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

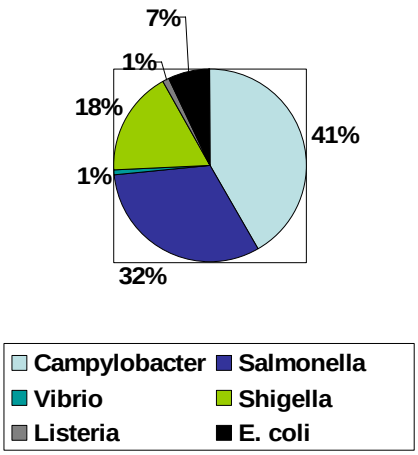
Epidemiology

- 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 cerus*
  - *Staphylococcus aureus*
- Person-to-person
  - *Shigella*
  - *Salmonella typhi*

Pathogenic Mechanisms

- Inoculum size
- Adherence
- Toxin Production
  - Enterotoxin
  - Cytotoxin
  - Neurotoxin
- Invasion

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)*

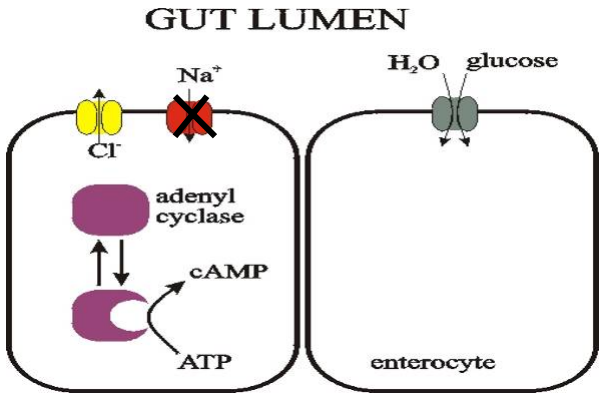
Pathogenic Mechanisms

- 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-stabile 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 phagasome (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

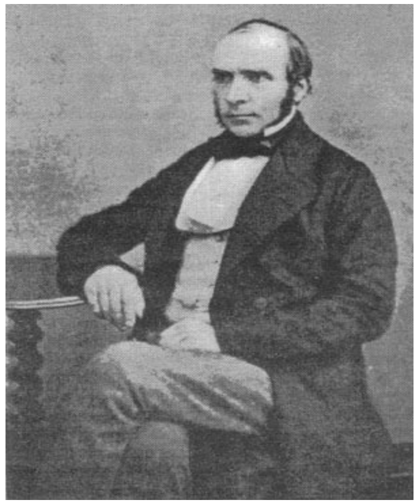
Clinical approach to Infectious Diarrheas

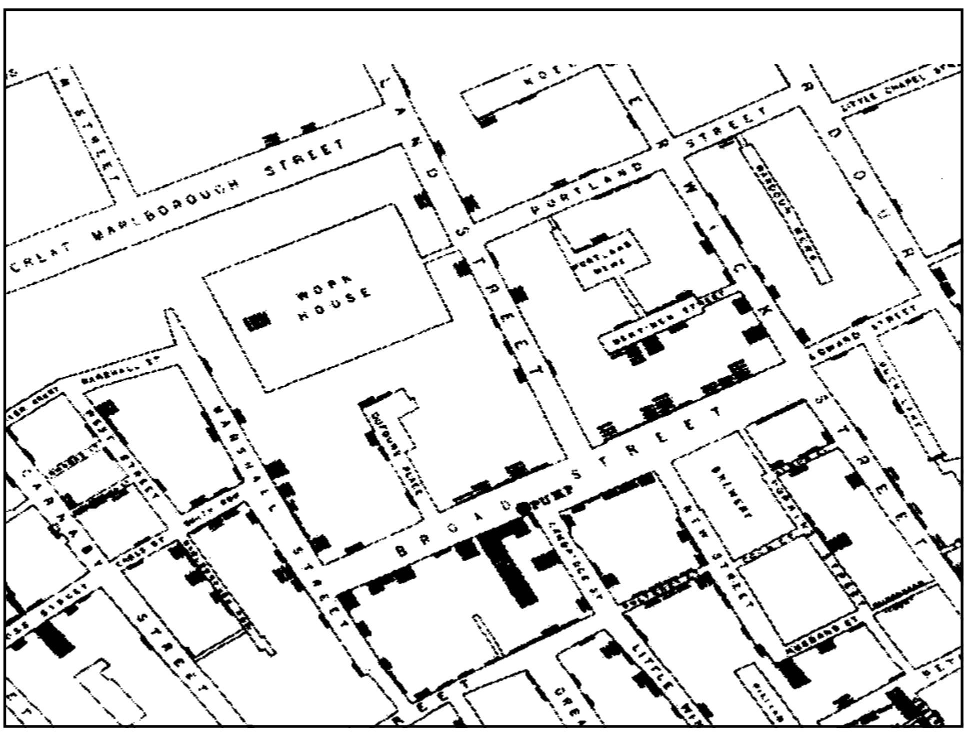
	Watery Diarrhea	**Bloody diarrhea (Dysentery)**	**Enteric Fever**
Mechanism	Non inflammatory (enterotoxin)	Inflammatory (invasion or cytotoxin)	Penetrating systemic infection
Location	Proximal small bowel	Colon or distal small bowel	Distal small bowel
Pathogens	*Vibrio cholera* ETEC *Clostridium Perfringens*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

A case of watery diarrhea

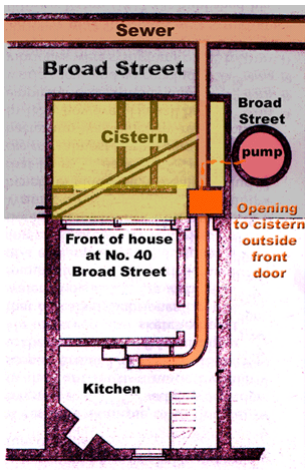
- 1 year old boy with abrupt onset of watery diarrhea and vomiting
- No fever, no bloody stool
- Development of sunken eyes, dry mouth, inability to feed, lack of urination
- Lethargic, unresponsive, death
- Father also with watery diarrhea (1 liter/hour), vomiting, cramps

A LONDON BOARD OF HEALTH HUNTING AFTER CASES LIKE CHOLERA




MARLBOROUGH STREET
WORK HOUSE
PORTLAND STREET
MARSHALL STREET
BROAD STREET
NEW STREET

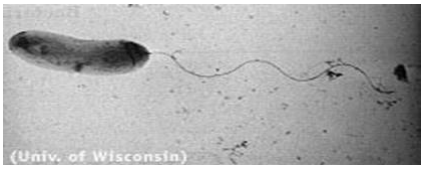
Index case



- "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

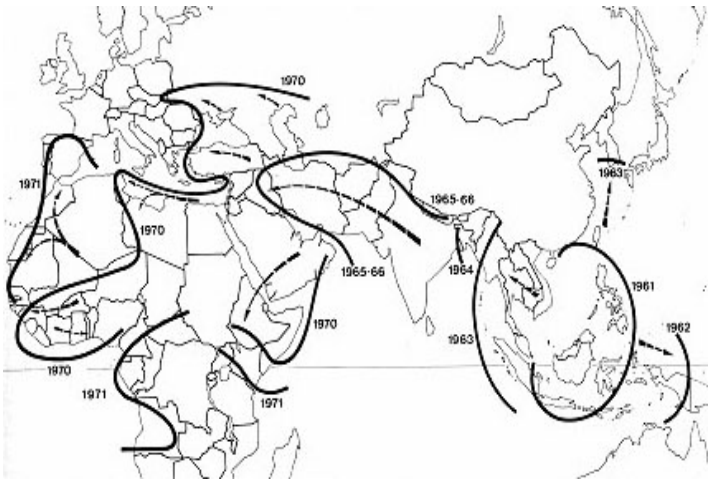
- Microbiology
  - Identified by Filippo Pacini in 1854 and Robert Koch in 1883
  - Curved gram negative bacillus with single polar flagellum
  - Over 200 serogroups, but only 01 and 0139 somatic antigens are associated with epidemic and pandemic cholera
    - Non-O1 or non-O139 can be pathogenic and 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



CDC

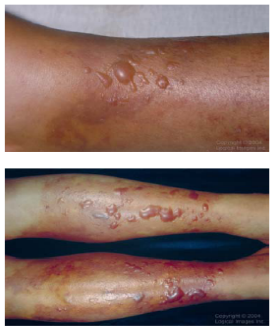
MMWR
Morbidity and Mortality Weekly Report

MMWR Dispatch
Vol. 54 / September 14, 2005

***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

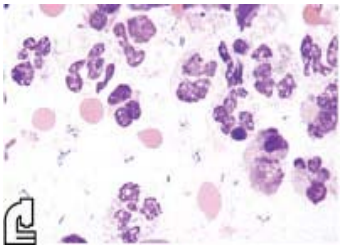
- Clinical
  - Variable
    - 75% Asymptomatic
    - 20% Abrupt watery diarrhea
    - 5% Severe watery diarrhea, vomiting, and dehydration
  - No tenesmus, strain or abdominal pain, or fever
  - Dehydration
  - Duration 1-3 days
- Treatment
  - Rehydration: IV followed by Oral Rehydration Solution (glucose 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): 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

E.Coli O157:H7 Outbreak Case Counts by State

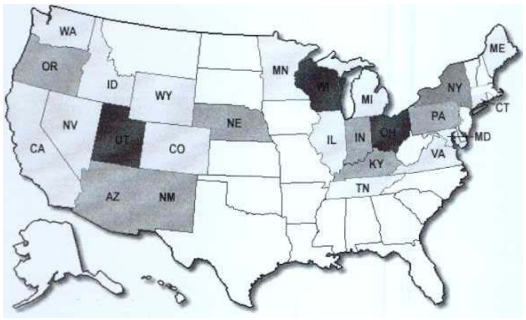
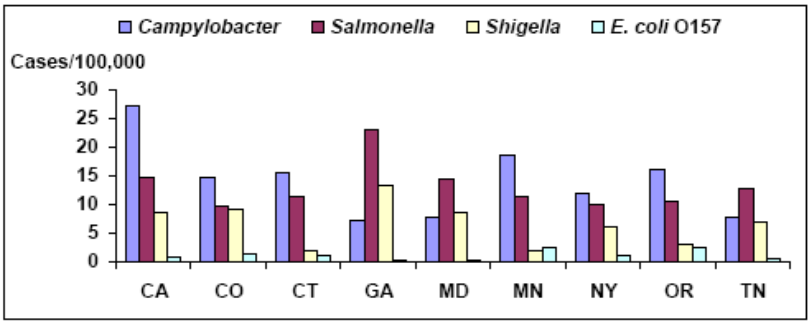
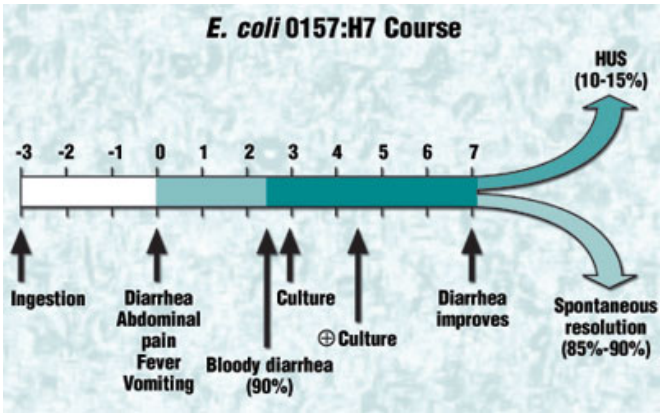


Figure 2. Cases per 100,000 population of foodborne disease caused by specific pathogens, FoodNet sites, 2003

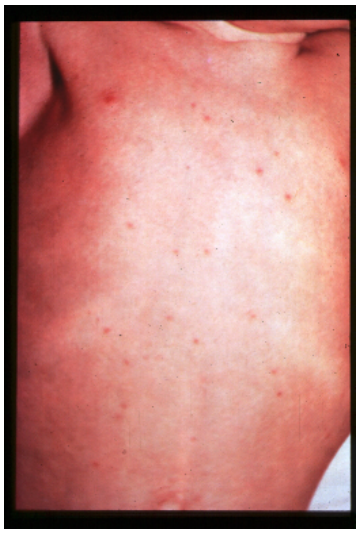


E. Coli 0157:H7



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 with through contaminated food
    - Up to 0.1% of eggs contain *S. enteritidis*

Salmonella

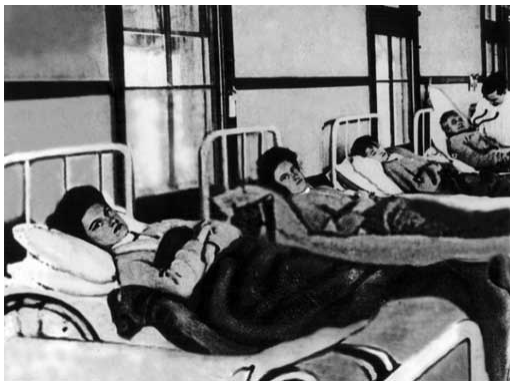
- Pathogenesis
  - Ingested Salmonella induce endocytosis by M cells and enterocytes in small intestines
  - Organisms replicate within phagosomes
  - Transcytose to basolateral surface and interact with macrophages and lymphocytes in Peyer's patch
  - Recruitment of additional mononuclear cells and 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

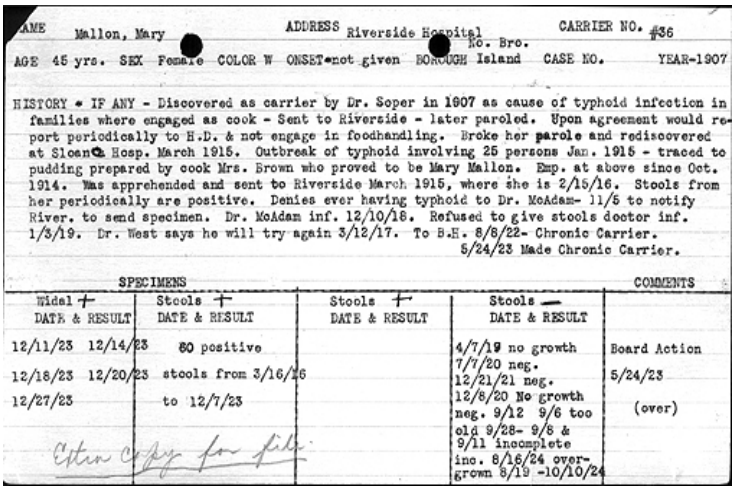
Salmonella

- 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%



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



NAME Mallon, Mary ADDRESS Riverside Hospital CARRIER NO. #36
No. Bro.
AGE 45 yrs. SEX Female COLOR W ONSET not given BOROUGH Island CASE NO. YEAR-1907

HISTORY & IF ANY - Discovered as carrier by Dr. Soper in 1907 as cause of typhoid infection in families where engaged as cook - Sent to Riverside - later paroled. Upon agreement would report periodically to H.D. & not engage in foodhandling. Broke her parole and rediscovered at Sloane Hosp. March 1915. Outbreak of typhoid involving 25 persons Jan. 1915 - traced to pudding prepared by cook Mrs. Brown who proved to be Mary Mallon. Emp. at above since Oct. 1914. Was apprehended and sent to Riverside March 1915, where she is 2/15/16. Stools from her periodically are positive. Denies ever having typhoid to Dr. McAdam- 11/5 to notify River. to send specimen. Dr. McAdam inf. 12/10/18. Refused to give stools doctor inf. 1/3/19. Dr. West says he will try again 3/12/17. To B.H. 8/8/22- Chronic Carrier.
5/24/23 Made Chronic Carrier.

SPECIMENS				COMMENTS
Widal + DATE & RESULT	Stools + DATE & RESULT	Stools + DATE & RESULT	Stools — DATE & RESULT	
12/11/23 12/14/23	60 positive		4/7/19 no growth	Board Action
12/18/23 12/20/23	stools from 3/16/16		7/7/20 neg.	5/24/23
12/27/23	to 12/7/23		12/21/21 neg.	
			12/8/20 No growth neg. 9/12 9/6 too old 9/28- 9/8 & 9/11 incomplete inc. 8/16/24 overgrown 8/19 -10/10/24	(over)

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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

Approach to patient

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

Approach to patient

- Stool evaluations
  - Fecal leukocytes
  - Bacterial culture
  - Toxin
    - Clostridium difficile toxin
    - Shiga toxin
    - Shiga-like toxin (EHEC)
  - Ova and parasites

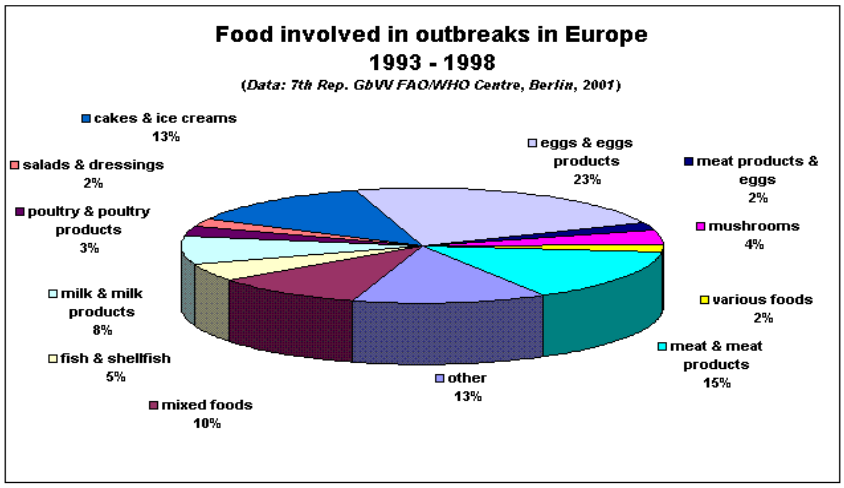
Treatment

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

Foodborne illnesses



Foodborne Illnesses from preformed toxins

Etiology	Incubation	Signs & symptoms	Duration of illness	Associated foods
Bacillus cereus	1-6 hrs	Nausea, vomiting	1 day	Rice, meats
Staph aureus	1-6 hrs	Nausea, vomiting	1-2 days	Meat, eggs, potatoes, salads
Bacillus cereus	10-16 hrs	Cramps, diarrhea	1-2 days	Meat, stews
Clostridium perfringens	8-16 hrs	Diarrhea, vomiting, cramps	1-2 days	Meats, poultry gravy
Clostridium botulinum	12-72 hrs	Vomiting, diarrhea, blurred vision, weakness	variable	Canned foods, cheese sauce

Foodborne Illnesses from Bacterial Infections

Etiology	Incubation	Signs & symptoms	Duration of illness	Associated foods
Listeria monocytogenes	9-48 hrs	Fever, muscle ache, N, D	Variable	Soft cheeses, milk, deli meats
Shigella spp.	24-48 hrs	Cramps, fever, diarrhea	Variable	Person to person, food
Yersinia enterocolytica	24-48 hrs	D,V, abd pain, fever	1-3 weeks	Pork, milk, water
Salmonella spp.	1-3 days	D, Fever, cramps	4-7 days	Poultry, milk, cheese, fruits
EHEC	1-8 days	Severe bloody diarrhea	5-10 days	Beef, milk, raw fruits,veg
Campylobacter jejuni	2-5 days	Diarrhea, cramps, fever	2-10 days	Poultry, milk, water

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”