Infectious Diarrheal Diseases

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Outline

• Epidemiology
• Pathogenic Mechanisms
• Host Defenses
• Representative Organisms
  – Non-inflammatory diarrhea
  – Inflammatory diarrhea
  – Enteric Fever
• Approach to the Patient
Epidemiology

• Major cause of morbidity and mortality in children developing world
  – Attack rate: 10-18 illnesses per child per year
  – In Asia, Africa, Latin America there are approximately 1 billion cases/yr resulting in 4-6 million deaths per year (12,600 deaths/day)
  – In some areas >50% of childhood deaths are attributable to acute diarrheal illnesses

Epidemiology

• Overall burden not well studied in developed world
  – Attack rate: 1-3 illnesses per child per year
  – Food-borne diarrheal disease in U.S.
    • 76 million illnesses per year
    • 350,000 hospitalizations
    • 5,000 deaths
  – Waterborne outbreaks
Epidemiology

- Most cases of acute infectious diarrhea are caused by viruses
- Bacterial pathogens isolated in 1-6% of cases
- Limitation of hospital based survey:
  - 22% examined
  - 5% submitted stool

Bacterial Pathogens

- Water/Foodborne
  - Campylobacter
  - Salmonella (nontyphi)
  - Enterohemorrhagic E. coli (EHEC) and Enterotoxigenic E. coli (ETEC)
  - Vibrio
  - Yersinia
  - Clostridium perfringens
  - Bacillus cereus
  - Staphylococcus aureus

- Person-to-person
  - Shigella
  - Salmonella typhi
Pathogenic Mechanisms

• Inoculum size
• Adherence
• Toxin Production
  – Enterotoxin
  – Cytotoxin
  – Neurotoxin
• Invasion

Pathogenic Mechanisms

• Inoculum size
  – 10-100 organisms
    • Shigella
  – <1000 organisms
    • Enterohemorrhagic E. coli (EHEC)
    • Salmonella typhi
    • Campylobacter jejuni
  – $10^5$ to $10^8$ organisms
    • Vibrio cholera
    • Salmonella (nontyphoidal)
Pathogenic Mechanisms

• Toxin Production
  – **Enterotoxin**: cause watery diarrhea by acting directly on secretory mechanisms in the intestinal mucosa
    • *Vibrio cholera*, *ETEC*, *Clostridium perfringens*
  – **Cytotoxin**: cause destruction of mucosal cells and associated with inflammatory diarrhea
    • *Shigella*, Shiga-like toxin or verotoxin (EHEC)
  – **Neurotoxin**: act directly on central or peripheral nervous system
    • *Staphylococcus aureus*, *Bacillus cereus*

Pathogenic Mechanisms

• Cholera Toxin (enterotoxin)
  – Composition of Toxin
    • A subunit (enzymatic activity)
    • B subunit (binds to enterocyte surface receptor, the ganglioside $G_{M1}$)
  – After binding to enterocyte, A subunit
    • translocated across cell membrane
    • catalyzes ADP ribosylation of a GTP-binding protein resulting in persistent activation of adenylate cyclase
Cholera Toxin

Pathogenic Mechanisms

- **Shiga Toxin (cytotoxin)**
  - Produced by *S. dysenteriae*
  - B subunit binds to host cell glycolipid (Gb3) and facilitates transfer of A subunit
  - A subunit disrupts protein synthesis by preventing binding of aminoacyl-transfer RNA to the 60S ribosomal subunit
  - Results in destruction of intestinal cells and villi, decreasing intestinal absorption
Pathogenic Mechanisms

• Staphylococcus Aureus enterotoxin (neurotoxin)
  – Heat-stable toxin
  – Increases peristalsis by sympathetic activation, resulting in intense vomiting

• Bacillus Cereus enterotoxin
  – Two enterotoxins
    • Emetic: incubation period 1-6 hours
    • Diarrheal: Incubation period 10-12 hours

Pathogenic Mechanisms

• Tissue Invasion
  – Salmonella Pathogenicity Island-1 and 2 (SPI-1 & SPI-2)
    • Binds to microfold cells (M cell) or enterocytes
    • Introduces salmonella-secreted invasion proteins (Sips or Ssps) into M cells resulting in membrane ruffling and phagocytosis
    • Replicates in phagosome (tolerant to acids)
    • Spreads to adjacent epithelial cells and lymphoid tissue.
Host Defenses

- Normal Flora
  - Anaerobes: acidic pH & fatty acid production prevent colonization by bacterial pathogens
- Gastric Acid
  - Increased frequency of Salmonella among patients with gastric bypass
- Intestinal Motility
  - Impaired motility allows for bacterial overgrowth
- Immunity
  - Secretory IgA, systemic IgG and IgM
  - Cell-mediated immunity
    - Binding of bacterial antigens to the luminal side of M cells in distal small intestines, subsequent presentation of antigen to subepithelial lymphoid tissue

Clinical approach to Infectious Diarrheas

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Watery Diarrhea (Non inflammatory)</th>
<th>Bloody diarrhea (Inflammatory)</th>
<th>Enteric Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Proximal small bowel</td>
<td>Colon or distal small bowel</td>
<td>Penetrating systemic infection</td>
</tr>
<tr>
<td>Location</td>
<td>Vibrio cholera ETEC</td>
<td>Shigella spp. Salmonella (Nontyphoidal) Campylobacter jejuni EIEC (EHEC) Clostridium difficile</td>
<td>Salmonella typhi Yersinia enterocolitica</td>
</tr>
<tr>
<td>Pathogens</td>
<td>Bacillus cereus Staphilococcus aureus</td>
<td>Clostridium Perfringens</td>
<td>Clostridium difficile</td>
</tr>
</tbody>
</table>
A case of watery diarrhea

- 1 year old boy with abrupt onset of watery diarrhea and vomiting
- No fever, no bloody stool
- Development of sunken eyes, dry mouth, inability to feed, lack of urination
- Lethargic, unresponsive, death
- Father also with watery diarrhea (1 liter/hour), vomiting, cramps
Index case

- “underneath the floorboards of the overcrowded cellars lurked … a fetid sea of cesspits as old as the houses, many of which had never been drained”
- London had over 200,000 cesspools
- No incentive for maintenance

Vibrio Cholera

- Microbiology
  - Identified by Filippo Pacini in 1854 and Robert Koch in 1883
  - Curved gram negative bacillus with single polar flagellum
  - Over 200 serogroups, but only 01 and 0139 somatic antigens are associated with epidemic and pandemic cholera
    - Non-O1 or non-O139 can be pathogenic and cause small outbreaks
  - Pathogenesis related to acquisition of the vibrio pathogenicity island (VPI) and bacteriophage (CTXΦ) which can be transmitted laterally between strains
Vibrio cholera

• Epidemiology
  – Lives in aquatic environments attached to algae or crustacean shells
  – Multiplies when temperature, salinity, and nutrients are suitable
  – Both an endemic and epidemic pattern
    • Endemic in South Asia, especially in Ganges Delta
    • Seven pandemics since 1817
      – Spread along trade-routes
      – New endemic areas
  – Transmission through contaminated food and water, person-to-person transmission is unusual

The 7th Cholera Pandemic
(O1 biotype EL Tor) 1961-1971
• 22 cases of Vibrio illness
• 5 deaths
  – V. vulnificus
  – V. parahaemolyticus
  – Non-O1 Non-O139
  – V. cholera

Vibrio cholera

• Clinical
  – Variable
    • 75% Asymptomatic
    • 20% Abrupt watery diarrhea
    • 5% Severe watery diarrhea, vomiting, and dehydration
  – No tenesmus, strain or abdominal pain, or fever
  – Dehydration
  – Duration 1-3 days
• Treatment
  – Rehydration: IV followed by Oral Rehydration Solution (glucose and electrolytes)
  – Doxycycline
A case of bloody diarrhea

- 4 yr old boy who goes to daycare
- 2 hour history of vomiting, diarrhea, fever, irritability and lethargy
- Physical exam
  - Fever
  - Tachycardia
  - Tachypnea
  - Mild dehydration

A case of bloody diarrhea

- Laboratory findings
  - Leukocytosis
    (WBC=13,200, 85% neutrophils)
  - negative blood cultures
  - Stool examination reveals fecal leukocytes, no ova and parasites
Shigella

• Microbiology
  – Small gram negative rod, member of Enterobacteriaceae, tribe Escherichiae
  – 40 serotypes. *Shigella sonnei* (40-80% cases in U.S.), *S. dysenteriae*, *S. flexneri*, *S. boydii*
  – *S. dysenteriae* 1 produces Shiga toxin

Shigella

• Pathogenesis
  – Low inoculum (<200 organisms)
    • Person-to-person spread, secondary cases common
  – Invasion of intestinal mucosa, moving from small to large intestines, with multiplication and mucosal destruction
  – Cytotoxin elaboration
  – Penetration beyond mucosa is rare
Shigella

- **Clinical manifestations**
  - 12 hours after ingestion, bacterial multiplication begins in the small intestines resulting in abdominal pain, cramping, watery diarrhea and fever
  - Resolution of fever in a few days
  - Onset of severe lower abdomen pain, accompanied by urgency, tenesmus, and bloody mucoid stools (dysentery)
  - Illness lasts for average of 7 days
  - Colonic shedding for 1-4 weeks
  - *S. dysenteriae* results in more serious diarrhea with risk of Hemolytic Uremic Syndrome (HUS)

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**E.coli**

- **Enterotoxigenic (ETEC):** traveler’s diarrhea
- **Enteroadherent (EAEC):** traveler’s diarrhea and persistent diarrhea in children
- **Enteropathogenic (EPEC):** children’s diarrhea, nursery outbreaks
- **Enterohemorrhagic (EHEC):** hemorrhagic colitis, associated with HUS in children
- **Enteroinvasive (EIEC):** shigella-like dysentery
E. Coli O157:H7 epidemics

- 1982: ground beef
- 1990: drinking water
- 1991: apple cider
- 1992: hamburger
  - 28 illnesses in 6 states, 5 cases of HUS
  - PFGE analysis links isolates from 18 patients to ground beef from ConAgra
  - ConAgra recalls 18.6 million lbs of beef
- 2006: spinach
  - 173 illnesses in 25 states, 28 cases of HUS, 92 hospitalizations and 1 death
  - Spinach implicated grown in Monterey, San Benito and Santa Clara, CA.
  - Recalls by Pacific Coast Fruit Company, Triple B Corporation, S.T. Produce, RLB Food Distributors, and Natural Food Selection Foods

E. Coli O157:H7 Outbreak Case Counts by State
Figure 2. Cases per 100,000 population of foodborne disease caused by specific pathogens, FoodNet sites, 2003

E. Coli 0157:H7
A case of Enteric Fever

- A 23 year old P&S student develops persistent fevers 2 weeks after returning from Mexico
  - Associated with headache, malaise and anorexia
  - Missed student health appointment prior to departure
  - Had self limited diarrhea while in Mexico
- Physical examination
  - Splenomegaly
  - Salmon pink rash
- Laboratory data
  - Leukopenia
  - Blood culture: gram negative rod
Salmonella

• Microbiology
  – Gram negative, facultative anaerobic rod
  – More than 2500 serotypes
    • S. typhi and S. paratyphi
    • Nontyphoidal Salmonella (S. enteritidis, S. typhimurium S. virchow, S. dublin, S. cholerasuis etc…)

• Epidemiology
  – S. typhi and S. paratyphi are strict human pathogens
  – Nontyphoidal salmonella colonizes virtually all animals; therefore, causes infection with through contaminated food
    • Up to 0.1% of eggs contain S. enteritidis

Salmonella

• Pathogenesis
  – Ingested Salmonella induce endocytosis by M cells and enterocytes in small intestines
  – Organisms replicate within phagosomes
  – Transcytose to basolateral surface and interact with macrophages and lymphocytes in Peyer’s patch
  – Recruitment of additional mononuclear cells and lymphocytes resulting in mucosal necrosis
  – Spread systemically to bone marrow, liver, spleen within macrophages
    • Risk of invasive salmonellosis greater in patients with impaired cell-mediated immunity (AIDS, transplant)
Salmonella

• Clinical Manifestations of Nontyphoidal Salmonella (S. typhimurium, S. enteritidis etc.)
  – Gastroenteritis
    • Nausea, vomiting, diarrhea 6-48 hours after ingestion
    • Fever, abdominal cramping
    • Self limited (3-7 days)
  – Bacteremia
    • Occurs more rapidly than Typhoid and lacks typical rose spots and leukopenia
    • Often in AIDS patients
  – Tissue invasion/localized infections
    • Arterial infections, cholecystitis, osteomyelitis, septic arthritis

Salmonella

• Clinical Manifestations of S. typhi and S. paratyphi
  – Enteric Fever
    • Fever begins 5-21 days after ingestion and persists 4-8 weeks in untreated patients
    • Rose spots (30%), hepatosplenomegaly (50%)
    • Most symptoms resolved by fourth week
    • Complications: death in 1-30%; intestinal perforation, abscesses, endocarditis; relapse in 10%.
  – Asymptomatic carriage
    • 1-4%
Typhoid Mary

- 1900-1907: Mary Mallon linked to 7 family epidemics
- 1907-1910: confined to Willard Parker Hospital
- 1915: A devastating outbreak linked to Mary
- Confined to North Brother Island until death in 1938
Approach to patient

- Inflammatory or non-inflammatory
  - Epidemiologic context of infection
    - Traveler’s diarrhea
    - Food poisoning
    - Hospital acquired diarrhea

- Degree of dehydration
  - Mild: dry mouth, decreased sweat and urine
  - Moderate: orthostasis, skin tenting, sunken eyes
  - Severe: hypotension, tachycardia, confusion, shock
Approach to patient

• History
  – Duration
  – Fever
  – Appearance of stool
  – Abdominal pain
  – Tenesmus
  – Vomiting
  – Common source
  – Antibiotic use
  – Travel

Approach to patient

• Stool evaluations
  – Fecal leukocytes
  – Bacterial culture
  – Toxin
    • Clostridium difficile toxin
    • Shiga toxin
    • Shiga-like toxin (EHEC)
  – Ova and parasites
Treatment

• Rehydration
• If non-inflammatory, continue symptomatic therapy
• If inflammatory, consider empiric antibiotic therapy
  – EHEC infection: increase incidence of HUS?
    • In vitro data vs. mouse models
  – Salmonella gastroenteritis: does not shorten illness but increases convalescent carriage

Prevention

• Environmental control
  – Chlorination of water, improved sanitation
  – Improvements in food processing
  – Handwashing
• Vaccines
  – Successful S. typhi vaccine to Vi antigen
  – Oral cholera vaccine (Dukoral) composed of killed organism and cholera B subunit
Foodborne illnesses

Food involved in outbreaks in Europe 1993 - 1998
(Data: 7th Rep. GAWF/FAO/WHO Centre, Berlin, 2001)

<table>
<thead>
<tr>
<th>Food group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cakes &amp; ice creams</td>
<td>13%</td>
</tr>
<tr>
<td>Salads &amp; dressings</td>
<td>2%</td>
</tr>
<tr>
<td>Poultry &amp; poultry products</td>
<td>3%</td>
</tr>
<tr>
<td>Milk &amp; milk products</td>
<td>8%</td>
</tr>
<tr>
<td>Fish &amp; shellfish</td>
<td>5%</td>
</tr>
<tr>
<td>Mixed foods</td>
<td>10%</td>
</tr>
<tr>
<td>Eggs &amp; egg products</td>
<td>22%</td>
</tr>
<tr>
<td>Meat products &amp; eggs</td>
<td>2%</td>
</tr>
<tr>
<td>Mushrooms</td>
<td>4%</td>
</tr>
<tr>
<td>Various foods</td>
<td>2%</td>
</tr>
<tr>
<td>Meat &amp; meat products</td>
<td>15%</td>
</tr>
</tbody>
</table>

Foodborne Illnesses from preformed toxins

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation</th>
<th>Signs &amp; symptoms</th>
<th>Duration of illness</th>
<th>Associated foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus cereus</td>
<td>1-6 hrs</td>
<td>Nausea, vomiting</td>
<td>1 day</td>
<td>Rice, meats</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>1-6 hrs</td>
<td>Nausea, vomiting</td>
<td>1-2 days</td>
<td>Meat, eggs, potatoes, salads</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>10-16 hrs</td>
<td>Cramps, diarrhea</td>
<td>1-2 days</td>
<td>Meat, stews</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>8-16 hrs</td>
<td>Diarrhea, vomiting, cramps</td>
<td>1-2 days</td>
<td>Meats, poultry gravy</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>12-72 hrs</td>
<td>Vomiting, diarrhea, blurred vision, weakness</td>
<td>variable</td>
<td>Canned foods, cheese sauce</td>
</tr>
</tbody>
</table>
Foodborne Illnesses from Bacterial Infections

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incubation</th>
<th>Signs &amp; symptoms</th>
<th>Duration of illness</th>
<th>Associated foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listeria monocytogenes</td>
<td>9-48 hrs</td>
<td>Fever, muscle ache, N, D</td>
<td>Variable</td>
<td>Soft cheeses, milk, deli meats</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>24-48 hrs</td>
<td>Cramps, fever, diarrhea</td>
<td>Variable</td>
<td>Person to person, food</td>
</tr>
<tr>
<td>Yersinia enterocolytica</td>
<td>24-48 hrs</td>
<td>D.V, abd pain, fever</td>
<td>1-3 weeks</td>
<td>Pork, milk, water</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>1-3 days</td>
<td>D. Fever, cramps</td>
<td>4-7 days</td>
<td>Poultry, milk, cheese, fruits</td>
</tr>
<tr>
<td>EHEC</td>
<td>1-8 days</td>
<td>Severe bloody diarrhea</td>
<td>5-10 days</td>
<td>Beef, milk, raw fruits, veg</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>2-5 days</td>
<td>Diarrhea, cramps, fever</td>
<td>2-10 days</td>
<td>Poultry, milk, water</td>
</tr>
</tbody>
</table>

Prevention

- **Food preparation**
  - Wash hands, clean surfaces
  - Refrigerate promptly (within 2 hours)
  - Cook to proper temperatures
    - Beef and pork to 160°F
    - Poultry to 160°F
    - Egg until yolk and white are firm
- **If at high risk (immunocompromised, gastric surgery, cirrhosis)**
  - Avoid raw shellfish, fish, meat, eggs
  - Avoid unpasteurized milks, cheeses, juice
Thomas Crapper (1836-1910)

- Plumber and inventor
- Did not invent the Water Closet
- Company produced and displayed bathroom fittings
- In 1917, American servicemen started calling WCs “The Crapper”