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
• Tissue invasiveness

Pathogenic Mechanisms

• Inoculum size
  – 10-100 organisms
    • *Shigella*
  – <1000 organisms
    • *Enterohemorrhagic E. coli (EHEC)*
    • *Salmonella typhi*
    • *Campylobacter jejuni*
  – $10^8$ 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 \( \text{GM}_1 \))
  – 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 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*
  - Vibrionacea
    • *Vibrio*
  - Campylobacteriaceae
    • *Campylobacter*

- **Gram-pos Rods**
  - *Bacillus*
  - *Clostridium*
# Clinical approach to Infectious Diarrheas

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## 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 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

- Sulaymaniayah, 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%)

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)

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
Course of EHEC in children

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
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 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%
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
Approach to the patient with acute diarrhea

Approach to patient

• History
  – Clinical features
    • 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

• 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)

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