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

Epidemiology

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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
  - Shigellosis
  - Salmonella typhi
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)

• Adherence

• Toxin Production
  – Enterotoxin
  – Cytotoxin
  – Neurotoxin

• Invasion

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

![Cholera Toxin Diagram]

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

• 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

- **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>Mechanism</th>
<th>Watery Diarrhea</th>
<th>Bloody diarrhea (Dysentery)</th>
<th>Enteric Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Non inflammatory</td>
<td>Inflammatory</td>
<td>Penetrating</td>
</tr>
<tr>
<td>Pathogens</td>
<td></td>
<td>Invasive or cytotoxic</td>
<td>systemic infection</td>
</tr>
</tbody>
</table>
- **Vibrio cholera**
- **ETEC**
- **Clostridium Perfringens**
- **Bacillus cereus**
- **Staphylococcus aureus**
- **Shigella spp.**
- **Salmonella (Nontyphoidal)**
- **Campylobacter jejuni**
- **EIEC (EHEC)**
- **Clostridium difficile**
- **Salmonella typhi**
- **Yersinia enterocolitica**

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
MID 12

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 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

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

Vibrio cholera

- Clinical
  - Variable
    - 75% Asymptomatic
    - 20% Abdominal pain, fever, nausea, vomiting, and dehydration
    - 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

Shigella

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

- 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)

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
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

- 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

- 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

- Clinical Manifestations of *S. typhi* and *S. paratyphi*
  - Enteric Fever
    - Fever begins 5-21 days after ingestion and persists 4-6 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

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

- 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 choler vaccine (Dukoral) composed of killed organism and cholera B subunit

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>
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Foodborne Illnesses from Bacterial Infections

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<tr>
<td>Listeria monocytogenes</td>
<td>0-48 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>Diarrhea, fever, cramps</td>
<td>1-3 weeks</td>
<td>Pork, milk, water</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>1-3 days</td>
<td>Diarrhea, fever, cramps</td>
<td>4-7 days</td>
<td>Pork, milk, cheese, fruits</td>
</tr>
<tr>
<td>EHEC</td>
<td>1-8 days</td>
<td>Severe bloody diarrhea</td>
<td>3-10 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>Pork, milk, water</td>
</tr>
</tbody>
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Foodborne illnesses

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”