Infectious Diarrheal Diseases

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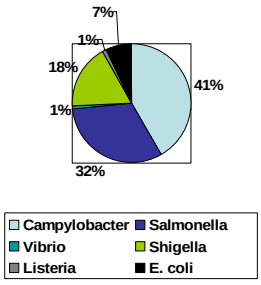
Epidemiology

- 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

Outline

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

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

- 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

Bacterial Pathogens

- Water/Foodborne
  - *Campylobacter*
  - *Salmonella* (nontyphi)
  - Enterohemorrhagic *E. coli* (EHEC) and Enterotoxigenic *E. coli* (ETEC)
  - *Vibrio*
  - *Yersinia*
  - *Clostridium perfringens*
  - *Bacillus cerus*
  - *Staphylococcus aureus*
- Person-to-person
  - *Shigella*
  - *Salmonella typhi*

Pathogenic Mechanisms

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

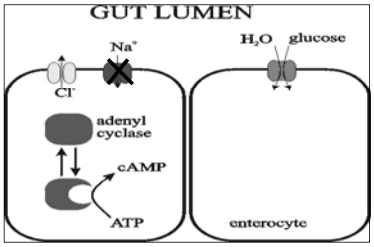
Pathogenic Mechanisms

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

Cholera Toxin



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-stabile 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

Microbiology of Infectious Diarrheas

- ***Aerobic Gram-neg Rods***
  - *Enterobacteriaceae*
    - *Escherichia*
    - *Salmonella*
    - *Shigella*
    - *Yersinia*
  - *Vibrionacea*
    - *Vibrio*
  - *Campylobacteriaceae*
    - *Campylobacter*
- *Gram-pos Rods*
  - *Bacillus*
  - *Clostridium*

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 phagasome (tolerant to acids)
    - Spreads to adjacent epithelial cells and lymphoid tissue.

Clinical approach to Infectious Diarrheas

	Watery Diarrhea	**Bloody diarrhea (Dysentery)**	**Enteric Fever**
Mechanism	Non inflammatory (enterotoxin)	Inflammatory (invasion or cytotoxin)	Penetrating systemic infection
Location	Proximal small bowel	Colon or distal small bowel	Distal small bowel
Pathogens	*Vibrio cholera* ETEC *Clostridium Perfringens* *Bacillus cereus* *Stapholococcus aureus*	*Shigella* spp. *Salmonella* (Nontyphoidal) *Campylobacter jejuni* EIEC (EHEC) *Clostridium difficile*	*Salmonella typhi* *Yersinia enterocolitica*

Host Defenses

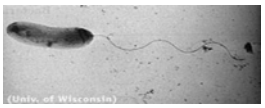
- Normal Flora
  - Anaerobes: acidic pH & fatty acid production prevent colonization by bacterial pathogens
- Gastric Acid
  - Increased frequency of Salmonella among patients with gastric bypass
- Intestinal Motility
  - Impaired motility allows for bacterial overgrowth
- Immunity
  - Secretory IgA, 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

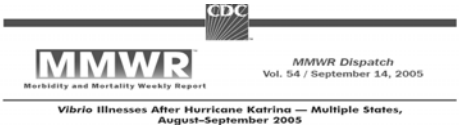
A case of watery diarrhea

- 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

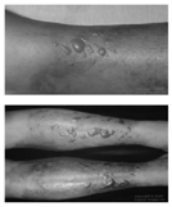
- Microbiology
  - Identified by Filippo Pacini in 1854 and Robert Koch in 1883
  - Curved gram negative bacillus with single polar flagellum
  - Over 200 serogroups, but only 01 and 0139 somatic antigens are associated with epidemic and pandemic cholera
    - Non-O1 or non-O139 can be pathogenic and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





- 22 cases of Vibrio illness
- 5 deaths
  - *V. vulnificus*
  - *V. parahaemolyticus*
  - Non-O1 Non-O139 *V. cholera*

FIGURE 3. Primary septicemic skin lesions caused by *Vibrio vulnificus*



Vibrio cholera

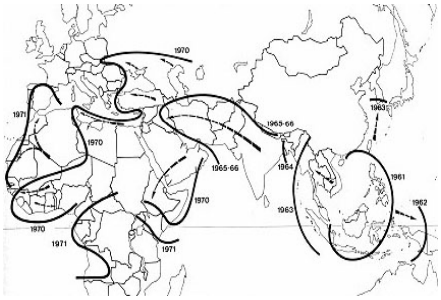
- Epidemiology
  - Lives in aquatic environments attached to algae or crustacean shells
  - Multiplies when temperature, salinity, and nutrients are suitable
  - Both an endemic and epidemic pattern
    - Endemic in South Asia, especially in Ganges Delta
    - Seven pandemics since 1817
      - Spread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

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%)

Girls in rural Iraq must fetch river water that may not be safe to drink. The IRC has launched a program aimed at restarting water and sanitation pumps, which will give 200,000 people access to clean water (photo: IRC/Peter Biro)

The 7th Cholera Pandemic (O1 biotype EL Tor)1961-1971



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

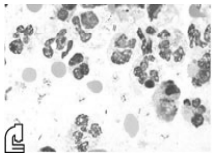
- 4 yr old boy who goes to daycare
- 2 hour history of vomiting, diarrhea, fever, irritability and lethargy
- Physical exam
  - Fever
  - Tachycardia
  - Tachypnea
  - Mild dehydration

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 Escherichieae
  - 40 serotypes. *Shigella sonnei* (40-80% cases in U.S.), *S. dysenteriae*, *S. flexneri*, *S. boydii*
  - *S. dysenteriae* 1 produces Shiga toxin

E.coli

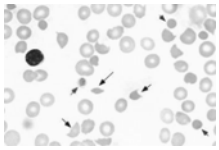
- Enterotoxigenic (ETEC): traveler's diarrhea
- Enteroadherent (EAEC): traveler's diarrhea and persistent diarrhea in children
- Enteropathogenic (EPEC): children's diarrhea, nursery outbreaks
- Enterohemorrhagic (EHEC or STEC): hemorrhagic colitis, associated with HUS in children
- Enteroinvasive (EIEC): 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

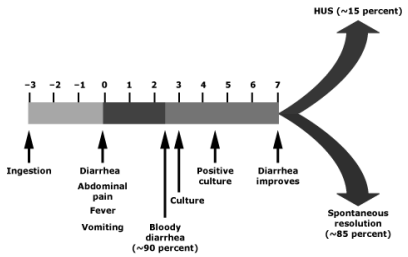
- Hemolytic anemia with fragmented erythrocytes
- Thrombocytopenia
- Acute renal injury



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



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

- 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%

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)

Who is this woman?

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

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

- 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

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)

Treatment

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

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)