

Infectious Diarrheal Diseases

Michael Yin, MD MS

Outline

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

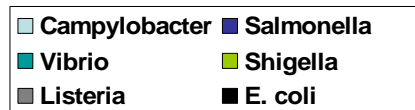
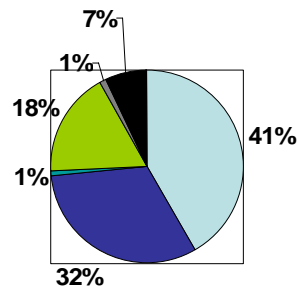
Epidemiology

- 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*
 - 10^5 to 10^8 organisms
 - *Vibrio cholera*
 - *Salmonella (nontyphoidal)*

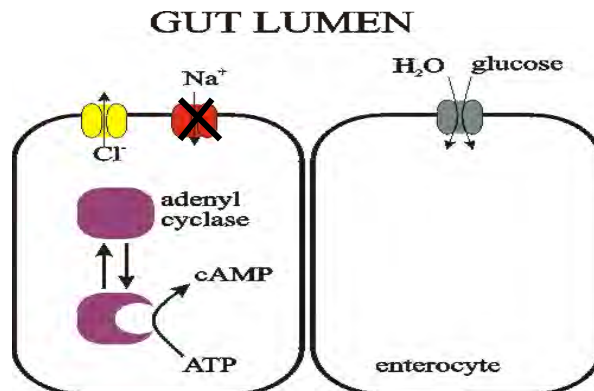
Pathogenic Mechanisms

- 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 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

	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	<i>Vibrio cholera</i> ETEC <i>Clostridium Perfringens</i> <i>Bacillus cereus</i> <i>Staphylococcus aureus</i>	<i>Shigella</i> spp. <i>Salmonella</i> (Nontyphoidal) <i>Campylobacter jejuni</i> EIEC (EHEC) <i>Clostridium difficile</i>	<i>Salmonella typhi</i> <i>Yersinia enterocolitica</i>

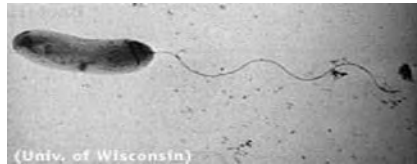
A case of watery diarrhea

- 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

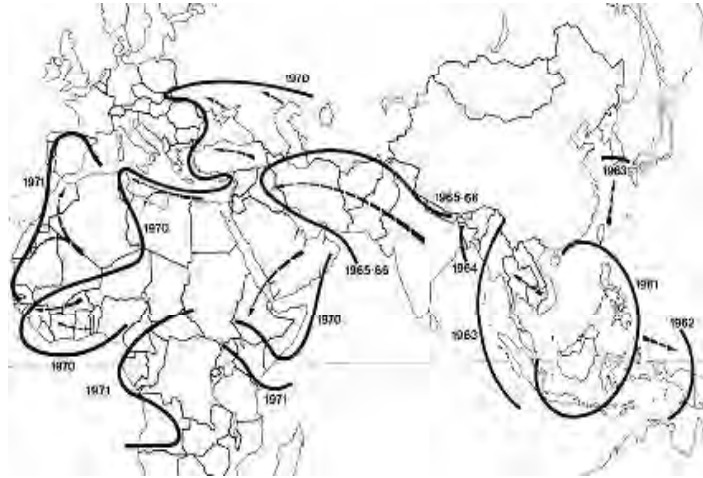
- Microbiology
 - Identified by Filippo Pacini in 1854 and Robert Koch in 1883
 - Curved gram negative bacillus with single polar flagellum
 - Over 200 serogroups, but only O1 and O139 somatic antigens are associated with epidemic and pandemic cholera
 - Non-O1 or non-O139 can be pathogenic and cause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

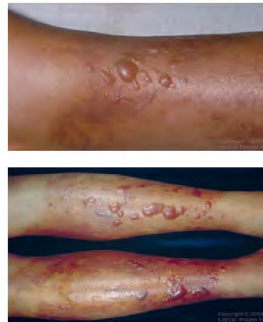
The 7th Cholera Pandemic (O1 biotype EL Tor) 1961-1971



Vibrio Illnesses After Hurricane Katrina — Multiple States, August–September 2005

- 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

- 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)

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

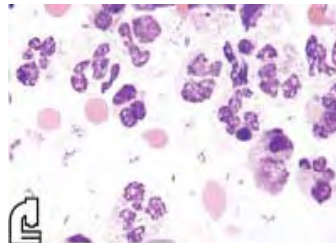


A case of bloody diarrhea

- 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 Escherichieae
 - 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

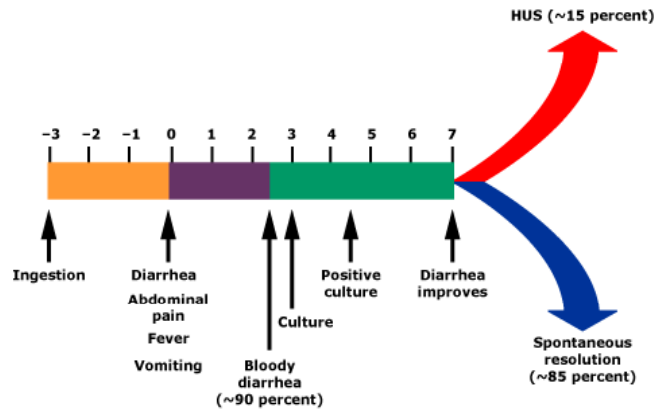
- Enterotoxigenic (ETEC): traveler's diarrhea
- Enteroadherent (EAEC): traveler's diarrhea and persistent diarrhea in children
- Enteropathogenic (EPEC): children's diarrhea, nursery outbreaks
- Enterohemorrhagic (EHEC or STEC): hemorrhagic colitis, associated with HUS in children
- Enteroinvasive (EIEC):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

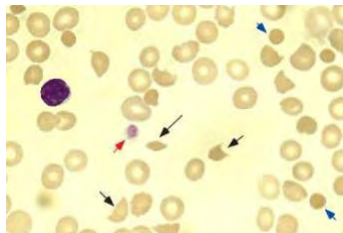


Course of EHEC in children



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. choleraesuis* 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