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
  - Food-borne diarrheal disease in U.S.
    - 76 million illnesses per year
    - 350,000 hospitalizations
    - 5,000 deaths
  - Waterborne outbreaks

Epidemiology

- Overall burden not well studied in developed world
  - Attack rate: 1-3 illnesses per child per year

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

Epidemiology

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

Bacterial Pathogens

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

- Inoculum size
- Adherence
- Toxin Production
  - Enterotoxin
  - Cytotoxin
  - Neurotoxin
- Tissue invasiveness

Pathogenic Mechanisms

- Cholera Toxin (enterotoxin)
  - Composition of Toxin
    - A subunit (enzymatic activity)
    - B subunit (binds to enterocyte surface receptor, the ganglioside G\textsubscript{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

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

- 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 autonomic 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

Microbiology of Infectious Diarrheas
• Aerobic Gram-neg Rods
  – Enterobacteriaceae
    • Escherichia
    • Salmonella
    • Shigella
    • Yersinia
  – Vibrionaceae
    • Vibrio
    – Campylobacteriaceae
      • Campylobacter
• Gram-pos Rods
  – Bacillus
  – Clostridium

Clinical approach to Infectious Diarrheas

<table>
<thead>
<tr>
<th>Location</th>
<th>Watery Diarrhea</th>
<th>Bloody diarrhea (Dysentery)</th>
<th>Enteric Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Non inflammatory (enterotoxin)</td>
<td>Inflammatory (invasion or cytotoxin)</td>
<td>Penetrating systemic infection</td>
</tr>
<tr>
<td>Pathogens</td>
<td>Vibrio cholera</td>
<td>ETEC</td>
<td>Clostridium Perfringens</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
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 O1 and O139 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

- **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
  - Transmission through contaminated food and water, person-to-person transmission is unusual

- **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

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

- Sulaymaniyah, Iraq
  - 3,182 cases of acute watery diarrhea, 9 deaths (CFR 0.3%) from 7/29-9/6/07
  - 283 confirmed cases of Vibrio cholerae from stool specimens
- Kirkuk, Iraq
  - 3,728 cases of acute watery diarrhea, 1 death (CFR 0.03%)
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

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

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

• 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)

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

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 or STEC): 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

### Hemolytic Uremic Syndrome

- Hemolytic anemia with fragmented erythrocytes
- Thrombocytopenia
- Acute renal injury

### 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

### Course of EHEC in children

<table>
<thead>
<tr>
<th>Days</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>2</td>
<td>Fever</td>
</tr>
<tr>
<td>3</td>
<td>Blood culture positive</td>
</tr>
<tr>
<td>4</td>
<td>Diarrhea improves</td>
</tr>
</tbody>
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MID 12
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 et al.)*
- **Epidemiology**
  - *S. typhi* and *S. paratyphi* are strict human pathogens
  - Nontyphoidal salmonella colonizes virtually all animals; therefore, causes infection 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 *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%

Who is this woman?

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

Salmonella

- **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
Approach to the patient with acute diarrhea

Approach to patient

• History
  – Epidemiological features
    • Travel to developing area
    • Consumption of unsafe foods (raw foods, unpasteurized dairy) or water
    • Illness in others with common food source
    • Sick contacts (kids in daycare, co-workers)
    • Oral-anal sexual contact
    • Recent antibiotics or hospitalization
    • Underlying medical conditions (AIDS, transplant, gastric bypass)

• Onset (abrupt, gradual) and duration
• Stool characteristics (watery, bloody, mucous) and frequency
• Associated symptoms (fever, tenesmus, nausea, vomiting, abdominal pain, rash)
• Systemic symptoms (thirst, tachycardia, orthostasis, decreased urination, lethargy, altered sensorium)

Approach to patient

• Stool evaluations (especially if bloody stool, and clinically severe)
  – Fecal leukocytes
  – Bacterial culture
  – Toxin
    • Clostridium difficile toxin
    • Shiga toxin
    • Shiga-like toxin (EHEC)
  – Ova and parasites

Treatment

• Rehydration
• Antibiotics
  – Traveller’s Diarrhea (ETEC)
  – Moderately-severe invasive disease (shigella, campylobacter, salmonella)
  – Avoid antibiotics for EHEC