



Diarrhea

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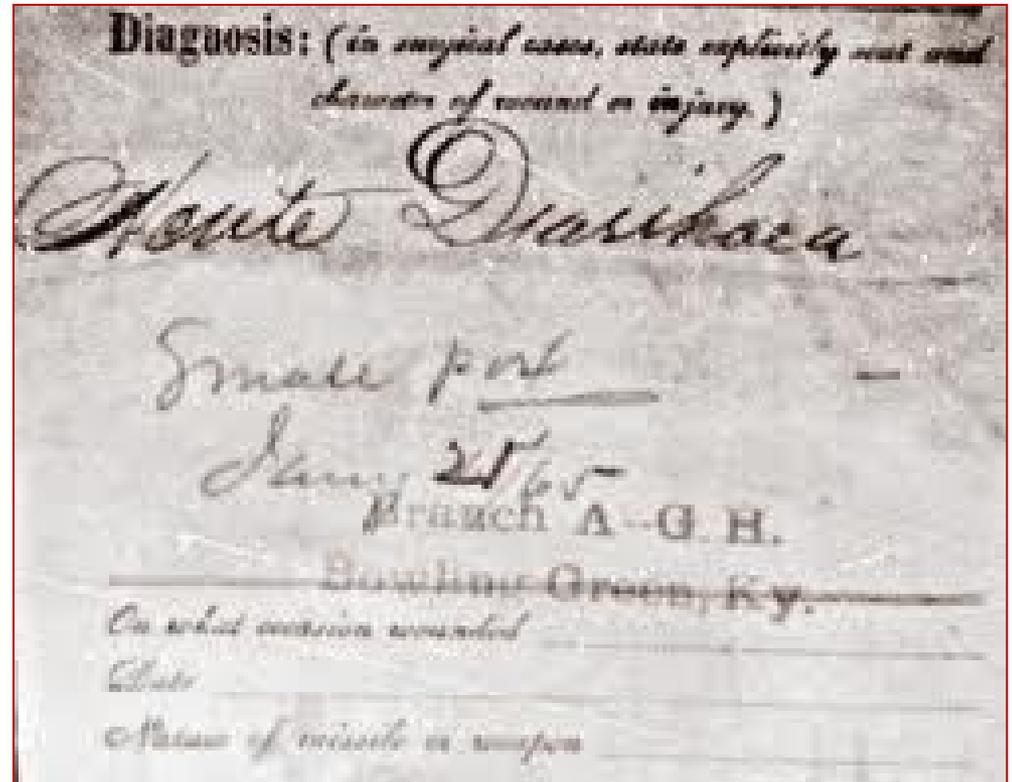
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Outline

- Introduction
- Military Disease Burden
- Causative Agents
- Clinical Presentations
- Diagnosis
- Treatment



"The death list from disease was a fearful one in the Department of the Gulf. Fever and diarrhea, the former disabling and the latter killing, were worse foes than bullets, ten to one." – Civil War Union Major and Surgeon S.C. Gordon



Definitions

- **Diarrhea:** Alteration in normal bowel movements; increase in water content, volume, or frequency of stools.
- **Acute diarrhea:** < 14 days in duration
- **Persistent diarrhea:** \geq 14 days in duration
- **Chronic diarrhea:** \geq 30 days in duration



Normal GI Physiology and Regulation

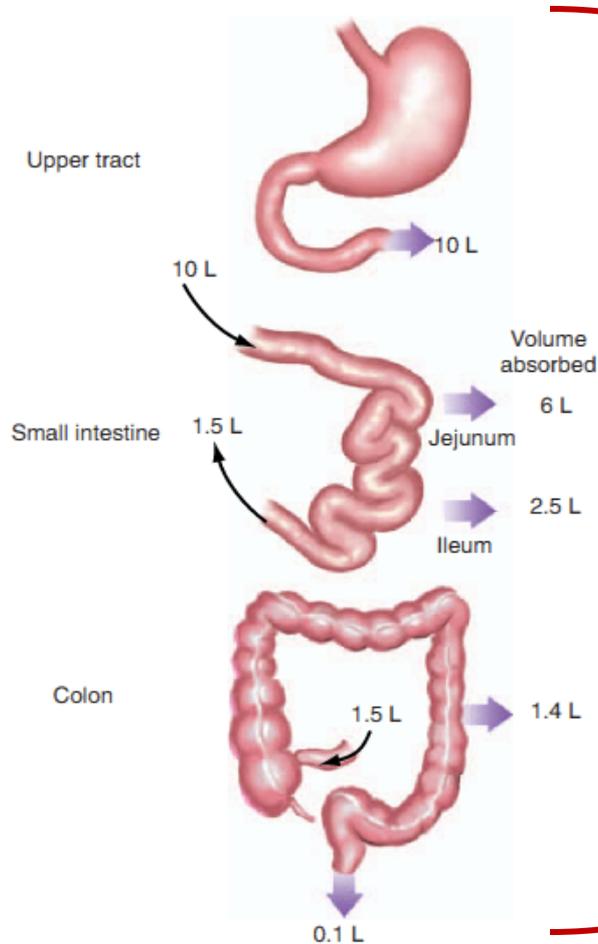


Figure 15-1. Fluid loads along the gastrointestinal tract. Each day, close to 10 L of fluid composed of ingested food and drink and secretions from the salivary glands, esophagus, stomach, pancreas, bile duct, and duodenum pass the ligament of Treitz. The jejunum absorbs approximately 6 L and the ileum 2.5 L, leaving about 1.5 L to pass into the colon each day. The colon absorbs more than 90% of this load, leaving approximately 0.1 L in the feces. Therefore, the overall efficiency of water absorption is 99%. Reduction of this efficiency by as little as 1% may lead to diarrhea. (From Schiller LR. Chronic diarrhea. In: McNally P, editor. *GI/Liver Secrets*. 2nd ed. Philadelphia, Pa: Hanley & Belfus; 2001. p 411.)

Impact factors

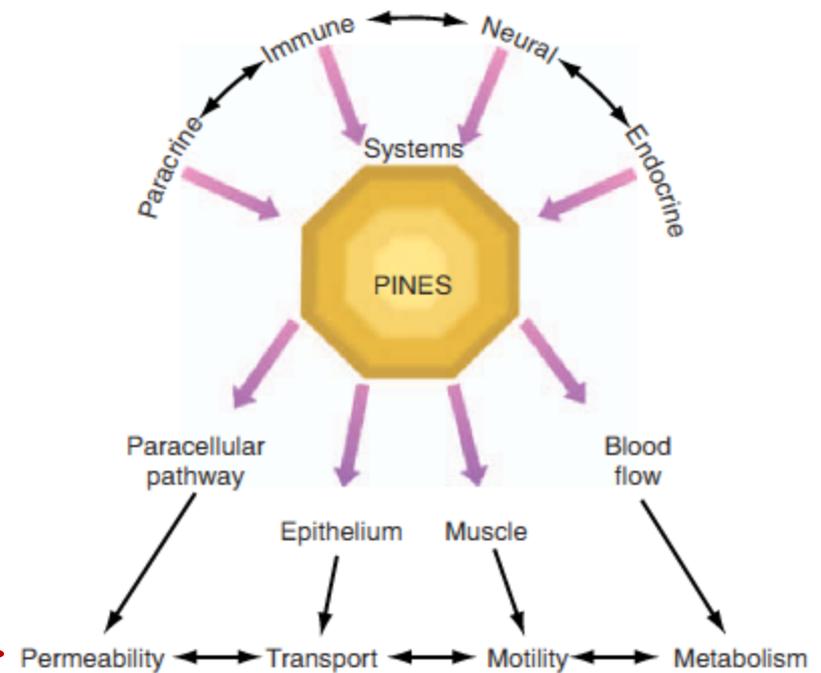


Figure 15-2. PINES regulatory system in the intestine. The regulatory system of the intestine integrates *paracrine*, *immune*, *neural*, and *endocrine* systems and produces coordinated changes in mucosal and muscular function that permit adaptive responses to changing conditions. The regulatory system can widen or narrow the paracellular pathway that governs passive transmucosal permeability of electrolytes, accelerate or retard the transepithelial transport of nutrients and electrolytes by affecting membrane channels and pumps, alter motility by relaxing or contracting the various muscle layers in the intestine, and increasing or decreasing mucosal blood flow, thereby influencing intestinal metabolism. Diarrhea may be an appropriate response to acute infection. Maladaptive responses may be responsible for chronic diarrhea. (From Sellin JH. Functional anatomy, fluid and electrolyte absorption. In: Feldman M, Schiller LR, editors. *Gastroenterology and Hepatology. The Comprehensive Visual Reference*, vol 7: Small Intestine. Philadelphia, Pa: Current Medicine; 1997. p 1.11.)



Differential Diagnosis of Diarrhea

Table 15-3 Differential Diagnosis of Diarrhea

Acute Diarrhea

Infection (see Table 15-4)

- Bacteria
- Parasites
- Protozoa
- Viruses

Food allergies

Food poisoning

Medications

Initial presentation of chronic diarrhea

Chronic Diarrhea

Fatty Diarrhea

Malabsorption syndromes

- Mesenteric ischemia
- Mucosal diseases (e.g., celiac disease, Whipple's disease)
- Short bowel syndrome
- Small intestinal bacterial overgrowth

Maldigestion

- Inadequate luminal bile acid concentration
- Pancreatic exocrine insufficiency

Inflammatory Diarrhea

Diverticulitis

Infectious diseases

- Invasive bacterial infections (e.g., tuberculosis, yersiniosis)
- Invasive parasitic infections (e.g., amebiasis, strongyloidiasis)
- Pseudomembranous colitis (*Clostridium difficile* infection)
- Ulcerating viral infections (e.g., cytomegalovirus, herpes simplex virus)

Inflammatory bowel diseases

- Crohn's disease
- Ulcerative colitis
- Ulcerative jejunoileitis

Ischemic colitis

Neoplasia

- Colon cancer
- Lymphoma

This lecture.

Radiation colitis

Watery Diarrhea

Osmotic diarrhea

Carbohydrate malabsorption

Osmotic laxatives (e.g., Mg^{2+} , PO_4^{3-} , SO_4^{2-})

Secretory diarrhea

Bacterial toxins

Congenital syndromes (e.g., congenital chloridorrhea)

Disordered motility, regulation

Diabetic autonomic neuropathy

Irritable bowel syndrome

Postsympathectomy diarrhea

Postvagotomy diarrhea

Diverticulitis

Endocrinopathies

Addison's disease

Carcinoid syndrome

Gastrinoma

Hyperthyroidism

Mastocytosis

Medullary carcinoma of the thyroid

Pheochromocytoma

Somatostatinoma

VIPoma

Idiopathic secretory diarrhea

Epidemic secretory (Brainerd) diarrhea

Sporadic idiopathic secretory diarrhea

Ileal bile acid malabsorption

Inflammatory bowel disease

Crohn's disease

Microscopic colitis

Collagenous colitis

Lymphocytic colitis

Ulcerative colitis

Laxative abuse (stimulant laxatives)

Medications and toxins (see Table 15-5)

Neoplasia

Colon carcinoma

Lymphoma

Villous adenoma in rectum

Vasculitis



Mandell. PPID. 8th Ed. Ch 15.



Differential Diagnosis of Diarrhea



Table 15-5 Medications and Toxins Associated with Diarrhea

Acid-reducing agents (e.g., histamine H₂ receptor antagonists, proton pump inhibitors)
Antacids (e.g., those that contain magnesium)
Antiarrhythmics (e.g., quinidine)
Antibiotics (most)
Anti-inflammatory agents (e.g., 5-aminosalicylates, gold salts, NSAIDs)
Antihypertensives (e.g., β -adrenergic receptor blocking drugs)
Antineoplastic agents (many)
Antiretroviral agents
Colchicine
Heavy metals
Herbal products
Prostaglandin analogs (e.g., misoprostol)
Theophylline
Vitamin and mineral supplements

NSAIDs, nonsteroidal anti-inflammatory drugs.



Definitions

- **Traveler's diarrhea:** Diarrhea developing while traveling and within 10 days of returning home.
 - **Classic:** 3 or more unformed stools within 24 hours and one of the following: nausea, vomiting, abdominal pain, cramps, fever, blood in stools
 - **Moderate:** 1 or 2 unformed stools in 24 hours plus one of the above symptoms –or- more than 2 stools in 24 hours without symptoms
 - **Mild:** passage of 1 or 2 unformed stools within 24 hours and no symptoms
- **Infectious diarrhea:** Diarrhea with an infectious etiology



Impact of Diarrheal Diseases in Modern Military Campaigns

- **World War II:** ‘A few months of the year, malaria would cause more man-days lost, but on the calendar-year average, gastrointestinal infections were well ahead.’¹
- **Vietnam War:** Diarrhea/dysentery largest single disease threat, leading to 4 times more hospitalizations than malaria.²
- **OIF:** Acute enteric illness was leading cause of hospital admission among British forces during first 12 months of operations in Iraq.³

(1) Ward TG: *History of Preventive Medicine*, US Army Forces in the Middle East, 19Oct41 - 23Jun44, Vol. 111. [Official record.]

(2) Wells RF, GI Diseases: Background and Buildup. In: *Internal Medicine in Vietnam Vol II: General Medicine and ID*, US Army Medical Dept 0:345-354.

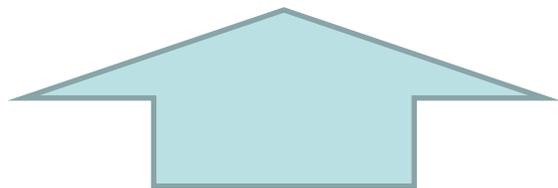
(3) Grange, C: *J Royal Army Medical Corps*, 2005:151(2):101-104.

Slide courtesy of CAPT S. Savarino



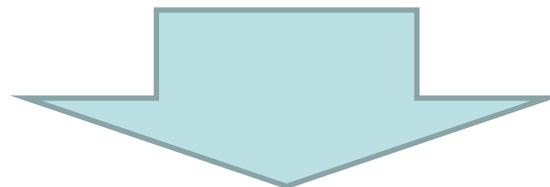
Force Health Impacts

Diarrhea with fever	9-25%
Dysentery	2-8%
Severe diarrhea	
Iraq	21-27%
Afghanistan	13-14%
Vomiting only	5-15%



clinical presentations

operational impact



↓ Job performance	45%
Confined to bedrest	13%
Hospitalized	2%
IV fluids	15-17%
Missed patrol	9-13%
Back-fill needed	12%
Grounded	6-12%
Fecal incontinence	32%

Slide courtesy of CAPT S. Savarino



I expect that our imaginations cannot fathom the problems attendant from the absolute urgency for relief from explosive vomiting and diarrhea when experienced within an armored vehicle under fire and at ambient temperature of $> 40^{\circ}\text{C}$.

David O. Matson, MD

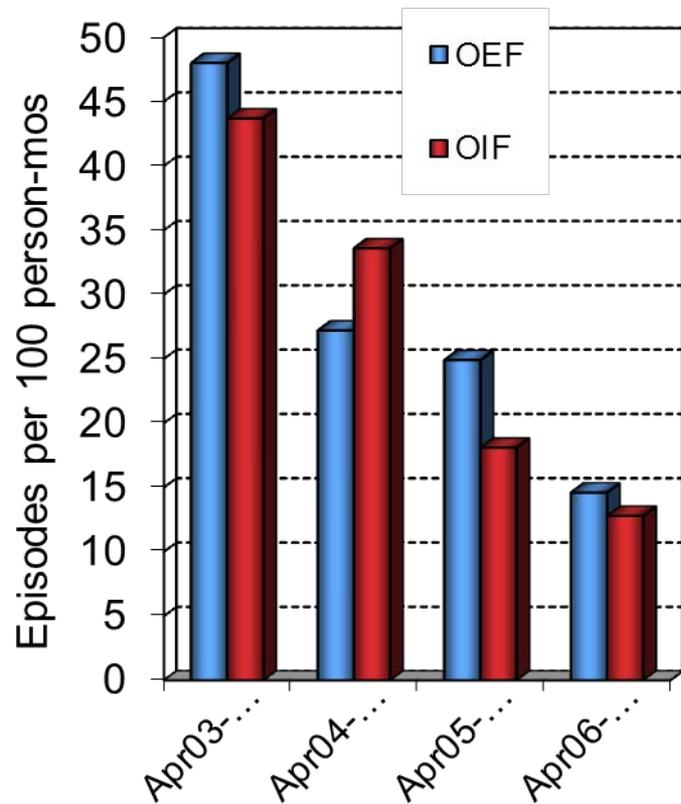
Infectious Diseases Section, Center for
Pediatric Research, Norfolk, Virginia

Slide courtesy of CAPT S. Savarino



OEF/OIF, 2001-2007

Disease Burden 'By the Numbers'



Cumulative deployments and disease burden

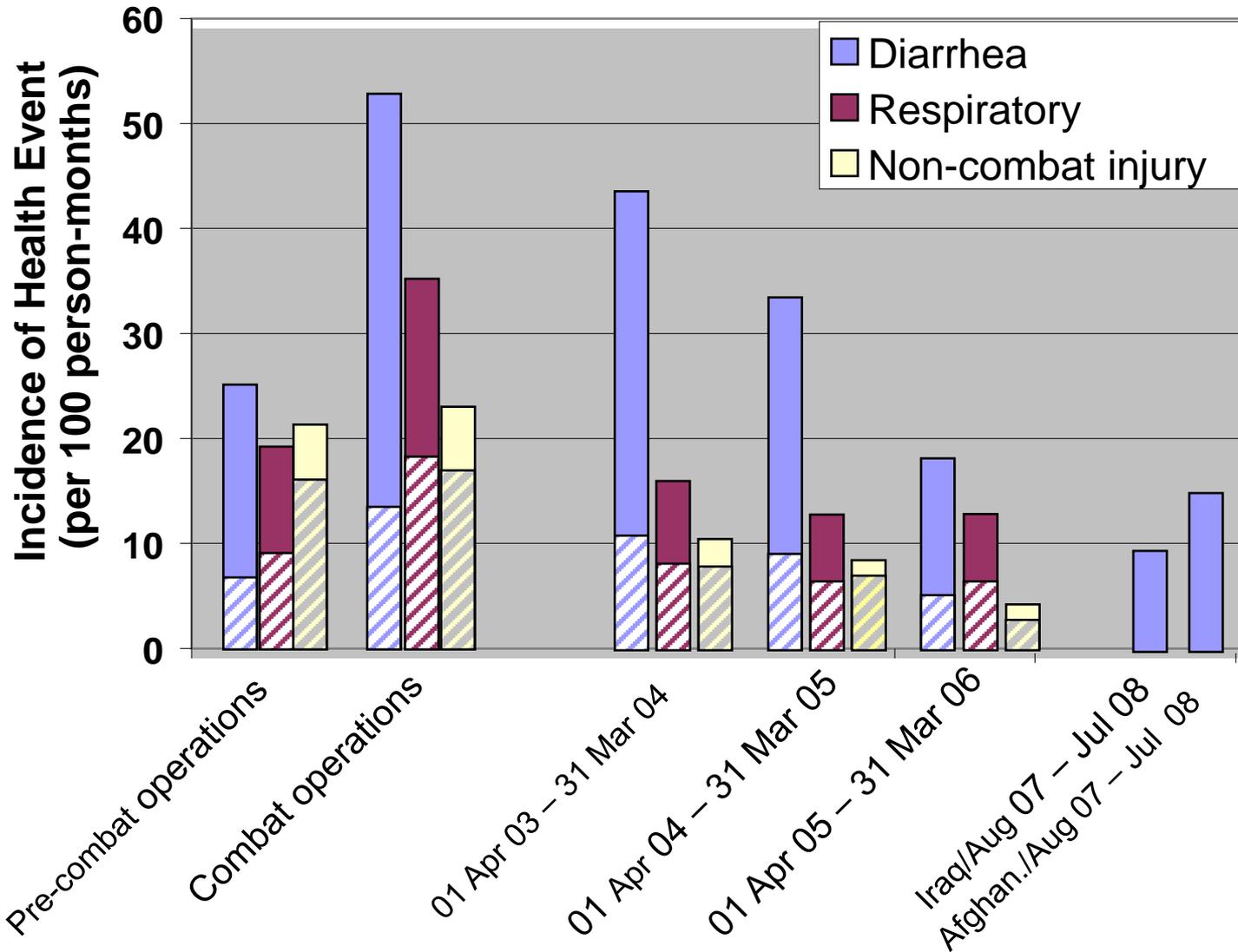
2,134,578	No. deployments (\bar{x} , 183 d)
145,871	No. deployments (\bar{x} , 19 d)
3,857,002	Cases of diarrhea
11,478,270	Diarrhea days
850,444	Ambulatory Medical Visits
17,356	Hospitalizations
1,114,208	Duty days lost
162,279	Liters of IV fluids infused

Slide courtesy of CAPT S. Savarino



Incidence of Illness based on Self-Reporting vs. DNBI

JW Sanders (2005) AJTMH; MS Riddle (2008) AJPH



Slide courtesy of CAPT S. Savarino



Deployment versus Traveler's Diarrhea

- **Q: Are deployed military personnel similar to travelers?**
 - A: Some ways yes, some ways no.
 - YES: Physically relocated. Variation in food and water source. Variation in environmental exposures.
 - NO: Stress. Poor sleep hygiene. Food and water not on economy.* Variations in physical activity.

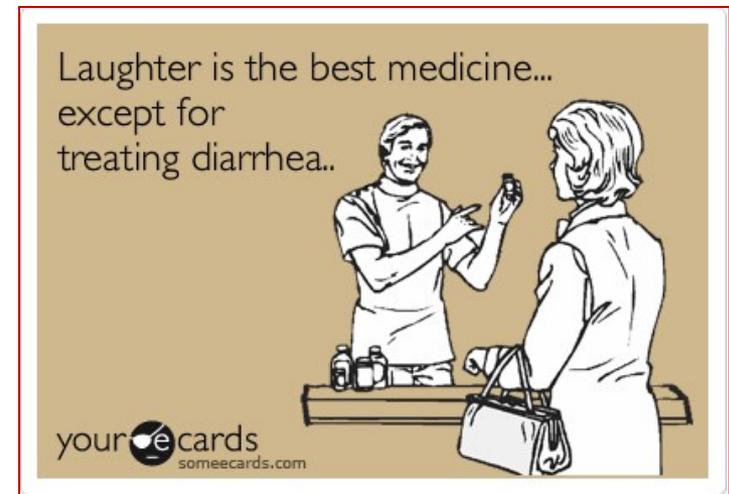


*Exceptions to this rule understood.

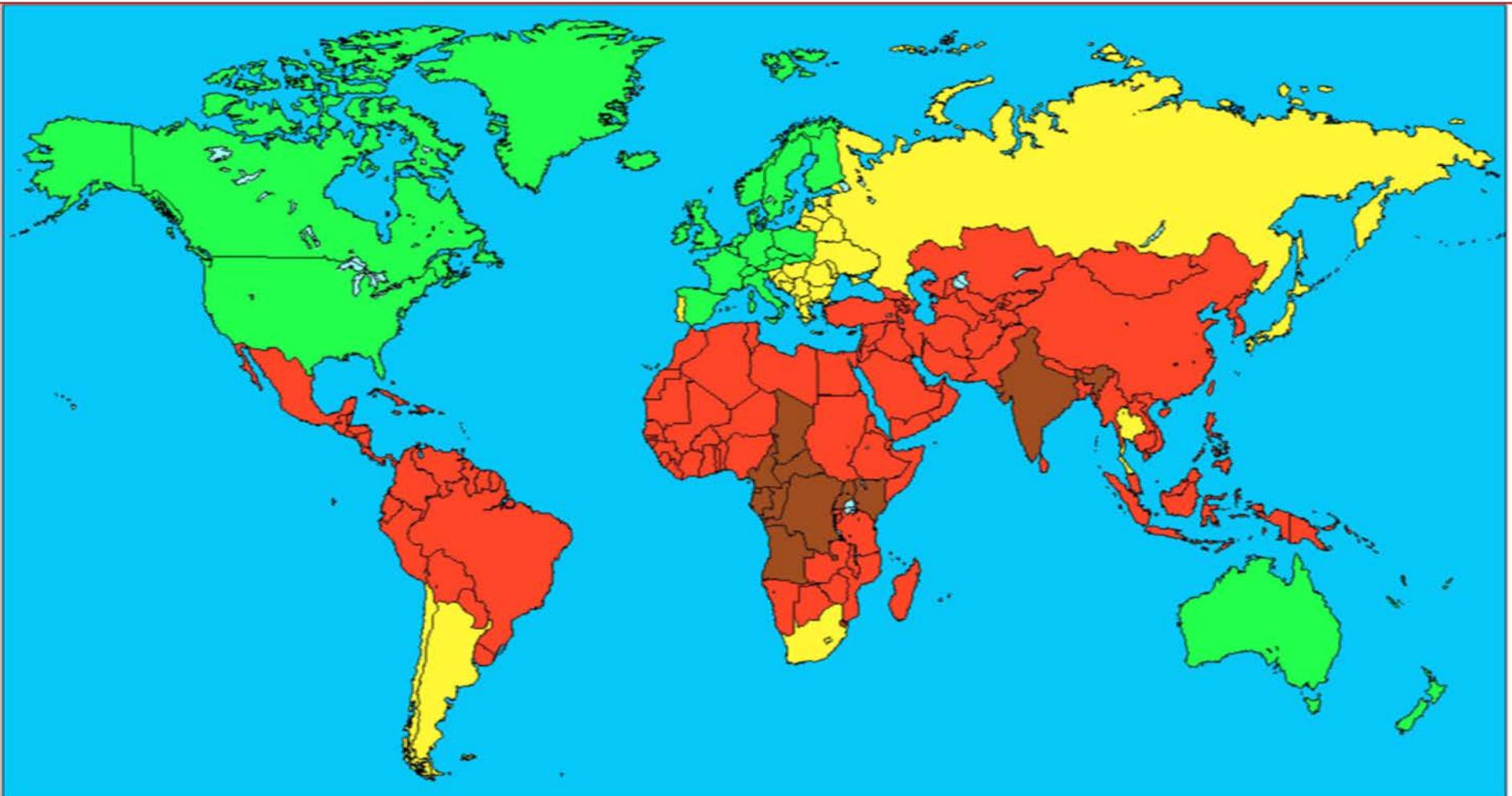


Risk Factors for Deployment or Traveler's Diarrhea

- Geographic location (hygiene standards)
- Number of viable organisms reaching the intestine
 - Eating habits (wash, peel, cook)
- History of gastric surgery
- Abnormal digestive motility
- Gastric ulcer, antihistaminic drugs
- Immunosuppression
 - Malignancy, HIV, medications, etc.



Geographic Risk of Traveler's Diarrhea



Risk: ■ Low <8% ■ Intermediate 8-20% ■ High 20-50% ■ Very high >50%



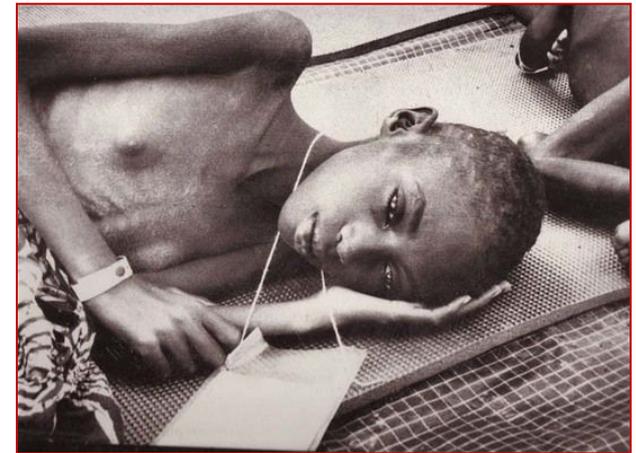
History and Physical Examination

- History
 - HPI
 - Duration of illness, number of stools each day, stool description (water, blood, pus, mucus), other symptoms such as F, S, C, N, or V, efforts to treat and response
 - ROS
 - Extra-intestinal (rash, headache, neurologic, etc.)
 - PMHx / PSHx
 - Immunosuppression, GI anatomy
 - SHx
 - Travel history
 - Food and water source for last 9-10 days
 - Sick contacts
 - Tobacco and ETOH
 - Meds
 - Antibiotics



History and Physical Examination

- Physical Examination
 - Vitals
 - HR, BP, Pulse pressure, Orthostatics, Temperature
 - HEENT
 - Sunken eyes, mucus membranes
 - Skin
 - Rash, turgor, perfusion
 - Cardiac
 - Tachycardia
 - Lungs
 - Respiratory rate, clarity of breath sounds
 - Abdomen
 - Bowel sounds, distention, TTP, rebound, etc.
 - Extremities
 - Perfusion



Clinical Presentations

- Watery diarrhea (80%)
 - ± Abdominal cramps
 - ± Nausea
 - ± Vomiting
 - ± Fecal urgency
 - ± Low-grade fever
- Dysentery (1-5%)
 - Fever
 - Tenesmus
 - Mucoid stools
 - Grossly bloody stools
- Gastroenteritis ($\leq 10\%$)
 - Recurrent vomiting



Pathogens, Epidemiologic Settings, Clinical

Pathogen	Common Epidemiologic Settings or Modes of Transmission*	Clinical Features					
		Fever	Abdominal Pain	Bloody Stool	Vomiting, Nausea, or Both	Fecal Evidence of Inflammation	Heme-Positive Stool
Salmonella	Outbreaks due to foodborne transmission, community-acquired	Common	Common	Occurs	Occurs	Common	Variable
Campylobacter	Community-acquired, consumption of undercooked poultry	Common	Common	Occurs	Occurs	Common	Variable
Shigella	Community-acquired, person-to-person	Common	Common	Occurs	Common	Common	Variable
Shiga toxin–producing <i>E. coli</i> (including O157:H7)†	Outbreaks due to foodborne transmission, especially through ingestion of undercooked hamburger or raw seed sprouts	Atypical	Common	Common	Occurs	Often not found	Common
<i>C. difficile</i> ‡	Nosocomial spread, antibiotic use	Occurs	Occurs	Occurs	NC	Common	Occurs

* If the illness can be linked to the ingestion of a particular food or meal, as in an outbreak, the incubation period can be deduced and the differential diagnosis narrowed accordingly. If the incubation period is less than 6 hours, *S. aureus* and *B. cereus* are likely causes; if the incubation period is 6 to 24 hours, *C. perfringens* and *B. cereus* are likely causes; and if the incubation period is 16 to 72 hours, possible causes include noroviruses, enterotoxigenic *E. coli*, vibrio, salmonella, shigella, campylobacter, yersinia, Shiga toxin–producing *E. coli*, giardia, cyclospora, and cryptosporidium. NC denotes not characteristic.

† Bloody diarrhea in an afebrile patient is suggestive of Shiga toxin–producing *E. coli* infection, although this is not always the cause.

‡ Leukocytosis is found in approximately 50 percent of patients.



Pathogens, Epidemiologic Settings, Clinical

Pathogen	Common Epidemiologic Settings or Modes of Transmission*	Clinical Features					
		Fever	Abdominal Pain	Bloody Stool	Vomiting, Nausea, or Both	Fecal Evidence of Inflammation	Heme-Positive Stool
Vibrio	Ingestion of seafood	Variable	Variable	Variable	Variable	Variable	Variable
Yersinia	Community-acquired, foodborne transmission	Common	Common	Occurs	Occurs	Occurs	Occurs
<i>E. histolytica</i> §	Travel to tropical regions, recent emigration from such regions	Occurs	Occurs	Variable	Variable	Variable	Common
Cryptosporidium¶	Outbreaks due to waterborne transmission, travel, immunocompromised hosts	Variable	Variable	NC	Occurs	None to mild	NC
Cyclospora	Outbreaks due to foodborne transmission, travel	Variable	Variable	NC	Occurs	NC	NC
Giardia	Day care, outbreaks due to waterborne transmission, IgA deficiency	NC	Common	NC	Occurs	NC	NC
Norovirus**	Winter outbreaks of vomiting or diarrhea in families, nursing homes, schools, or on cruise ships, or after ingestion of under-cooked shellfish	Variable	Common	NC	Common	NC	NC

§ Classically, patients with intestinal amebiasis present with heme-positive or bloody stools.

¶ Although cryptosporidiosis is typically considered to be noninflammatory in the United States, fecal evidence of inflammation is common in children with cryptosporidiosis in developing countries.

|| Fatigue, which may be profound, is reported in more than 90 percent of patients with cyclosporiasis.

**Vomiting occurs more frequently than diarrhea in children; diarrhea occurs more frequently in adults.



Pathogens and Clinical Syndromes

Pathogen	Clinical features
Bacteria	
Enterotoxigenic <i>Escherichia coli</i>	'Turista': short incubation, fecal diarrhea without blood or pus (enterotoxin) Cholera-like diarrhea
Enteroaggregative <i>E. coli</i>	'Turista'
<i>Campylobacter jejuni</i>	Dysentery: bloody diarrhea, abdominal pain, tenesmus, fever (enteroinvasion) Fecal diarrhea
<i>Salmonella</i> spp.	Dysentery (enteroinvasion) Fecal diarrhea
<i>Shigella</i> spp.	Dysentery (enteroinvasion) Aqueous diarrhea (enterotoxin) Fecal diarrhea
<i>Vibrio parahaemolyticus</i>	Dysentery (enteroinvasion) or aqueous diarrhea (enterotoxin)
<i>Aeromonas hydrophila</i>	Aqueous diarrhea (enterotoxin) or dysentery (enteroinvasion)
<i>Plesiomonas shigelloides</i>	Cholera-like diarrhea
<i>Yersinia enterocolitica</i>	Dysentery (enteroinvasion)

Viruses	
Rotavirus	Vomiting, aqueous diarrhea
Enteric adenovirus	Vomiting, aqueous diarrhea
Parasites	
<i>Giardia lamblia</i>	Chronic diarrhea, predominant upper gastrointestinal signs
<i>Cryptosporidium parvum</i>	Children, chronic diarrhea
<i>Cyclospora cayetanensis</i>	Chronic diarrhea, predominant upper gastrointestinal signs
<i>Microsporidium</i> spp.	Frequent with AIDS, chronic diarrhea
<i>Isospora belli</i>	Frequent with AIDS, chronic diarrhea
<i>Entamoeba histolytica</i>	Chronic diarrhea or acute bloody diarrhea



Pathogens: Acute Watery Diarrhea

- Bacteria
 - Enterotoxigenic *Escherichia coli* (ETEC)
 - Enteroaggregative *Escherichia coli* (EAEC)
 - *Vibrio cholerae*
- Viruses
- Parasites
- Food poisoning

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid



Pathogens: Acute Bloody Diarrhea

- Bacteria
 - Enterohemorrhagic *E.coli* (EHEC)
 - Enteroinvasive *E.coli* (EIEC)
 - *Shigella* species
 - *Campylobacter* species
 - Nontyphoidal *Salmonella*
 - *Entamoeba histolytica*



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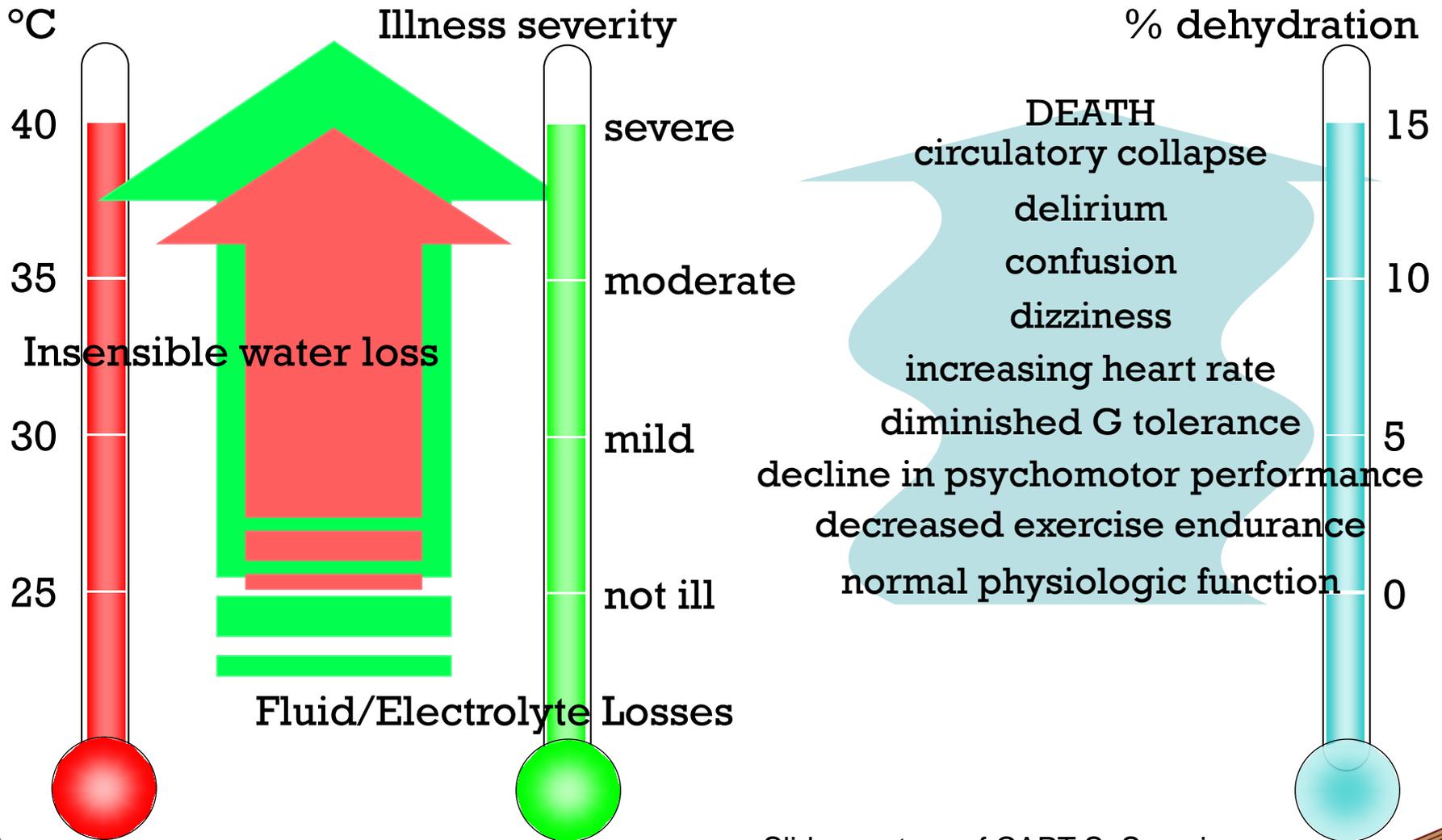


Persistent Travelers' Diarrhea

- Travelers' diarrhea is often self-limited
 - Majority of cases resolve after several days
- Persistent illness
 - Lasting >1 week: 10% of cases
 - Lasting >1 month: 2% of cases
- Etiological considerations with persistent diarrhea
 - EAEC (occasionally, *Campylobacter*, *Salmonella*)
 - Parasitic diarrhea
 - *Giardia lamblia*
 - *Cryptosporidium parvum*
 - *Cyclospora cayatanensis*



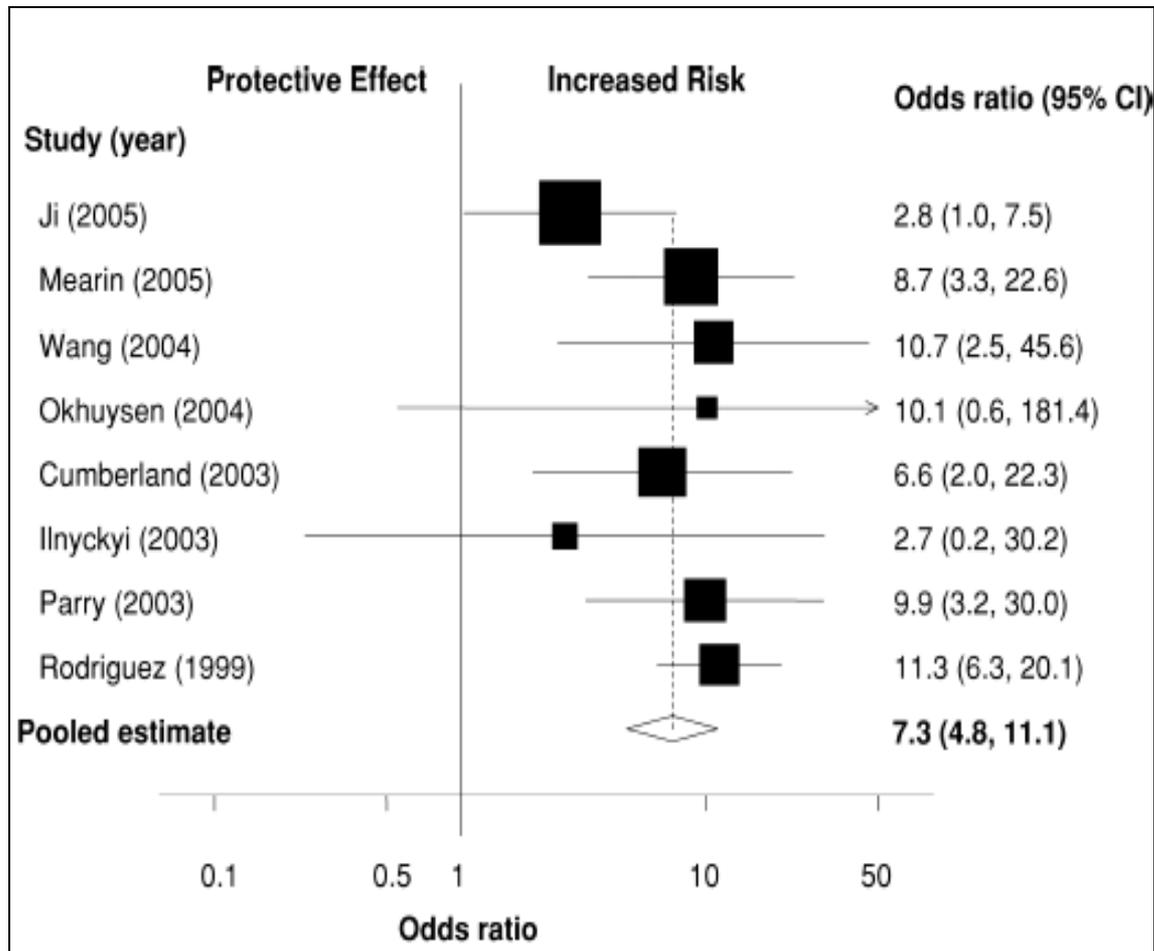
Stressors Amplify Diarrhea Morbidity



Slide courtesy of CAPT S. Savarino



Post-infectious Irritable Bowel Syndrome

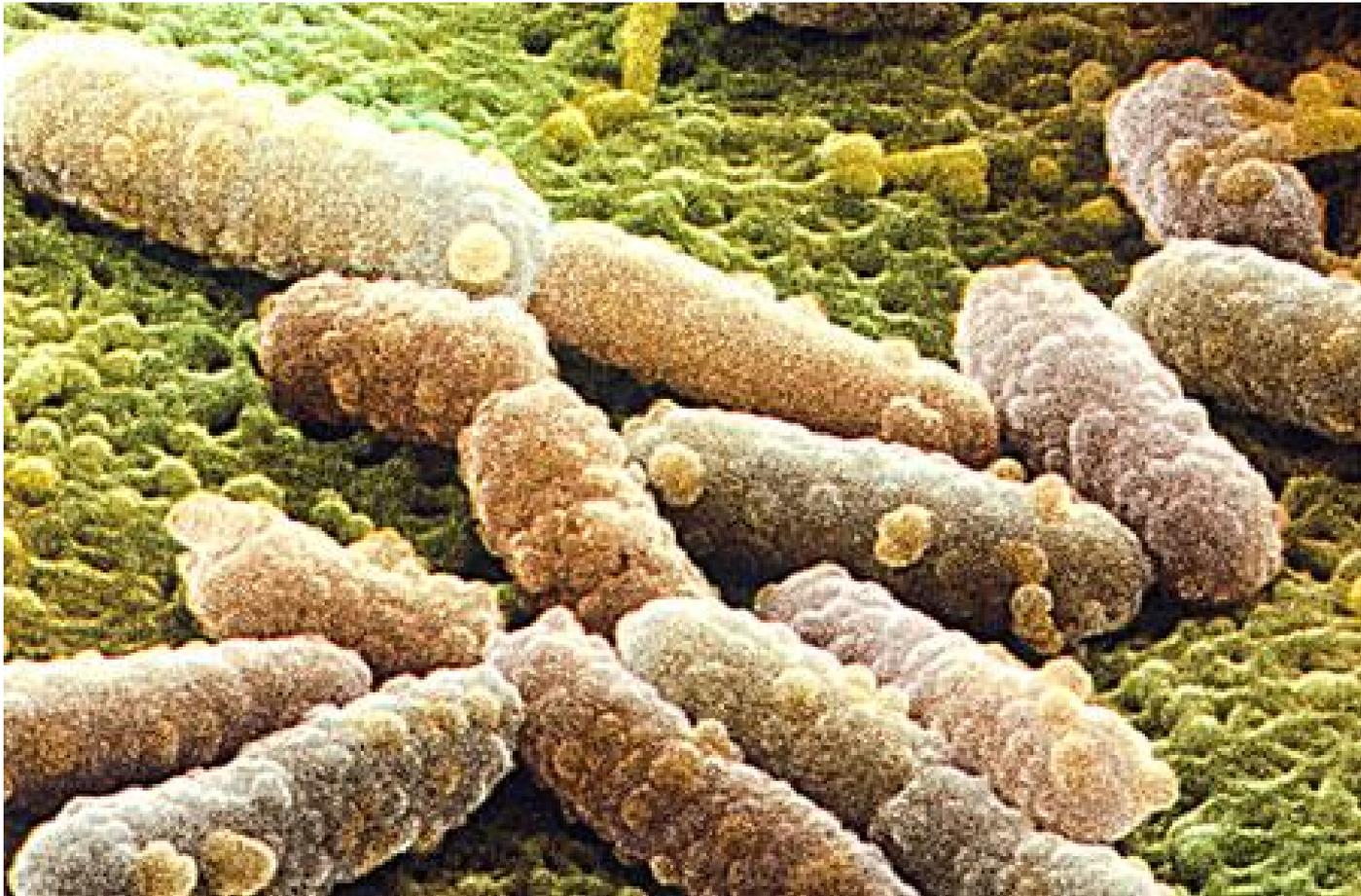


- First described among British Forces during WWII (Stewart. *Br Med J* 1950; 1(4650):405-9)
- Approx. 1 in 12 people develop PI-IBS after infectious diarrhea
- Higher risk associated with prolonged illness and invasive pathogens
- Onset usually occurs within 6 months after infection
- Can persists 5-6 years in 60 - 70% of people

Halvorson *et al*, *Am J Gastroenterol*. 2006; 101:1894-9.



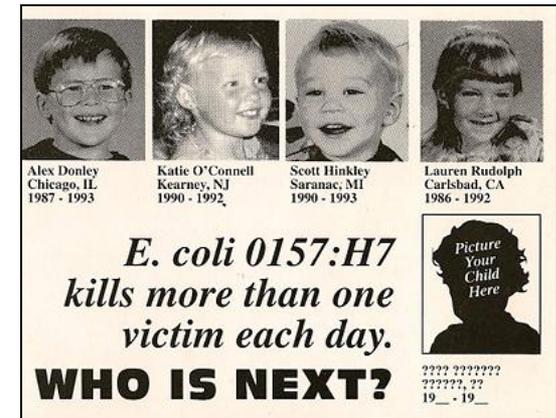
Pathogens – Clinical Syndromes



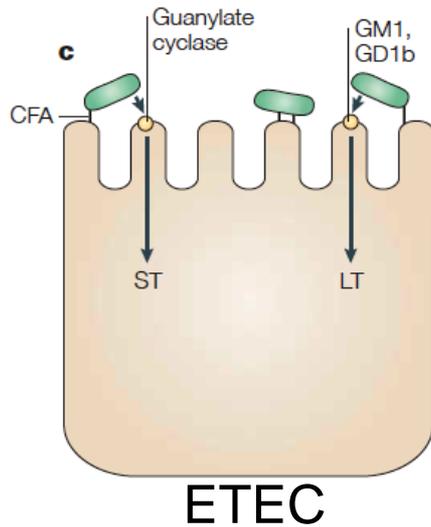
Types of *Escherichia coli* (*E. coli*)

- *E. coli* consists of a diverse group of bacteria
- Pathogenic *E. coli* strains are categorized into pathotypes
- Six pathotypes are associated with diarrhea

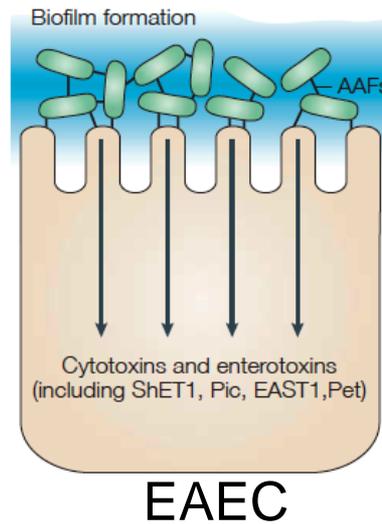
- 1). Enterotoxigenic *E. coli* (ETEC)
- 2). Enterohemorrhagic *E. coli* (EHEC)
[Shiga toxin-prod. *E. coli* (STEC)]
- 3). Enteroaggregative *E. coli* (EAEC)
- 4). Enteroinvasive *E. coli* (EIEC)
- 5). Enteropathogenic *E. coli* (EPEC)
- 6). Diffusely adherent *E. coli* (DAEC)



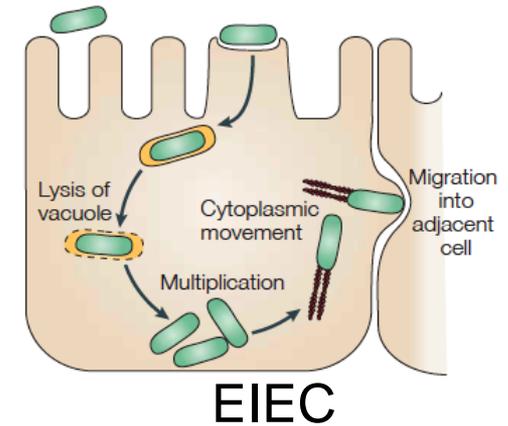
Diarrheagenic *Escherichia coli*: Pathogenesis



- **Fimbrial colonization factors** mediate enterocyte adherence
- Elaboration of secretory heat-labile (LT), heat-stable (ST) **enterotoxins**



- Enterocyte adherence and **biofilm formation**
- Elaboration of secretory enterotoxins and cytotoxins

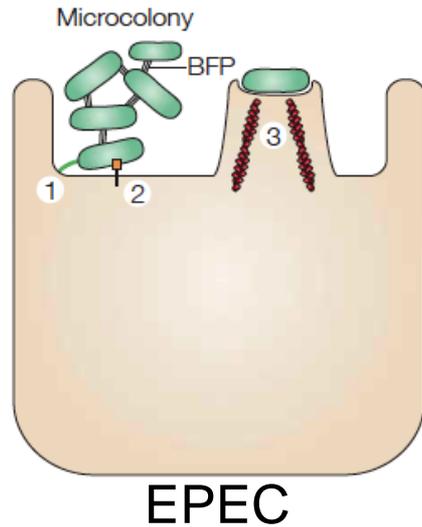


- Colonic epithelial cell invasion
- Lysis of phagosome
- Cell-to-cell spread via actin microfilament nucleation

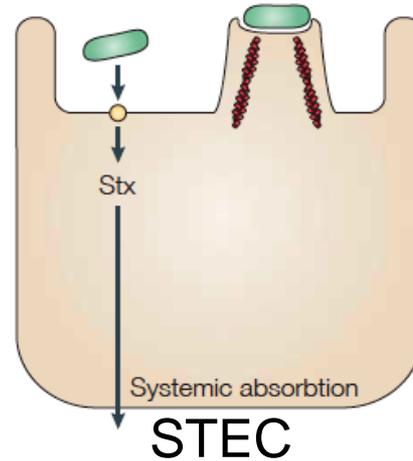
adapted from Kaper JB et al *Nat Rev Microbiol* 2004



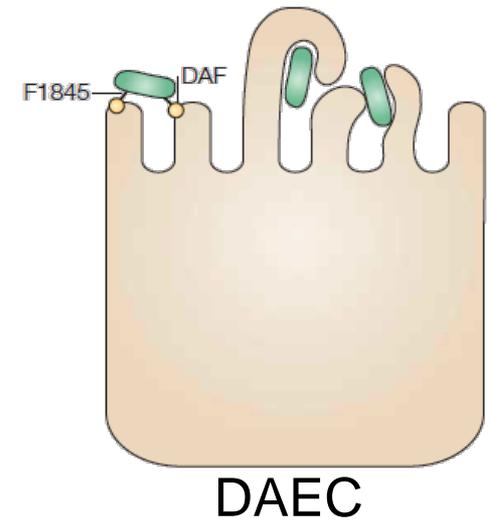
Diarrheagenic *Escherichia coli*: Pathogenesis



- **Intimate adherence** to small bowel enterocytes
- **Attaching and effacing** lesion, with cytoskeletal derangement
- Induction of inflammatory response



- Induction of **attaching and effacing** (AE) lesions in the colonic epithelium
- Elaboration and absorption of **Shiga toxin** (STx)



- Signal transduction effects
- Cellular projections induced that enwrap bacteria

adapted from Kaper JB et al *Nat Rev Microbiol* 2004



Enterotoxigenic *E. coli* (ETEC)

- Watery Diarrhea
- Low-grade fever, nausea, malaise, abdominal cramping, and diarrhea
- Occurs within 1 to 3 days of ingestion
- Resolves within 3 to 4 days.
- Leading cause of travelers' diarrhea.
- Virulence due to a heat-labile and heat-stable toxin
- Contaminated water or food is responsible for transmission
- High infective dose of the bacteria is necessary



Enterohemorrhagic E coli (EHEC) / Shiga Toxin Producing E. Coli (STEC)

- Watery diarrhea → bloody stools (few days)
- Abdominal pain (RLQ), cramping, fever absent / low-grade.
- As many as 10% develop hemolytic uremic syndrome (HUS). Case fatality rate of 3% to 5%, common cause of renal failure, neurologic sequelae, hemolytic anemia, and thrombocytopenia.
- Incubation period 2-10 days; symptoms up to 2 weeks.
- Adheres to gut epithelium, produces Shiga toxins, (also called verotoxins), similar or identical to the toxin elaborated by Shigella. Best known EHEC serotype is 0157:H7. Antibiotics may pre-dispose to HUS.



Campylobacter jejuni

- Watery to dysenteric diarrhea
- Abdominal pain and cramps, and fever. Nausea, vomiting, headache, and malaise frequently occur.
- Complications may include Guillain-Barre syndrome, hemolytic uremic syndrome, toxic megacolon, cholecystitis, meningitis, and reactive arthritis.
- Incubation period 1-10 days, disease 2-7 days, may be biphasic illness.
- Animal-to-human transmission is common. Improperly cooked chicken is a major source of illness.



Nontyphoidal *Salmonella*

- Watery or dysenteric diarrhea
- Nausea, vomiting, abdominal cramping, fever (50%), RLQ or peri-umbilical pain, 10% with bacteremia, carrier state.
- Reiter syndrome is a long-term sequel, ~2% to 29% of patients, especially among persons with the HLA-B27.
- Incubation 6-48 hours, >1 week reported, persists 4-7 days
- Contaminated foods of both plant and animal origin. Fecal-oral transmission from infected animals or persons. Poultry are prone to colonization by *Salmonella*; disease transmission while handling birds, consuming undercooked poultry, and eating inadequately cooked eggs. Handling of pet reptiles is another well known source of infection.



Salmonella (typhi and paratyphi)

- “Pea soup” diarrhea
- Initially, symptoms are absent, then bacteremia, then high fever, abdominal pain, “rose spots.” Fever becomes more constant with the development of altered mental status.
- Intestinal perforation and hemorrhage may occur. Multi-organ system involvement is frequently present. Untreated typhoid fever carries a mortality rate of 12% to 30%.
- Incubation 1-2 weeks, illness lasts about 1 month, relapse
- A prolonged, antibiotic-resistant carrier state usually indicates the presence of the disease in the gallbladder and is an indication for cholecystectomy.



Shigella

- Dysenteric stools, blood, mucus
- Lower abdominal pain and small-volume, dysenteric stools. High fever and rectal burning. Illness 1-7 days, may be biphasic, frank hematochezia in the second phase.
- Potential complications include seizures, meningitis, appendicitis, hemolytic-uremic syndrome, reactive arthritis, and postinfection irritable bowel syndrome.
- The incubation period is usually 12 to 96 hours
- Species: *S dysenteriae*, *S flexneri*, *S boydii*, and *S sonnei*
- Person-to-person contact, food, water, and fly transmission





Vibrio cholerae

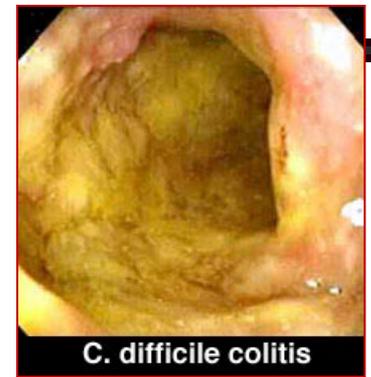


- Voluminous “rice water” stools
- “Classic” cholera: vomiting, abdominal distension, rapid intravascular volume loss, fever and bacteremia in minority
- Incubation 6 hours - 5 days
- Multiple pathogenic species of Vibrio exist (ex. O1, O139)
- Contaminated food and water responsible for most illness
- Clinical significance of the organism is due to the virulence of the various toxins elaborated by different strains.





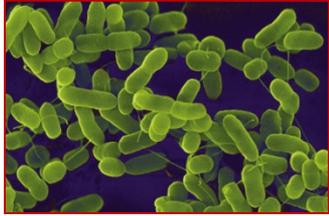
Clostridia difficile



- Watery diarrhea, may contain blood, mucus
- Cramping and tenderness in the lower abdomen, malaise, mild temperature elevation
- Toxic megacolon with fever, abdominal distention / pain
- Risk factors include comorbidities, advanced age, recent (within 3 months) antibiotics, ↑ gastric pH
- All antibiotics may cause, Clindamycin, cephalosporins, fluoroquinolones, penicillins most implicated
- Antibiotic-altered gut flora, colonization by C difficile, inflammatory exotoxins toxin A and toxin B



Yersinia enterocolitica

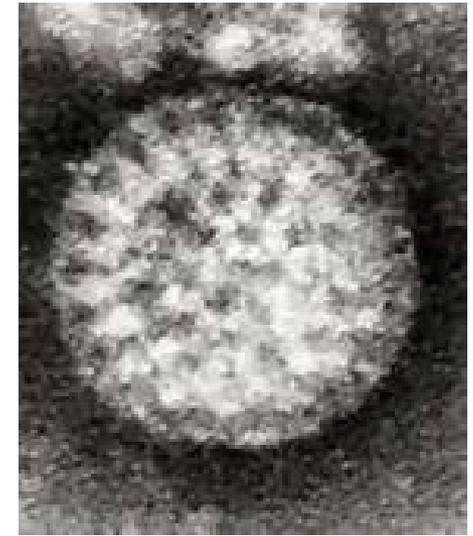


- Diarrhea, may be frankly bloody
- Abdominal pain and fever, RLQ pain may mimic appendicitis. Symptoms typically persist for 1 to 3 weeks.
- The incubation period for yersiniosis is 1 to 10 days
- Tonsillitis and mesenteric adenitis may be present.
- Postinfection sequelae may include erythema nodosum, erythema multiforme, and reactive polyarthrits.



Rotavirus

- Watery diarrhea
- Begins abruptly with nausea, vomiting, fever and headache.
- Incubation period of 1-4 days. May persist for 4 to 5 days.
- Primary mode of transmission is fecal-oral.
- Most pediatric infections due to Group A rotavirus strains. Groups B and C are also known to be pathogenic.
- Viruses survive on dry fomites for up to 60 days.
- Good hand-washing technique is critical when caring for patients with rotavirus gastroenteritis.



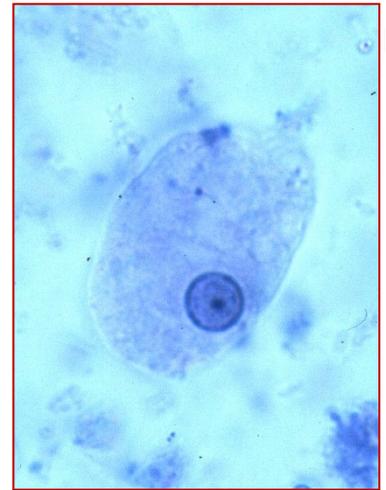
Norovirus



- Watery diarrhea.
- Nausea, vomiting, abdominal cramps. Low-grade fever and myalgias. Dehydration may occur in severe cases.
- Incubation of 24-36 hours. Resolution within 24-48 hours.
- Transmission is thought to be primarily fecal oral. It appears that aerosolization may also lead to infection.
- Numerous outbreaks related to consumption of raw shellfish, particularly oysters, have also been reported.
- Viral shedding may be present for 2 or more weeks.



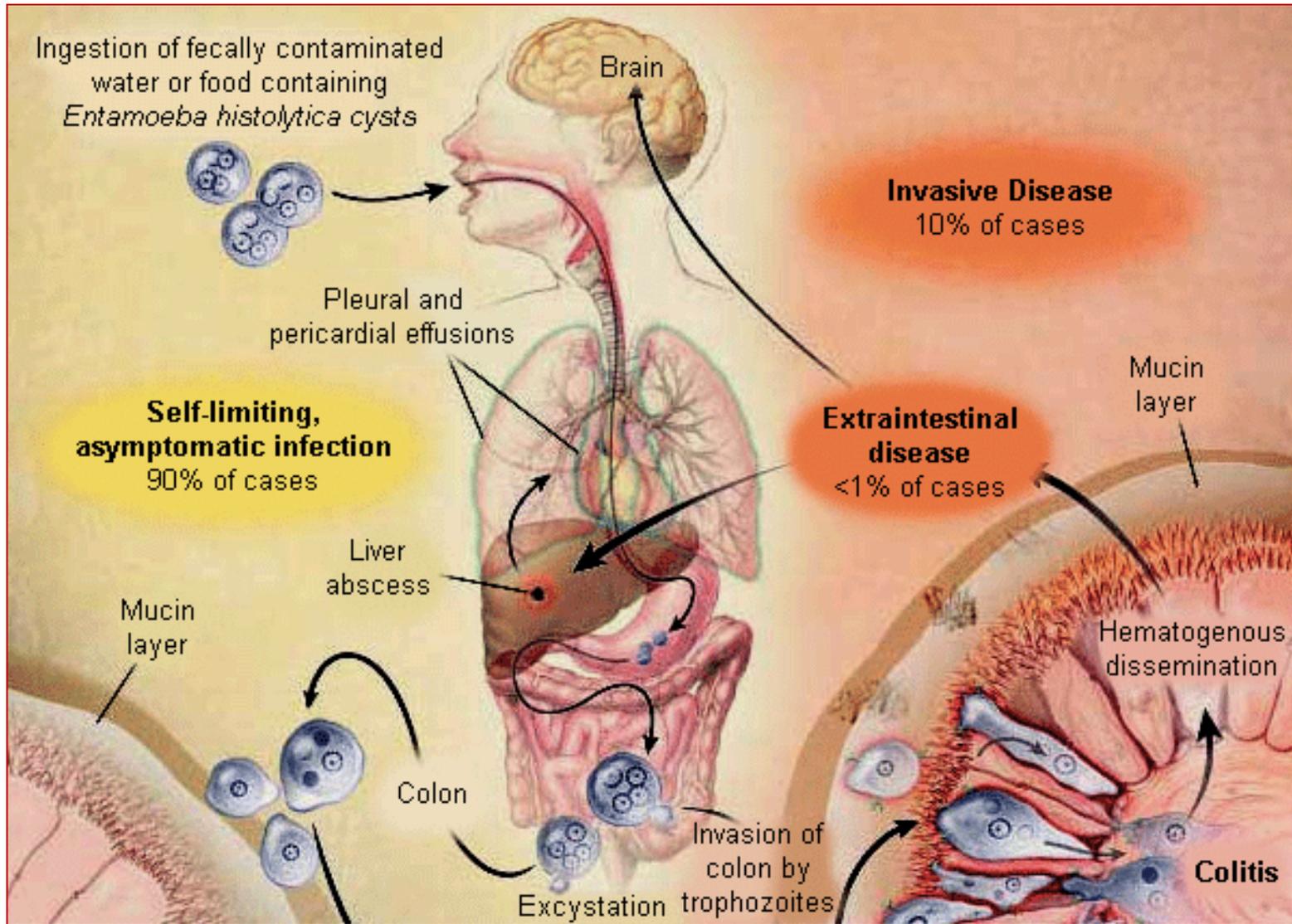
Entamoeba histolytica



- Mild diarrhea followed by dysentery.
- Low-grade fever, abdominal cramping, and anemia. Severe pancolitis mimicking inflammatory bowel disease. Amebic liver abscess formation is a well-known entity.
- Illness 2 to 4 weeks after exposure.
- Common in tropics where poverty is prevalent. North America, most frequently seen among institutionalized persons, MSM, and immigrants or travelers.
- Contaminated food or water.



Entamoeba histolytica Life Cycle

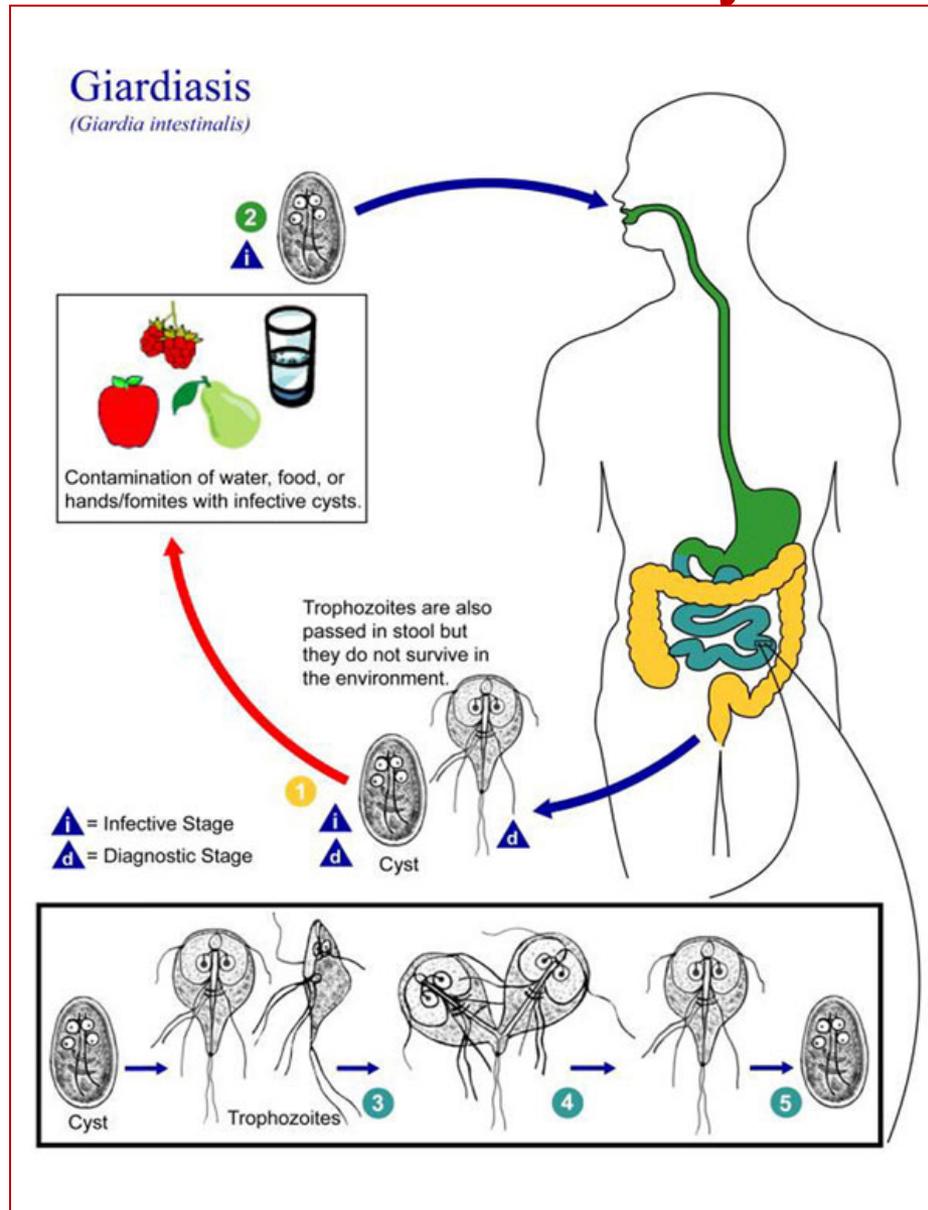


Giardia lamblia

- Diarrhea with steatorrhea
- Abdominal pain and cramping, flatulence, nausea and vomiting.
- Ill 2 to 4 weeks after ingestion.
- Contaminated food or water, or direct fecal-oral contact.
- Daycare centers, international travelers, and MSM.
- Post-infection irritable bowel symptoms have been reported in significant number of patients.

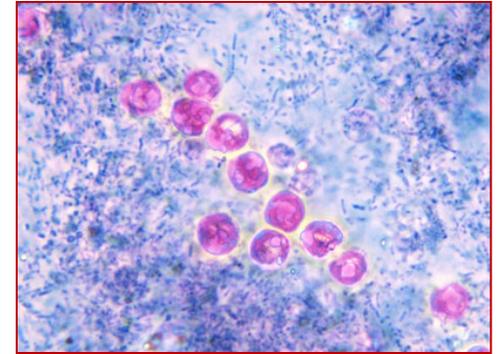


Giardiasis Life Cycle

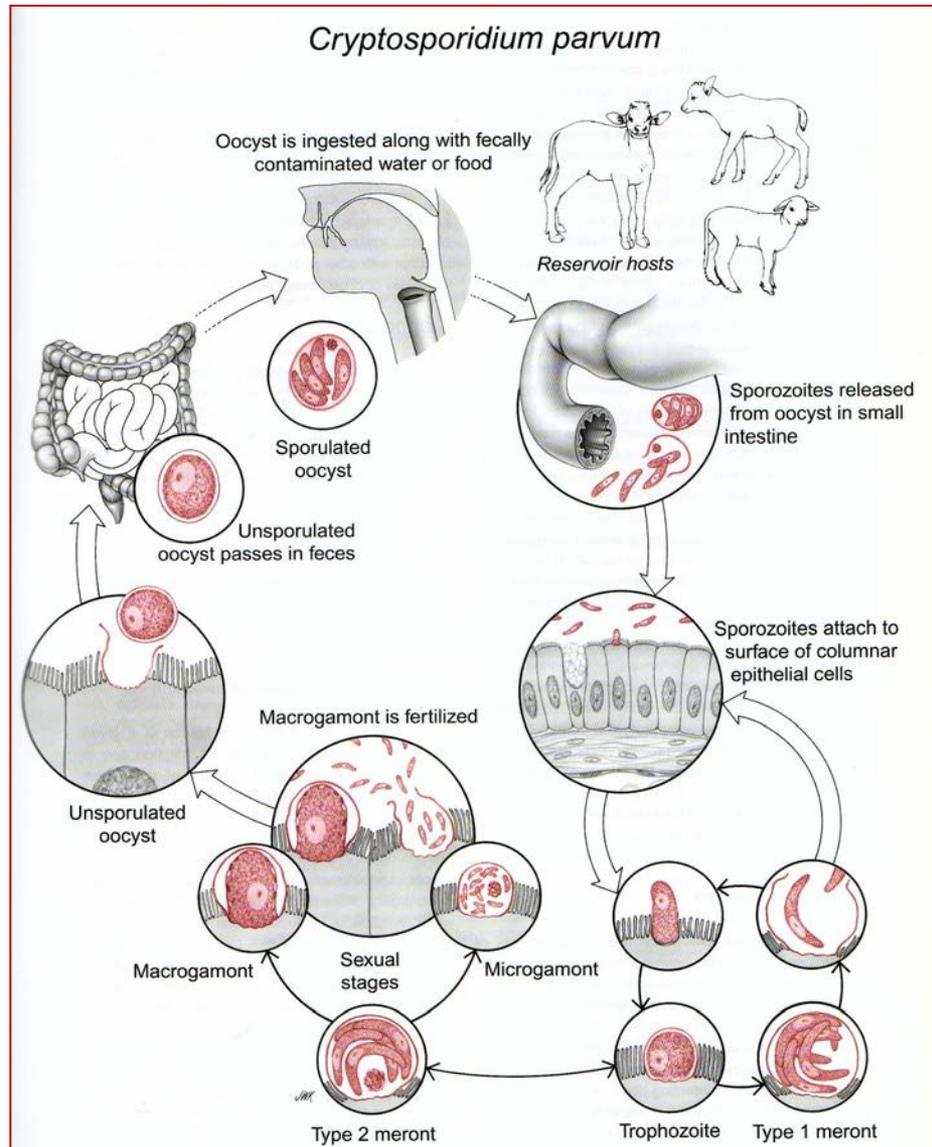


Cryptosporidium

- Watery diarrhea
- Infection may be asymptomatic but often leads to abdominal cramping, malaise. Systemic manifestations occasionally occur.
- *C. parvum* and *C. hominis* cause disease.
- Particularly problematic among HIV-infected individuals.
- Waterborne illness, may also be traced to contaminated food or person-to-person contact.
- To prevent transmission, persons who have been infected with *Cryptosporidium* should not swim for at least 2 weeks after cessation of diarrhea.



Cryptosporidiosis

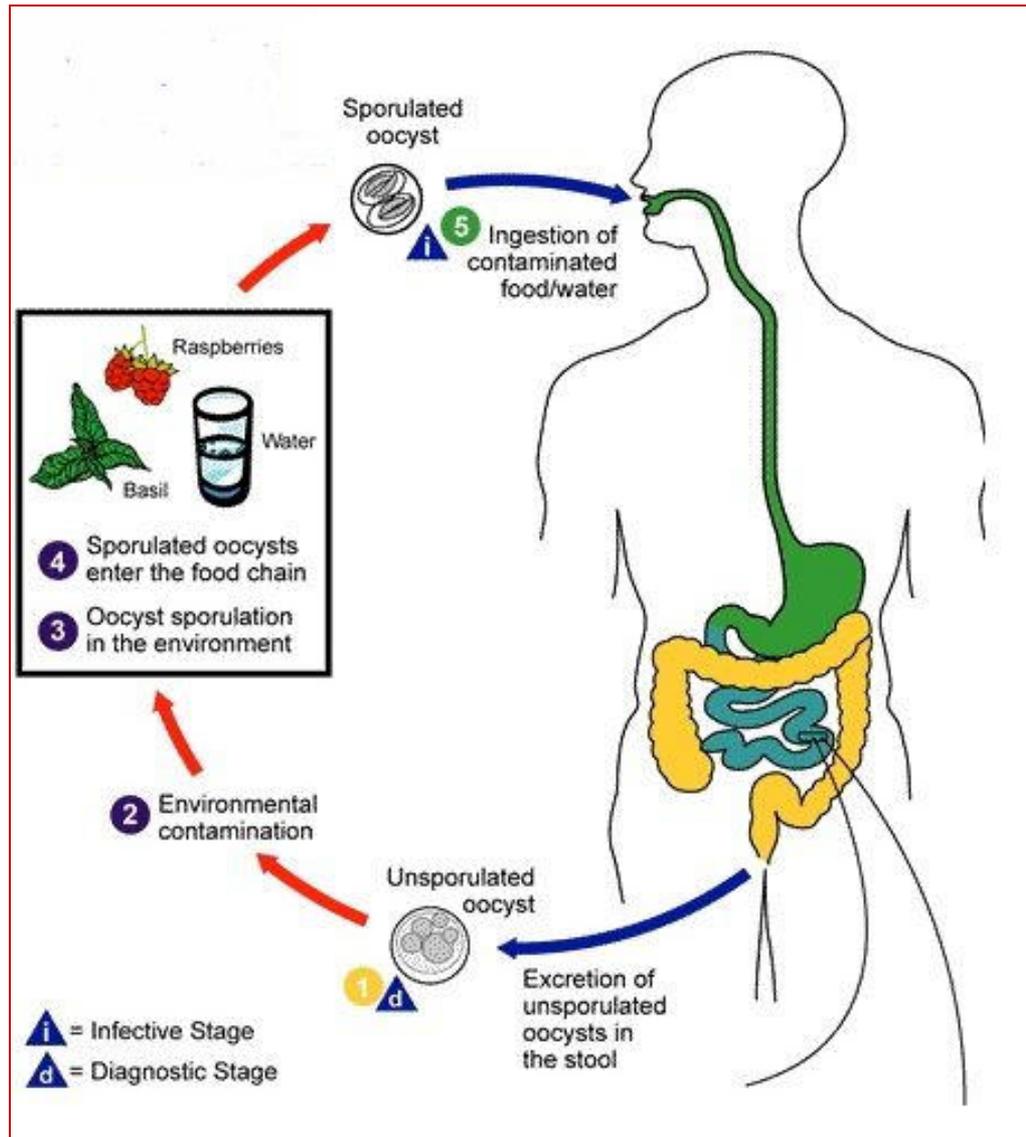


Cyclosporiasis

- Persistent diarrhea.
- Anorexia, nausea/vomiting, abdominal cramps, flatulence, low grade fever, weight loss. Chronic diarrhea in immunosuppressed.
- Contaminated food and water; no person-to-person.
- *C. cayatanensis* found only in humans.



Cyclosporiasis



Complications of Bacterial Diarrhea

Complication	Associated Agents	Clinical Considerations
Dehydration	Any bacterial pathogen	Most important complication of watery diarrhea
Bacteremia	<i>Salmonella</i> spp., <i>C. fetus</i>	Certain conditions predispose to systemic <i>Salmonella</i> infection
Hemolytic-uremic syndrome (HUS)	STEC, <i>S. dysenteriae</i> type 1	Pathogenesis due to shiga toxin absorption and damage
Guillain-Barré syndrome	<i>Campylobacter jejuni</i>	40% cases of GBS caused by <i>C. jejuni</i> ; molecular mimicry LOS
Reactive arthritis	<i>C. jejuni</i> , <i>Salmonella</i> , <i>S. flexneri</i>	Occurs in 2.1 per 100 000 <i>Campylobacter</i> infections
Irritable bowel syndrome	Most bacterial pathogens	≤ 10% incidence following bacterial enteric infection



Diagnosis

- Risk factors
 - Geography, baseline health, exposures
- Clinical picture
 - Inflammatory vs. non-inflammatory diarrhea
- Laboratory
 - Assets may be non-existent
 - Some pathogens evade routine laboratory tests
 - Diarrheagenic *E. coli* (ETEC, EAEC, EIEC)
 - Norovirus



Diagnosis: Stool Culture

- Stool culture: clinical indications
 - Severe diarrhea (≥ 6 loose/liquid stools/24 hrs)
 - Febrile enteritis and/or dysentery
 - Persistent diarrhea (≥ 14 days duration)
 - Bloody diarrhea (at risk for Shigella, STEC)
 - Inflammatory enteritis (by stool diagnostics)

- Stool parasitology: clinical indications
 - Persistent diarrhea (≥ 14 days duration)
 - Diarrhea in traveler from known high risk region



Personal Prevention Measures

- **Food**

- **Eat**

- Food that is cooked and served hot
 - Hard-cooked eggs
 - Fruits and vegetables you have washed in clean water or peeled yourself
 - Pasteurized dairy products



Personal Prevention Measures

- **Food**

- **Don't Eat**

- Food served at room temperature
 - Food from street vendors
 - Raw or soft-cooked (runny) eggs
 - Raw or undercooked (rare) meat or fish
 - Unwashed or unpeeled raw fruits and vegetables
 - Condiments (such as salsa) made with fresh ingredients
 - Salads
 - Flavored ice or popsicles
 - Unpasteurized dairy products
 - "Bushmeat" (monkeys, bats, or other wild game)



Personal Prevention Measures

- **Beverages**

- **Drink**

- Water, sodas, or sports drinks that are bottled and sealed (carbonated is safer)
 - Water that has been disinfected (boiled, filtered, treated)
 - Ice made with bottled or disinfected water
 - Hot coffee or tea
 - Pasteurized milk



Personal Prevention Measures

- **Beverages**
 - **Don't Drink**
 - Tap or well water
 - Fountain drinks
 - Ice made with tap or well water
 - Drinks made with tap or well water (such as reconstituted juice)
 - Unpasteurized milk



Personal Prevention Measures

- **Bathing and Swimming**

- Unclean water can also make you sick if you swallow or inhale it while bathing, showering, or swimming. Try not to get any water in your nose or mouth.
- In some areas, tap water may not even be safe for brushing your teeth, and you should use bottled water.
- People who are elderly or have weakened immune systems might want to stay away from areas where there is a lot of steam and water vapor that can be inhaled, such as showers and hot tubs.



Treatment: Volume Replacement

- Cornerstone of diarrhea treatment
- Military settings, insensible fluid losses increased with high ambient temperature, intense physical activity
- Oral rehydration
 - Physiological principle: Integrity of coupled transport of Na⁺ (plus H₂O and other electrolytes) with glucose or amino acids
 - Effective in majority of patients
- Intravenous rehydration
 - Severe dehydration
 - Altered sensorium
 - Intractable vomiting



Treatment: Symptomatic

- Loperamide (Imodium): antimotility agent of choice
 - Slows down peristalsis, intestinal transit
 - Increased fluid and salt absorption
 - 4 mg po, 2 mg prn liquid stool (up to 16 mg per day)
 - Okay to use for non-bloody, non-febrile diarrhea.
- Bismuth subsalicylate (Pepto Bismol)
 - Reduces number of stools
 - Does not limit duration of disease
 - 525 mg (2 tabs) every 30 min for 8 doses
 - Contraindicated in persons on salicylates, warfarin
 - Can interfere with doxycycline absorption
 - Stools will be black



Treatment: Antibiotics

- Indicated for moderate to severe diarrhea/dysentery
- Combination of antibiotic PLUS loperamide leads to rapid resolution of illness
- Re-evaluate patient if no improvement after 1 wk

Antibiotic (po)	Dosage (adult)	Considerations
Fluoroquinolones		
Norfloxacin	800 mg once or 400 mg bid	Re-evaluate 12-24 h after single dose. Continue for up to 3 d if diarrhea not resolved
Ciprofloxacin	750 mg once or 500 mg bid	
Ofloxacin	400 mg once or 200 mg bid	
Levofloxacin	500 mg once or 500 qd	
Azithromycin	1000 mg once or 500 mg bid x 3d	Use when <i>C. jejuni</i> suspected
Rifaximin	200 mg tid	Effective for non-invasive <i>E coli</i>



Questions?



BACK-UP SLIDES



Increasing Fluoroquinolone Resistance among *Campylobacter* in Travelers

Region	1994-2000			2001-2006		
	No. isolates	No. resistant isolates	Resistance rate (%)	No. isolates	No. resistant isolates	Resistance rate (%)
Africa	162	22	13.6	114	36	31.6
Asia	208	74	35.6	95	67	70.5
Caribbean, Central & So. America	36	10	27.8	33	20	60.6

Vlieghe ER et al, *J Travel Med* 2008;15:419-25

- Study site: Travel clinic, Antwerp, Belgium
- Erythromycin resistance showed modest increase over same period to 8.6% resistance in 2006
- Use Azithromycin in SE ASIA, 1000 mg x 1 = enough

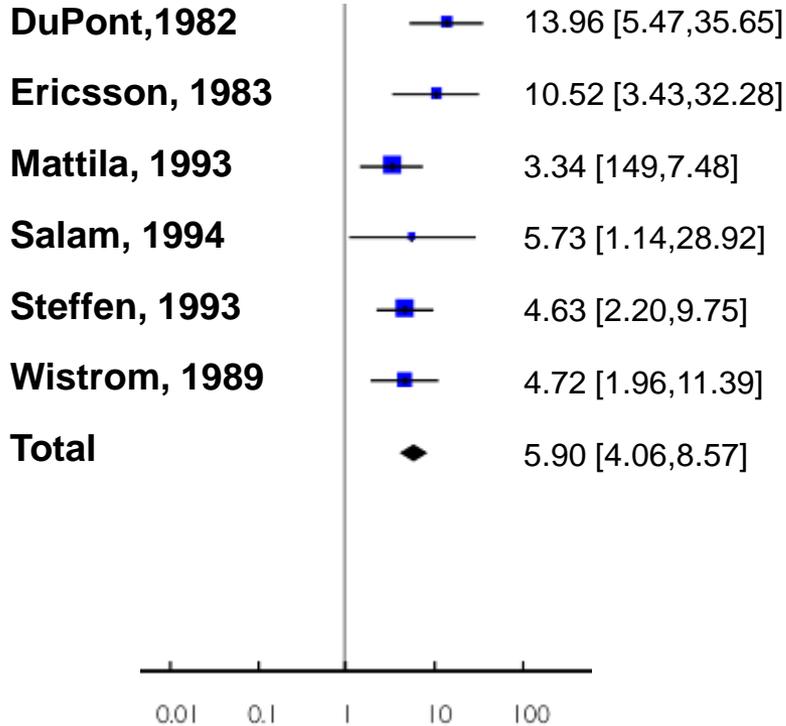


Antibiotics + Loperamide

Placebo vs antibiotics alone
(outcome: cure at 72 hours)
Bruyn G et al Cochrane Collab 2004

Favors Placebo

Favors Antibiotics

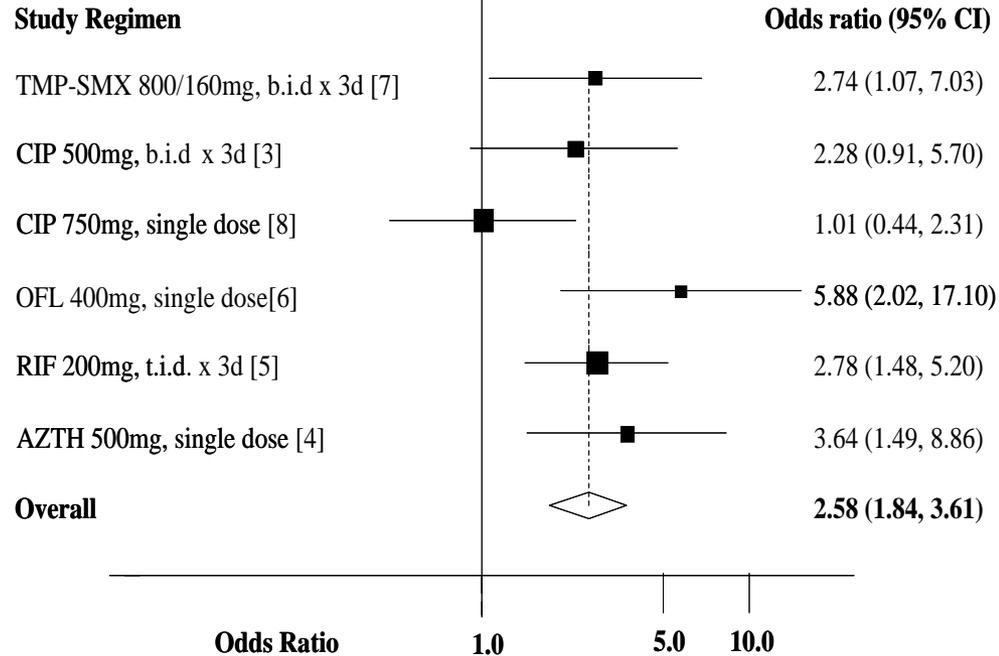


TLUS = 24 – 36 hours

Antibiotics alone or plus loperamide
(outcome: cure at 24 hours)
Riddle MS et al, CID 2008

Favors solo antibiotic therapy

Favors combination therapy



TLUS ~ 12 hours



Rifaximin and Chemoprophylaxis of Travelers' Diarrhea

- Poorly adsorbed po antibiotic
 - Absent side effects
- Low levels of resistance among enteric pathogens
- Prophylaxis against travelers' diarrhea for short-term travelers
 - ETEC predominant regions
 - $\geq 70\%$ protection conferred
- Limited studies to date
 - Geographically limited
 - Predominance of ETEC/EAEC
 - Short duration travel
- Impact of widespread usage for prophylaxis unknown



Table 2. Summary of recommendations for managing infectious diarrhea.

Recommendation	Ranking ^a
Initiate rehydration (oral whenever possible)	A-I
Perform a thorough clinical and epidemiological evaluation for any significant diarrheal illness (profuse dehydrating, bloody or febrile diarrhea, or illness in infants, elderly, or immunocompromised patients). That is, ascertain how the illness began; stool characteristics (frequency and quantity); symptoms or signs of hypovolemia; travel history; whether the patient attends a day care center; whether the patient has ingested raw or undercooked meat, raw seafood, or raw milk; whether the patient's contacts are ill; the patient's sexual contacts, medications, and other medical conditions, if any.	A-II
Perform selective fecal studies (as shown in figure 1)	B-II
Institute selective therapy for	
Traveler's diarrhea	A-I
Shigellosis	A-I
<i>Campylobacter</i> infection	B-II
Avoid administering antimotility agents with bloody diarrhea or proven infection with Shiga toxin-producing <i>Escherichia coli</i>	E-I
Selectively administer available vaccines ^b and, for travelers to (or residents of) areas where typhoid is endemic, administer typhoid vaccine (parenteral Vi or oral Ty21A)	B-II

^a Letters indicate the strength of the recommendation and Roman numerals indicate the quality of evidence supporting it, respectively (see Table 1).

^b Oral live (103 HgR) and killed (WCBS) cholera vaccines are available outside the United States for travelers to areas where cholera is endemic, although diarrhea is uncommon in careful travelers (B-II).



I. Diseases typified by vomiting after a short incubation period with little or no fever

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
A. <i>Staphylococcus aureus</i>	30 min - 8 hours; usually 2-4 hours	Vomiting, diarrhea	preformed enterotoxin	sliced/chopped ham and meats, custards, cream fillings	<u>Food:</u> enterotoxin assay (FDA), culture for quantitation and phage typing of staph, gram stain <u>Handlers:</u> culture nares, skin, skin lesions, and phage type Staph. <u>Cases:</u> culture stool and vomitus, phage type Staph.
B. <i>Bacillus cereus</i>	1-6 hours	Vomiting; some patients with diarrhea; fever uncommon	? preformed enterotoxin	cooked rice	<u>Food:</u> culture for quantitation <u>Cases:</u> stool culture
C. Heavy metals • Antimony • Cadmium • Copper • Iron • Tin • Zinc	5min-8 hours; usually <1 hour	Vomiting, often metallic taste		foods and beverages prepared / stored / cooked in containers coated / lined / contaminated with offending metal	Toxicologic analysis of food container, vomitus, stomach contents, urine, blood, feces



II. Diseases typified by diarrhea after a moderate to long incubation period, often with fever

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
A. <i>Clostridium perfringens</i>	6-24 hours	Diarrhea, abdominal cramps; vomiting and fever uncommon	enterotoxin formed <i>in vivo</i>	meat, poultry	<u>Food:</u> enterotoxin assay done as research procedure by FDA, culture for quantitation and serotyping <u>Cases:</u> culture stool for quantitation and serotyping of <i>C. perfringens</i> ; test for enterotoxin in stool. <u>Controls:</u> culture stool for quantitation and serotyping of <i>C. perfringens</i>
B. <i>Bacillus cereus</i>	6-24 hours	Diarrhea, abdominal cramps, and vomiting in some patients; fever uncommon	?enterotoxin	custards, cereals, puddings, sauces, meat loaf	<u>Food:</u> culture <u>Cases:</u> stool culture
C. <i>Vibrio parahaemolyticus</i>	4-30 hours	Diarrhea	tissue invasion, ?enterotoxin	seafood	<u>Food:</u> culture on TCBS, serotype, Kanagawa test <u>Cases:</u> stool cultures on TCBS, serotype, Kanagawa test
D. Salmonella (non-typhoid)	6 hours-10 days; usually 6-48 hours	Diarrhea, often with fever and abdominal cramps	tissue invasion	poultry, eggs, meat, raw milk (cross-contamination important)	<u>Food:</u> culture with serotyping <u>Cases:</u> stool culture with serotyping <u>Handlers:</u> stool culture with serotyping as secondary consideration



II. Diseases typified by diarrhea after a moderate to long incubation period, often with fever - continued

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
E. Norovirus (formerly, "Norwalk-like viruses")	15-77 hours; usually 24-48 hours	Vomiting, cramps, diarrhea, headache, fever	unknown	raw or undercooked shellfish; water; many others	Detection of viral RNA in stool or vomitus by reverse transcriptase-polymerase chain reaction (RT-PCR)
F. Rotavirus	16-48 hours	Vomiting, chills, and diarrhea, especially in infants and children	unknown	foodborne transmission not well documents	<u>Cases:</u> stool examination by EM or ELISA; serology <u>Food:</u> culture and serotype
G. <i>Escherichia coli</i> enterotoxigenic (ETEC)	6-48 hours	Diarrhea, abdominal cramps, nausea; vomiting and fever less common	enterotoxin	uncooked vegetables, salads, water, cheese	<u>Cases:</u> stool culture; serotype and demonstration of enterotoxin production; invasiveness assay
H. <i>Escherichia coli</i> enteroinvasive (EIEC)	Variable	diarrhea (might be bloody), fever, abdominal cramps	tissue invasion	same as ETEC above	same as ETEC above
I. <i>Listeria monocytogenes</i> - Invasive Disease	2-6 weeks	Meningitis, neonatal sepsis, fever	?	Milk, soft cheeses	<u>Food:</u> culture, serotype <u>Cases:</u> stool / blood cultures, serotype, serology
<i>Listeria monocytogenes</i> , - Diarrheal Disease	Unknown (3-70 days?)	Diarrhea, fever, abdominal cramps	?	Milk, soft cheeses	same as above
J. <i>Vibrio cholerae</i> non-01 and non-0139	1-5 days	Watery diarrhea	enterotoxin formed <i>in vivo</i> , ?tissue invasion	shellfish	<u>Food:</u> culture on TCBS, serotype <u>Cases:</u> stool cultures on TCBS, serotype



II. Diseases typified by diarrhea after a moderate to long incubation period, often with fever - continued

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
K. <i>Vibrio cholerae</i> O1 or 0139	1-5 days	Watery diarrhea, often accompanied by vomiting	enterotoxin formed <i>in vivo</i>	shellfish, water or foods contaminated by infected person or obtained from contaminated environmental source	<u>Food:</u> culture on TCBS, serotype <u>Cases:</u> stool culture on TCBS, serotype
L. <i>Shigella</i> spp.	12 hours - 6 days; usually 2-4 days	Diarrhea (often bloody), often accompanied by fever and abdominal cramps	tissue invasion	foods contaminated by infected foodhandler; usually not foodborne	<u>Food:</u> culture and serotype <u>Cases:</u> stool culture and serotype <u>Handlers:</u> stool culture and serotype
M. <i>Escherichia coli</i> enterohemorrhagic (<i>E. coli</i> O157:H7 and others)	1-10 days; usually 3-4 days	Diarrhea (often bloody), abdominal cramps (often severe), little or no fever	cytotoxin	beef, raw milk, water, apple cider, lettuce	<u>Cases:</u> stool culture on sorbitol-MacConkey; isolation of <i>E. coli</i> O157:H7 or other Shiga-like toxin-producing <i>E. coli</i> from clinical specimen
N. <i>Yersinia enterocolitica</i>	1-10 days; usually 4-6 days	Diarrhea, abdominal pain (often severe)	tissue invasion, ?enterotoxin	pork products, milk, food contaminated by infected human or animal	<u>Food:</u> culture on CIN agar, cold enrichment <u>Cases:</u> stool culture on CIN



II. Diseases typified by diarrhea after a moderate to long incubation period, often with fever - continued

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
O. <i>Cyclospora cayentanensis</i>	1-11 days; median: 7 days	Fatigue, protracted diarrhea, often relapsing	tissue invasion	raw produce; water	<u>Food/water:</u> consult DPD <u>Cases:</u> stool examination for organisms; PCR (developmental) and testing for oocyst sporulation at DPD
P. <i>Cryptosporidium parvum</i>	2-28 days; median: 7 days	Diarrhea, nausea, vomiting; fever	tissue invasion	uncooked foods; water	<u>Food/water:</u> consult DPD <u>Cases:</u> stool examination for organisms or antigen; PCR and serologic test developmental (consult DPD)
Q. <i>Giardia lamblia</i>	3-25 days; median: 7 days	Diarrhea, gas, cramps, nausea, fatigue	?	uncooked foods; water	<u>Food/water:</u> consult DPD <u>Cases:</u> detection of antigen or organism in stool, duodenal contents, or small-bowel biopsy specimen

III. Botulism

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
<i>Clostridium botulinum</i>	2 hours - 8 days; usually 12-48 hours	Illness of variable severity; common symptoms include diplopia, blurred vision, and bulbar weakness; paralysis, which is usually descending and bilateral, might progress rapidly	preformed toxin	improperly canned or similarly preserved foods	<u>Food:</u> toxin assay <u>Cases:</u> serum and stool for toxin assay; stool culture for <i>C. botulinum</i>



IV. Diseases most readily diagnosed from history of eating a particular type of food

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
A. Poisonous mushrooms	variable	Usually vomiting and diarrhea, other symptoms differ with toxin		wild mushrooms	<u>Food:</u> speciation by mycetologist
B. Other poisonous plants	variable	variable		wild plant	<u>Cases:</u> vomitus, blood, urine. <u>Food:</u> speciation by botanist; stool may sometimes be helpful in confirmation.
C. Scombroid toxin (histamine)	1 min-3 hours; usually <1 hour	Flushing, dizziness, burning of mouth and throat, headache, gastrointestinal symptoms, urticaria, and generalized pruritus	histamine	scombroid fish (tuna, mackerel, etc.); mahi-mahi, others	<u>Food:</u> histamine levels
D. Ciguatoxin	1-48 hours; usually 2-8 hours	Usually GI symptoms (diarrhea, nausea, vomiting) followed by neurologic symptoms (including paresthesia of lips, tongue, throat, or extremities) and reversal of hot and cold sensation	ciguatoxin	large ocean fish, e.g., grouper, barracuda	<u>Food:</u> stick test for ciguatoxin (not widely available)



IV. Diseases most readily diagnosed from history of eating a particular type of food - continued

<u>Agent</u>	<u>Incubation period</u>	<u>Clinical Syndrome</u>	<u>Pathophysiology</u>	<u>Characteristic Foods</u>	<u>Specimens</u>
E. Paralytic shellfish poisoning	< 1 hour	vomiting, diarrhea, paresthesias of face and extremities, sometimes more severe neurologic symptoms	saxitoxin	mussels, clams, scallops, oysters	<u>Food:</u> Detection of toxin in epidemiologically implicated food
F. Pufferfish poisoning (tetrodotoxin)	10 min - 3 hours	Nausea, vomiting, paresthesias, dizziness, may progress to paralysis and death in hours	tetrodotoxin	pufferfish, others	<u>Food:</u> Detection of toxin in epidemiologically implicated food

