
</tr>
</thead>
</table>
| Beef and Pork | Salmonella  
              | Staphylococcus aureus  
              | Clostridium perfringens  
              | Enterohemorrhagic Escherichia coli  
              | Bacillus cereus  
              | Yersinia enterocolitica  
              | Listeria monocytogenes  
              | Brucella  
              | Trichinella spiralis |
| Poultry    | Salmonella  
              | Staphylococcus aureus  
              | Campylobacter  
              | Clostridium perfringens  
              | Listeria monocytogenes |
| Eggs       | Salmonella  
<pre><code>          | Staphylococcus aureus |
</code></pre>
<table>
<thead>
<tr>
<th>Food</th>
<th>Associated Organisms and Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk and Cheese</td>
<td>Salmonella</td>
</tr>
<tr>
<td></td>
<td>Campylobacter</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli (EIEC and EHEC)</td>
</tr>
<tr>
<td></td>
<td>Yersinia enterocolitica</td>
</tr>
<tr>
<td></td>
<td>Group A streptococci</td>
</tr>
<tr>
<td></td>
<td>Brucella</td>
</tr>
<tr>
<td></td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Clostridium botulinum</td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
</tr>
<tr>
<td></td>
<td>Bacillus cereus</td>
</tr>
<tr>
<td></td>
<td>Norwalk virus</td>
</tr>
<tr>
<td>Fish</td>
<td>Clostridium botulinum</td>
</tr>
<tr>
<td></td>
<td>Ciguatera</td>
</tr>
<tr>
<td></td>
<td>Scombroid fish poisoning</td>
</tr>
<tr>
<td></td>
<td>Diphyllobothrium latum</td>
</tr>
<tr>
<td></td>
<td>Anisakiasis</td>
</tr>
</tbody>
</table>
# Foods Associated with Some Foodborne Diseases

<table>
<thead>
<tr>
<th>Food</th>
<th>Associated Organisms and Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellfish</td>
<td>Vibrio parahaemolyticus&lt;br&gt;Vibrio cholerae (O1 and non-O1)&lt;br&gt;Hepatitis A&lt;br&gt;Norwalk and Norwalk-like viruses&lt;br&gt;Paralytic shellfish poisoning&lt;br&gt;Neurotoxic shellfish poisoning</td>
</tr>
<tr>
<td>Chinese Food</td>
<td>Bacillus cereus (in fried rice)</td>
</tr>
<tr>
<td>Carbonated Drinks</td>
<td>Heavy metal poisoning</td>
</tr>
<tr>
<td>Honey</td>
<td>Clostridium botulinum</td>
</tr>
</tbody>
</table>
## Food Poisoning Syndromes Characterized by Nausea and Vomiting

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incubation</th>
<th>Duration</th>
<th>Fever &gt;38.5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus intoxication</td>
<td>1-6 h</td>
<td>&lt;24 h</td>
<td>Rare</td>
</tr>
<tr>
<td>Bacillus cereus intoxication (emetic)</td>
<td>1-6 h</td>
<td>&lt;24 h</td>
<td>Rare</td>
</tr>
<tr>
<td>Heavy metal poisoning</td>
<td>5-120 min</td>
<td>&lt;24 h</td>
<td>Absent</td>
</tr>
<tr>
<td>Anisakiasis</td>
<td>12 h - 2 wk</td>
<td>Variable</td>
<td>Present</td>
</tr>
<tr>
<td>Diphyllobothriasis</td>
<td>Days</td>
<td>Years</td>
<td>Absent</td>
</tr>
<tr>
<td>Organism</td>
<td>Incubation</td>
<td>Duration</td>
<td>Fever &gt; 38.5°C</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>6-24 h</td>
<td>24 h</td>
<td>Rare</td>
</tr>
<tr>
<td>Norwalk virus</td>
<td>24-48 h</td>
<td>24-48 h</td>
<td>Occasional</td>
</tr>
<tr>
<td>Bacillus cereus (diarrheal)</td>
<td>6-24 h</td>
<td>20-36 h</td>
<td>Rare</td>
</tr>
<tr>
<td>Enterotoxigenic Escherichia coli</td>
<td>16-72 h</td>
<td>5-10 d</td>
<td>Occasional</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>16-72 h</td>
<td>5-7 d</td>
<td>Absent</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>2 wk</td>
<td>Days-months</td>
<td>Absent</td>
</tr>
</tbody>
</table>
### Food Poisoning Syndromes Characterized by Inflammatory Diarrhea

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incubation</th>
<th>Duration</th>
<th>Fever $&gt;38.5^\circ C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontyphoidal Salmonella</td>
<td>6-48 h</td>
<td>&lt; 7 d</td>
<td>Present</td>
</tr>
<tr>
<td>Shigella</td>
<td>16-72 h</td>
<td>1 d - 1 mo.</td>
<td>Present</td>
</tr>
<tr>
<td>EIEC</td>
<td>16-48 h</td>
<td>Self-limited</td>
<td>Present</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>16-48 h</td>
<td>Self-limited</td>
<td>Present</td>
</tr>
<tr>
<td>Vibrio parahaemolyticus</td>
<td>5-24 h</td>
<td>Self-limited</td>
<td>Rare</td>
</tr>
<tr>
<td>Yersinia</td>
<td>16-48 h</td>
<td>1-3 wk</td>
<td>Present</td>
</tr>
<tr>
<td>EHEC</td>
<td>1-8 d</td>
<td>3-6 d</td>
<td>Rare</td>
</tr>
<tr>
<td>Typhoidal Salmonella</td>
<td>1-3 wk</td>
<td>3-4 wk</td>
<td>Present</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Variable</td>
<td>Variable</td>
<td>Occasional</td>
</tr>
</tbody>
</table>
## Food Poisoning Syndromes Characterized by Neurologic Symptoms

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incubation</th>
<th>Duration</th>
<th>Fever &gt; 38.5°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium botulinum infection</td>
<td>12-36 h</td>
<td>Weeks-months</td>
<td>Rare</td>
</tr>
<tr>
<td>Ciguatera fish poisoning</td>
<td>1-30 h</td>
<td>Days-months</td>
<td>Absent</td>
</tr>
<tr>
<td>Scombroid fish poisoning</td>
<td>10-180 min</td>
<td>4-6 h</td>
<td>Absent</td>
</tr>
<tr>
<td>Paralytic shellfish poisoning</td>
<td>5-240 min</td>
<td>Hours-days</td>
<td>Absent</td>
</tr>
<tr>
<td>Neurotoxic shellfish poisoning</td>
<td>5-240 min</td>
<td>Hours-days</td>
<td>Absent</td>
</tr>
<tr>
<td>Toxic encephalopathic shellfish poisoning</td>
<td>1-38 h</td>
<td>Days-weeks</td>
<td>Absent</td>
</tr>
<tr>
<td>Mushroom poisoning</td>
<td>1-12 h</td>
<td>Depends on mushroom type</td>
<td>Absent</td>
</tr>
<tr>
<td>Monosodium glutamate reaction</td>
<td>&lt; 1 h</td>
<td>1-6 h</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Recommendations for cost-effective testing for enteric pathogens

- Routine cultures should always include *Campylobacter*, *Salmonella*, and *Shigella*; other agents included in the routine culture panel should be determined on the basis of in-house or regional survey data.

- Submit additional samples for less common bacteriologic agents as a second-line test after the common agents have been ruled out.

- Up to two stool samples should be submitted for oval and parasite examination for optimal sensitivity. Wait for the results of the first culture and/or examination before sending additional samples, rather than ordering multiple tests.
Recommendations for cost-effective testing for enteric pathogens (continued)

- Two to three samples may also be needed to rule out *Clostridium difficile* disease, and samples should be spaced several days apart.

- Use the 3-day rule for routine stool cultures and/or parasitological examinations for hospitalized patients.

- Because there are new tests for *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*, consider testing specifically for these agents initially and forego the initial routine ova and parasite examination, especially when other parasitic agents are unlikely.