

# Infectious & Toxin-Mediated Diarrhea

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# Scope of the Problem

- 47.8 million foodborne-related illnesses occur annually (one out of every six persons) in the United States.
- Each year 31 major pathogens acquired in the United States caused 20% of the episodes:
  - 9.4 million episodes of diarrheal illness,
  - 55,961 hospitalizations, and
  - 1,351 deaths.
- Each year other unspecified agents resulted in 80% of the episodes:
  - ~38.4 million episodes of domestically acquired foodborne illnesses.
  - 71,878 hospitalizations and
  - 1,686 deaths,

# Scope of the Problem

- Over 44 million US residents traveled abroad to non-Canadian and non-European destinations in 2014, resulting in:
  - 4 to 17 million cases of traveler's diarrhea (TD) based on 10–40% attack rates
- The cost of acute and chronic illness attributable to these infections is estimated to be upwards of US \$145 billion to the US economy.

# Helpful Questions to the Patient with Diarrhea

- **Food ingestion:**

- **Poultry:** salmonella, campylobacter, shigella.
- **Ground beef, unpasteurized juice:** Enterohemorrhagic E. coli.
- **Pork:** tapeworm.
- **Seafood/shellfish:** v. cholerae, v. vulnificus, v. parahemolyticus, salmonella, anisakis, tapeworm.
- **Cheese, milk:** listeria.
- **Eggs:** salmonella.
- **Mayonnaise & cream pies:** S. aureus & clostridium.
- **Fried rice:** B. cereus.
- **Fresh berries:** cyclospora.
- **Canned foods:** clostridium
- **Spring or contaminated water:** v. cholerae, Norwalk agent, giardia, cryptosporidium.

# Helpful Questions to the Patient with Diarrhea

## Exposure

- **Pet & livestock:** salmonella, giardia, campylobacter, cryptosporidium.
- **Day-care center:** shigella, campylobacter, cryptosporidium, giardia, c. difficile, virus.
- **Antibiotics, chemotherapy:** c. difficile, K. oxytoca (amoxicillin +/- clavunate), c. perfringes (plasmid cpe).
- **Swimming pool:** giardia, cryptosporidium.
- **Rectal intercourse:** N. gonorrhea, N. meningitides, Chlamydia, syphilis, CMV, HSV
- **Anilingus:** all enteric bacteria, virus, and parasites.

# Infectious Doses of Enteric Pathogens

- *Cryptosporidium parvum*  $1-10^3$
- *Entamoeba histolytica*  $10-10^2$
- *Giardia lamblia*  $10-10^2$
- *Shigella*  $10-10^2$
- *Campylobacter jejuni*  $10^2-10^6$
- *Salmonella*  $10^5$
- *Escherichia coli*  $10^8$
- *Vibrio cholerae*  $10^8$

# Types of Diarrhea

- Non-Inflammatory
- Mucosal Penetrating
  - Inflammatory

# Non-Inflammatory Diarrhea

Site, Mechanism, Features, & Pathogens

- **Site:**
  - Proximal Small Bowel
- **Mechanism:**
  - Enterotoxin/adherence/superficial invasion
- **Features:**
  - *Clinical: Watery diarrhea*
  - **Laboratory:**
    - No fecal WBC
    - Minimal or no Lactoferrin
- **Pathogens (Proximal Small Bowel)**
  - Salmonella (\*)
  - E. coli
  - C. perfringes
  - S. aureus
  - Aeromonas hydrophila
  - B. cereus
  - V. cholerae
  - Rotavirus
  - Norwalk-like agents
  - Cryptosporidium (\*)
  - Microsporidium (\*)
  - Giardia
  - Cyclospora
  - Isospora

(\*) Dominant involvement: Proximal small bowel



# Mucosal Penetrating Diarrhea

Site, Mechanism, Features, & Pathogens

- **Site:**
  - Distal small bowel
- **Mechanism:**
  - Mucosal penetration
- **Features:**
  - **Clinical:** Enteric fever
  - **Laboratory Features:**
    - Fecal mononuclear leukocytes
- **Pathogens**  
(Distal Small Bowel)
  - Salmonella typhi
  - Yersinia enterocolitica
  - Campylobacter fetus

# Inflammatory Diarrhea

## Site, Mechanism, Features, & Pathogens

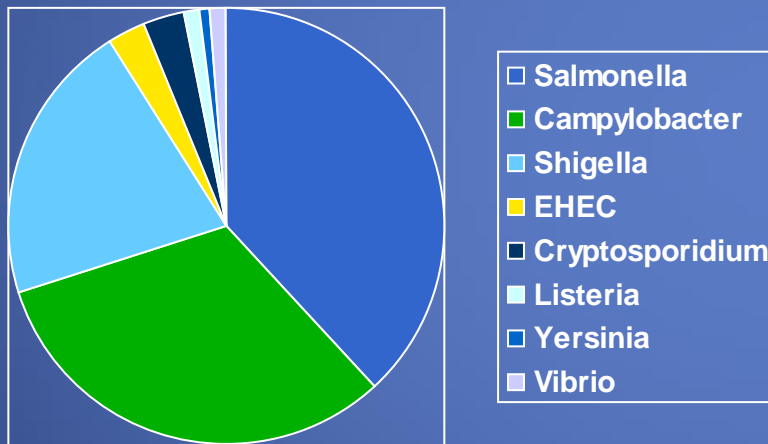
- **Site:**
  - Colon
- **Mechanism:**
  - Invasion and/or cytotoxin
- **Features:**
  - **Clinical:** dysentery
  - **Laboratory Features:**
    - (+) fecal WBC
    - High Lactoferrin
- **Pathogens (Colon)**
  - Campylobacter (\*)
  - Shigella
  - C. difficile (WBC(+) in 30%)
  - Yersinia
  - V. parahemolyticus
  - Enteroinvasive E. coli
  - Plesiomonas shigelloides
  - Klebsiella oxytoca
  - **CMV (\*)**
  - **Adenovirus**
  - **HSV**
  - **Entamoeba histolytica (WBC absent b/o destruction)**

(\*) Dominant involvement: Colon

# Common Infectious Etiologies

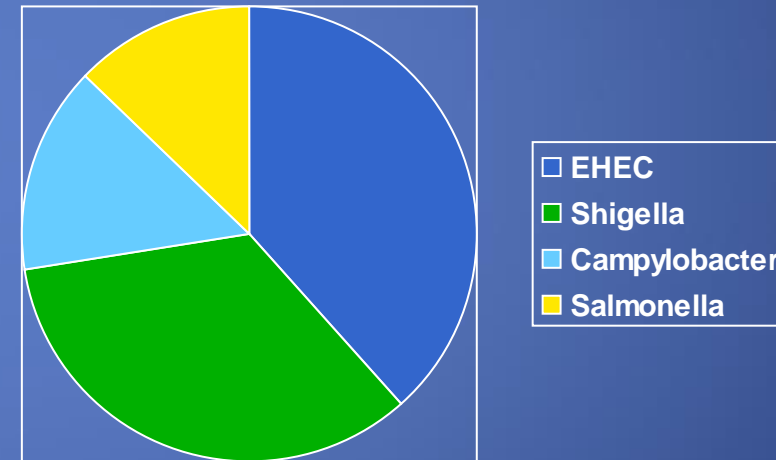
## WATERY DIARRHEA

6% of Stool studies (+)



## BLOODY DIARRHEA

20-30% Stool studies (+)



# Complications & Extraintestinal Manifestations of Infectious Diarrhea

- **V. cholerae, E. coli:** volume depletion, shock & death
- **B. cereus:** Fulminant liver failure
- **V. vulnificus, V. parahaemolyticus:** shock & death in: cirrhosis, Fe overload, or alcoholics.
- **C. difficile:** protein losing enteropathy, toxic megacolon.
- **Enterohemorrhagic E. coli (EHEC):** HUS & TTP
- **Salmonella:** sepsis, peritonitis, cholecystitis, pancreatitis, osteomyelitis, mycotic aneurism, intraabdominal abscess, Reiter S.
- **Campylobacter:** Guillian-Barre syndrome, Reiter S
- **Shigella:** seizures and encephalopathy, Reiter S.
- **Yersinia:** Thyroiditis, pericarditis, glomerulonephritis, myocarditis, HUS, Guillian-Barre, Reiter S.

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

## Stool Testing

- **Stool culture and culture-independent methods** if available should be used in:
  - individual patient **at high risk of spreading disease** to others, and
  - **known or suspected outbreaks.**
  - Level: (Strong recommendation, low level of evidence)
- **Stool diagnostic studies** may be used if available in:
  - cases of **dysentery**,
  - **moderate–severe disease**, and
  - **symptoms lasting > 7 days** to clarify the etiology.
  - Level: (Strong recommendation, very low level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

## Stool Testing

- **Sensitivity of Stool Test:**
  - Traditional methods of diagnosis (bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing) fail to reveal the etiology of the majority (80%) of cases of acute diarrheal infection.
  - **FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct** to traditional methods.
  - Level: (Strong recommendation, low level of evidence).
- **Antibiotic sensitivity testing is not recommended.**
  - (Strong recommendation, very low level of evidence)

# FDA Approved Molecular Tests For Enteric Pathogens

Manufacturer	Test system	Platform	Pathogens detected		Detection time (h)
			Type	No.	
Biofire Diagnostics	<b>GI Panel</b>	FilmArray	B, V, P	22	1–2
Luminex	<b>GPP</b>	xTAG	B, V, P	15	<5
Nanosphere	EP	Verigene	B	6	2
Hologic/Gen-Probe	ProGastro SCS	—	B	4	4
BD Diagnostics	EBP	BD MAX	B	4	3–4

can detect microbes at non-pathogenic levels

# FilmArray Gastrointestinal (GI) Panel

Reverse transcription PCR with detection of 22 pathogens in a freeze-dried format in 1 hour

- **Bacteria**

- Aeromonas
- Campylobacter
- Clostridium difficile (Toxin A/B)
- Plesiomonas shigelloides
- Salmonella
- Yersinia enterocolitica
- **Diarrheagenic E. coli/Shigella**
  - Enteroaggregative E. coli (EAEC)
  - Enteropathogenic E. coli (EPEC)
  - Enterotoxigenic E. coli (ETEC) lt/st
  - Shiga-like toxin-producing E. coli (STEC) stx1/stx2
  - E. coli O157
  - Shigella/Enteroinvasive E. coli (EIEC)

- **Vibrio**

- Vibrio cholerae

- **Virus**

- Adenovirus F 40/41
- Astrovirus
- Norovirus GI/GII
- Rotavirus A
- Sapovirus

- **Parasites**

- Cryptosporidium
- Cyclospora cayetanensis
- Entamoeba histolytica
- Giardia lamblia



# Molecular Diagnostic Testing

## xTAG GPP (Luminex)

can detect microbes at non-pathogenic levels

- **Bacteria & Toxins:**

- Campylobacter
- C. difficile toxin A/B
- E coli 0157
- Enterotoxigenic E coli L/T S/T (ETEC)
- Shiga-like toxin producing E coli (STEC) stx1/stx2
- Salmonella
- Shigella

- **Parasites:**

- Giardia lamblia
- Cryptosporidium

- **Virus:**

- Norovirus GI/GII (Norwalk virus)
- Rotavirus A

## ACG Guidelines for Acute Diarrheal Infections in Adults 2016

# Oral Hydration

- Most individuals with acute diarrhea or gastroenteritis can keep up with fluids and salt by consumption of water, juices, sports drinks, soups, and saltine crackers.
  - Level: (Strong recommendation, moderate level of evidence)
- **Balanced electrolyte rehydration (ORS) (Normalyte, Trioral) is preferred in:**
  - 1. Elderly with severe diarrhea or
  - 2. Traveler with cholera-like watery diarrhea.

## ACG Guidelines for Acute Diarrheal Infections in Adults 2016

# Symptomatic & Empiric Therapy

- **Probiotics or prebiotics** in adults are **not recommended**, except in cases of postantibiotic-associated illness.
  - Level: (Strong recommendation, moderate level of evidence)
- **Bismuth subsalicylates** to control rates of passage of stool in:
  - **travelers** during bouts of **mild-to-moderate illness**.
  - Level: (Strong recommendation, high level of evidence)
- If receiving **antibiotics for traveler's diarrhea**:
  - adjunctive **loperamide therapy should be administered** to decrease duration of diarrhea and increase chance for a cure.
  - Level: (Strong recommendation, moderate level of evidence)

## ACG Guidelines for Acute Diarrheal Infections in Adults 2016

# Empiric Antibiotic Therapy

- **Do not give empiric anti-microbial therapy** for routine acute diarrheal infection, except in:
  - cases of TD where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics.
  - Level: (Strong recommendation, high level of evidence)
- Use of **antibiotics for community-acquired diarrhea should be discouraged** because:
  - Most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and
  - Diarrhea is not shortened by the use of antibiotics.
  - Level: (Strong recommendation, very low-level evidence)

## Evaluation of Persistent Diarrhea

- In patients with persistent symptoms (between 14 and 30 days):
  - Recommended:
    - Stool culture and /or culture independent microbiologic studies (if not already done after 7 days of diarrhea)
  - Not recommended:
    - Serological and clinical lab testing.
    - Endoscopic evaluation for cases with negative stool work-up.
  - Level: (Strong recommendation, very low level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

## Prevention and Counseling

- **Community Acquired Diarrhea**

- Patient level counseling on prevention of acute enteric infection is not routinely recommended.
  - May be considered in the individual or close contacts of the individual who is at high risk for complications.
- **Level: (Conditional, very low level of evidence)**

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

## Prevention and Counseling

- **Travelers Diarrhea:**

- Individuals should undergo pre-travel counseling regarding: high-risk food/beverage avoidance to prevent traveler's diarrhea.
  - Level: (Conditional, very low level of evidence)
- **Frequent and effective hand washing and alcohol-based hand sanitizers** are of limited value but may be useful where low-dose pathogens are expected, as during:
  - cruise ship outbreak of norovirus infection,
  - institutional outbreak, or
  - endemic diarrhea prevention.
  - Level: (Conditional recommendation, low level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

## Prevention and Counseling

- **Drugs for Prevention of Travelers Diarrhea:**
  - **Bismuth subsalicylates** (moderate effectiveness): for travelers without contraindications to its use and who can adhere to the frequent dosing. (Pepto-Bismol 2 tab QID; 50% protection)
    - Level: (Strong recommendation, high level of evidence)
  - **Antibiotic chemoprophylaxis** (moderate to good effectiveness): in high-risk groups for short-term use. (Rifaximin 200 mg TID x 14 days; 60% protection)
    - Level: (Strong recommendation, high level of evidence)
  - **Not Recommended: Probiotics, prebiotics, and synbiotics.**
    - Level: (Conditional recommendation, low level of evidence)



# Antibiotic Therapy in Diarrhea

- **Risk of Empiric antibiotic therapy:**
  - Increases risk of HUS in EHEC (STEC, VTEC), and
  - Prolongs shedding of salmonella,
  - Do not give when you suspect:
    - C. difficile colitis (targeted therapy is OK), or
    - EHEC, or
    - Salmonella (except in special cases; see later)
- **Consider antibiotics for:**
  - Travelers diarrhea with > 4 BM/d, or with fever, blood, pus in stool,
  - Diarrhea in immunocompromised
  - Diarrhea longer than 7 d (after microbiology studies are sent),
  - Diarrhea > 3 days + fever > 101 °F (after microbiology studies are sent)
  - Dysentery (bloody diarrhea) with fever > 101 °F (after microbiology studies are sent)

# Approach to empiric therapy and diagnostic-directed management of the adult patient with acute diarrhea (suspect infectious etiology)

Antibiotic <sup>a</sup>	Dose	Treatment duration
Levofloxacin	500 mg by mouth	Single dose <sup>b</sup> or 3-day course
Ciprofloxacin	750 mg by mouth or 500 mg by mouth	Single dose <sup>b</sup> 3-day course
Ofloxacin	400 mg by mouth	Single dose <sup>b</sup> or 3-day course
<b>Azithromycin<sup>c,d</sup></b>	<b>1,000 mg by mouth or</b>	<b>Single dose<sup>b</sup></b>
	<b>500 mg by mouth</b>	<b>3-day course<sup>d</sup></b>
Rifaximin <sup>e</sup>	200 mg by mouth three times daily	3-days

<sup>a</sup> Antibiotic regimens may be combined with loperamide, 4 mg first dose, and then 2 mg dose after each loose stool, not to exceed 16 mg in a 24-h period.

<sup>b</sup> If symptoms are not resolved after 24 h, complete a 3-day course of antibiotics.

<sup>c</sup> Use empirically as first line in Southeast Asia and India to cover fluoroquinolone-resistant *Campylobacter* or in other geographical areas if *Campylobacter* or resistant ETEC are suspected.

<sup>d</sup> Preferred regimen for dysentery or febrile diarrhea.

<sup>e</sup> Do not use if clinical suspicion for *Campylobacter*, *Salmonella*, *Shigella*, or other causes of invasive diarrhea.

# Antisecretory Drugs

- **Bismuth SS** will reduce the stools passed by ~40%.
- **Crofelemer (FULYZAQ):**
  - cystic fibrosis transmembrane regulator chloride-channel blocker
  - Effective in some forms of diarrhea including TD and AIDS-associated diarrhea.
- **Zaldaride:**
  - calmodulin-inhibiting drug that has antisecretory properties related to intracellular concentrations of calcium.
- **Racecadotril (Hidrasec):**
  - Specific enkephalinase inhibitor that prevents degradation of the endogenous antisecretory peptide neurotransmitter enkephalins that inhibit cyclic nucleotide secretory pathways
  - No effect on gut motility
  - Used successfully in pediatric diarrhea and in adults.
- **Loperamide** works through two mechanisms:
  - Primary effect: production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption.
  - Secondary: inhibition of calmodulin leading to reduced mucosal secretion
  - 4 mg first dose, and then 2 mg dose after each loose stool, not to exceed 16 mg / 24-h period

# Viral Foodborne Infections

## Specific Causes of Foodborne Diarrhea - Viral

# Norovirus / Norwalk Virus

- 40-60% of acute viral gastroenteritis epidemics in older children & adults
- **Pathology:** Villous shortening, crypt hyperplasia, PMN & MN cells in lamina propria.
- **Spread:** person-to-person, contaminated food or water.
- **Incubation:** 12-48 hours
- **Duration:** 12-48 hours
- **Symptoms:** nausea, vomiting, diarrhea, abdominal pain, muscle aches, headache, tiredness and low-grade fever.
- **Diagnosis:** Serology, stool PCR or E/M for stool virus
- **Immunity:** lasts only weeks to 4 months
- **Treatment:**
  - ORS, supportive.

# Specific Causes of Foodborne Diarrhea - Viral

## Rotavirus

- 60% of diarrhea in children < 2 years-old
- **Pathology:** Kills mature villous-tip cells
- **Spread:** fecal-oral
- **Season:** late-fall, winter, early-spring
- **Duration:** 3-10 days
- **Symptoms:**
  - Diarrhea, nausea, vomiting, cough, rhinitis, otitis.
  - Subclinical in adults.
- **Diagnosis:** Stool antigen (Rotazyme for type A), PCR
- **Treatment:**
  - ORS, supportive.

Foodborne Bacterial Infections  
with diarrhea due to  
**Mucosal Invasion**

## Salmonella Gastroenteritis

- Causes 25-40% of food-borne infections in adults
- **Spread:** food-borne (food, flies, fingers, feces, fomites); meat, poultry, eggs, dairy products.
- **Incubation:** 8-48 hours
- **Duration:** usually 3-4 days (up to 3 weeks).
- **Symptoms:**
  - nausea, vomiting, abdominal cramps, low grade fever < 102 °F, watery diarrhea; sometimes severe dysentery.
- **Complications:**
  - osteomyelitis, septic or reactive arthritis, sepsis, peritonitis, cholecystitis, pancreatitis, mycotic aneurism, intraabdominal abscess, Reiter S.
- **Treatment:** ORS & support. Antibiotics prolong the disease.
  - **Treat with antibiotics only in:** immunosuppressed, age < 3 mo or > 50 y, hemolytic anemia, surgical prosthesis, valvular heart disease, severe atherosclerosis, cancer, uremia.
  - TMP-SMX DS p.o. BID x 7 days; 14 days if immunosuppressed.



## Specific Causes of Foodborne Diarrhea – Mucosal Invasion

# Campylobacter jejuni

- Most common cause of bacterial enteritis in many parts of the world.
- More frequent in young children, with secondary infections in household.
- **Spread:** fecal-oral, food-borne, water-borne.
- **Incubation:** 24-72 hours.
- **Duration:** usually 1 week
- **Symptoms:**
  - prodrome of malaise, coryza, headache, and fever;
  - then colicky periumbilical pain with profuse diarrhea, that improves and then worsens, with WBC's in stool.
- **Complications:**
  - Endocarditis, meningitis, Guillian-Barre, cholecystitis, pancreatitis, septic abortion, glomerulonephritis, reactive arthritis (HLA-B27), Reiter S.
- **Treatment:**
  - Erythromycin stearate 500 mg BID x 5 days

## Specific Causes of Foodborne Diarrhea – Mucosal Invasion

# Shigella

- **Spread:** person to person; most common in age 6 mo-10 y; adult infected from children. Well water contaminated with feces.
- **Incubation:** 36-72 hours.
- **Duration:** 1-30 days (1 week) without therapy
- **Symptoms:**
  - biphasic illness: fever in 30-40%;
  - cramps & voluminous watery diarrhea for 2-3 days, then dysentery, with small bloody stool and tenesmus.
  - Cough & meningismus in 40% of small children.
- **Complications:**
  - Reiter syndrome, HUS, protein-losing enteropathy, e. nodosum, keratoconjunctivitis, pneumonia, seizures, and encephalopathy.
- **Treatment:**
  - **Treat all patients.**
  - Ciprofloxacin 500 mg BID x 5 days, or TMP-SMX DS po BID x 5 days.

## Specific Causes of Foodborne Diarrhea – Mucosal Invasion

# Yersinia Enterocolitica

- **Spread:** food-borne (undercooked meats & oysters) & contact with infected pets.
- **Symptoms Children < 5y:**
  - fever, abdominal cramps, diarrhea for 1 or more weeks.
- **Symptoms Children > 5 y:**
  - mesenteric adenitis, or ileitis; sometimes ileal perforation.
- **Symptoms Adults:**
  - acute diarrhea,
  - followed 2-3 weeks later by arthritis, erythema nodosum, or erythema multiformis.
- **Post-infectious complications:**
  - Reiter S., thyroiditis, myocarditis, pericarditis, glomerulopathy, ankylosing spondylitis, IBD, e. nodosum, e. multiformis, & HUS.
- **Treatment:** ORS & support.
  - In septicemia: gentamicin 5 mg/kg iv; 50% mortality despite treatment.

## Specific Causes of Foodborne Diarrhea – Mucosal Invasion

# *Plesiomona shigelloides*

- **Source:** contaminated water or shellfish. Common in Japan.
- **Symptoms:**
  - Variable; from watery diarrhea, with abdominal pain, vomiting and fever, to dysentery and sepsis.
  - Usually self-limited, but 30% have diarrhea > 3 weeks.
  - Sepsis in cirrhosis and immunocompromised.
- **Complications:**
  - Meningitis, osteomyelitis. Endophthalmitis.
- **Diagnosis:** Stool culture or PCR.
- **Treatment:**
  - Treat only in severe (> 8 BM/d) or prolonged disease (> 7 days);
  - Ciprofloxacin 500 mg BID

# Foodborne Bacterial Infections with **Toxin Mediated Diarrhea**

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Cholera

- Endemic in the Gulf Coast (Louisiana & Texas)
- Vibrio colonizes small bowel and produces cytotoxic toxin, activating adenylate cyclase, causing secretory diarrhea.
- **Spread:** Water or food contaminated with stools.
- **Incubation:** 18-40 hours
- **Symptoms:**
  - vomiting and abdominal distension, followed by diarrhea of > 1 Liter/hour;
  - dehydration & shock.
- **Diagnosis:** Stool culture neutralized by antisera. Stool PCR.
- **Treatment:**
  - ORS; IV fluids only until ORS covers needs.
  - Tetracycline 500 mg QID x 5 days.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Staphylococcus aureus

- Second cause of food-borne diarrhea in USA (after salmonella).
- **Spread:**
  - Contaminated food with preformed cytotoxic, heat-stable, enterotoxin A.
  - Contamination most common in high salt & high sugar foods.
- **Incubation:** 1-6 hours
- **Duration:** 24-48 hours
- **Symptoms:**
  - Nausea, profuse vomiting, abdominal cramps followed by diarrhea.
  - No WBC in stool.
- **Treatment:**
  - Supportive.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Enterotoxigenic E. coli (ETEC)

- Major cause of Traveler's diarrhea, and of diarrhea in infants and toddlers in underdeveloped areas.
- Cytotoxic toxins (3: one heat-labile, and two heat-stable), activate adenylate cyclase & guanylate cyclase.
- **Spread:** fecal-oral.
- **Symptoms:**
  - Profuse watery diarrhea, with abdominal cramps and nausea.
  - May have low-grade fever.
- **Duration:** 3-5 days
- **Diagnosis:** stool culture and serotype; Stool PCR.
- **Treatment:** ORS.
  - *Mild:* Pepto-Bismol 2 tab QID, or Loperamide.
  - *Severe/dysentery:* Bactrim DS 1 BID x 3d; Ciprofloxacin 500 mg BID x 3 days.



## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Enterohemorrhagic E. coli (EHEC)

- Serotypes E. coli **O157:H7** (sorbitol negative), & **O26:H11**,
- Has shiga-like verocytotoxin I & II; (STEC or VTEC)
  - cytotoxic to endothelial cells and enterocyte.
- Sporadic and epidemic illness.
- **Spread:**
  - Ingestion of contaminated ground beef, unpasteurized milk or apple cider. Lives in the intestine of ruminants.
  - Person-to-person.
- **Symptoms:**
  - watery diarrhea with abdominal cramps and tenderness,
  - followed by bloody stool with low-, or no fever.
- **Complications:**
  - HUS or TTP in 7%.
- **Treatment:** support.
  - Antibiotics increase risk of HUS or TTP

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Clostridium perfringens

- **Source:**
  - Food poisoning due to meats cooked in bulk, with inadequate internal temperature to kill spores, and later inadequate cooling before reheating for consumption. [C. perfringens with **chromosomal** enterotoxin gene (cpe)]
  - C. perfringens can also cause antibiotic associated diarrhea without pseudomembranes (**plasmid** cpe gene).
  - Heat-labile cytotoxic enterotoxin.
- **Incubation:** 8-24 hours.
- **Duration:** 24 hours.
- **Symptoms:**
  - severe watery diarrhea, with intense abdominal cramps.
- **Diagnosis:** c. perfringens enterotoxin in stool, by Latex agglutination.
- **Treatment:**
  - a) Food poisoning: support,
  - b) Antibiotic associated colitis: Flagyl 500 mg po TID x 10 days

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Bacillus cereus - Diarrhea

- **Source:** foods cooked slowly at low temperature, permitting bacterial proliferation.
  - B. cereus colonizes the small bowel and produces heat-labile cytotoxic toxin.
- **Incubation:** 6-14 hours
- **Duration:** 20-36 hours
- **Symptoms:**
  - diarrhea and generalized abdominal cramps;
  - vomit is less frequent.
- **Diagnosis:** clinical features
- **Treatment:** ORS, support.

## Specific Causes of Foodborne Illness – Toxin Mediated

# Bacillus cereus - Vomiting

- **Source:** cooked food that stays unrefrigerated for long time, and has short “final cooking”, like “fried rice”.
  - Preformed heat-stable toxin
- **Incubation:** 2 hours
- **Duration:** few hours
- **Symptoms:**
  - Vomiting and abdominal cramps.
  - Diarrhea is infrequent.
- **Complications:**
  - Acute liver failure & lactic acidosis due to mitochondrial toxicity from cereulide.
- **Diagnosis:** clinical features
- **Treatment:** support.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Vibrio Parahaemolyticus

- **Source:** raw or poorly cooked fish or shellfish.
- **Pathogenesis:** variable; cytotoxic and/or cytotoxic toxin, and/or mucosal invasion
- **Incubation:** 12-24 hours
- **Duration:** hours to 10 days
- **Symptoms:**
  - Explosive watery diarrhea, abdominal cramps, nausea, vomiting, headache; fever in 25%.
  - Infrequent dysentery/ bloody stool
- **Diagnosis:** stool culture in TCBS agar medium.
- **Treatment:** support.
  - For prolonged illness: Tetracycline

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Vibrio vulnificus & V. alginolyticus

- **Source:** contaminated seawater or seafood; oysters; Gulf of Mexico, East & West Coast
- **Incubation:** 3-7 days.
- **Symptoms:**
  - Diarrhea, otitis media, cellulitis with myonecrosis or fasciitis.
  - Cirrhotic, immunocompromised host, Fe overload patient, diabetic, & alcoholic: Sepsis, with skin necrosis or bullae in 50-75%; 55% mortality.
- **Diagnosis:** culture from blood or necrotic tissue.
- **Treatment:**
  - Doxycycline 100 mg IV BID + ceftazidime 2 g IV q 8 h, or
  - Ciprofloxacin 400 mg IV BID

# Antibiotic Related Diarrhea

## Antibiotic Related Diarrhea (ARD)

# Enigmatic ARD

- **Cause:** antibiotic drug associated;
  - probably carbohydrate and/or bile salt malabsorption due to altered bowel flora.
- **Frequency:** causes 80 % of ARD
- **Symptoms:**
  - Watery diarrhea.
  - No pseudomembranes nor hemorrhage.
- **Treatment:**
  - Discontinue antibiotics,
  - Zn supplementation,
  - Probiotics (Culturelle – Lactobacillus GG); hydration,
  - Loperamide up to 16 mg/d



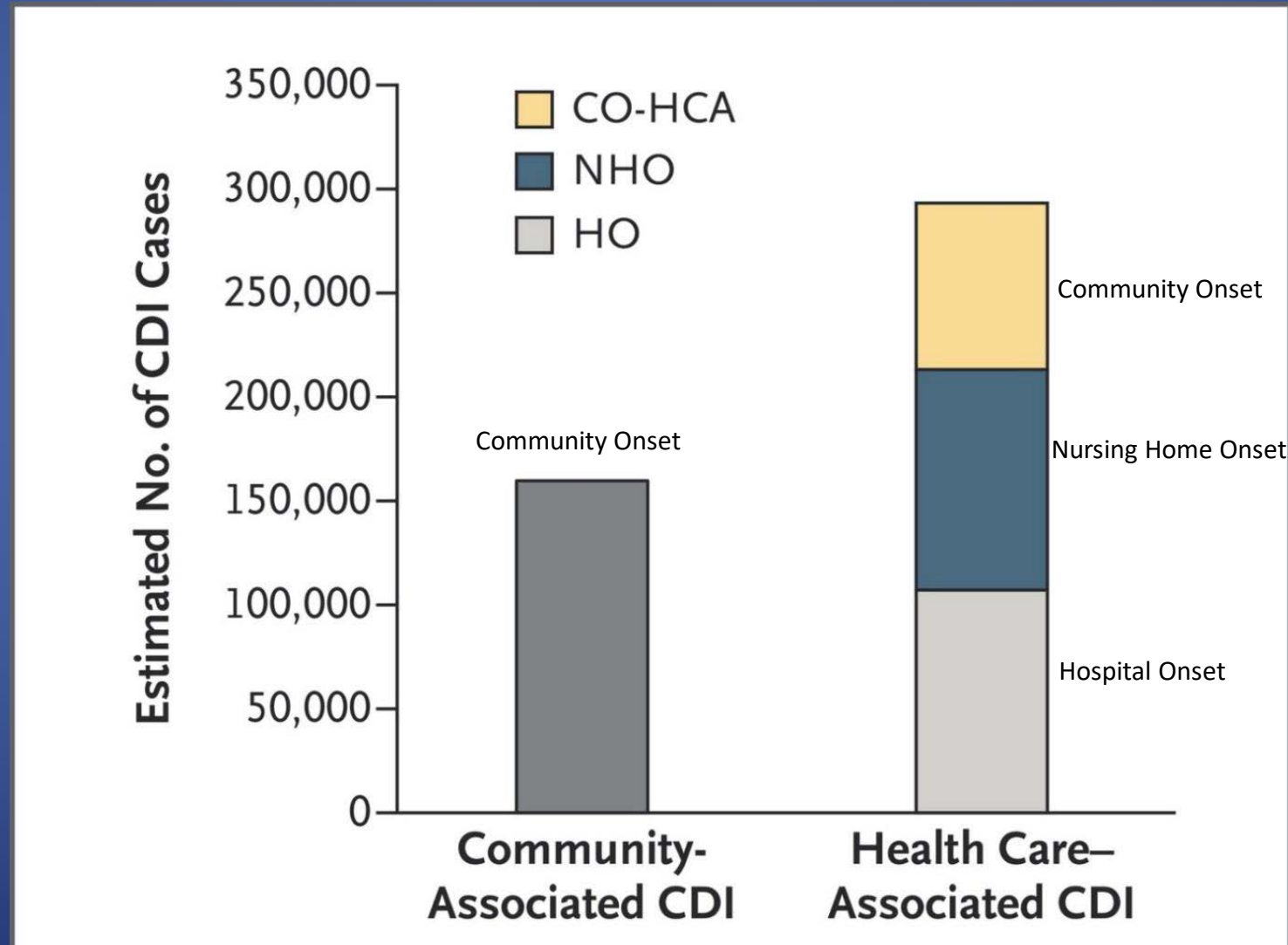
## Antibiotic Related Diarrhea (ARD)

# Clostridium difficile

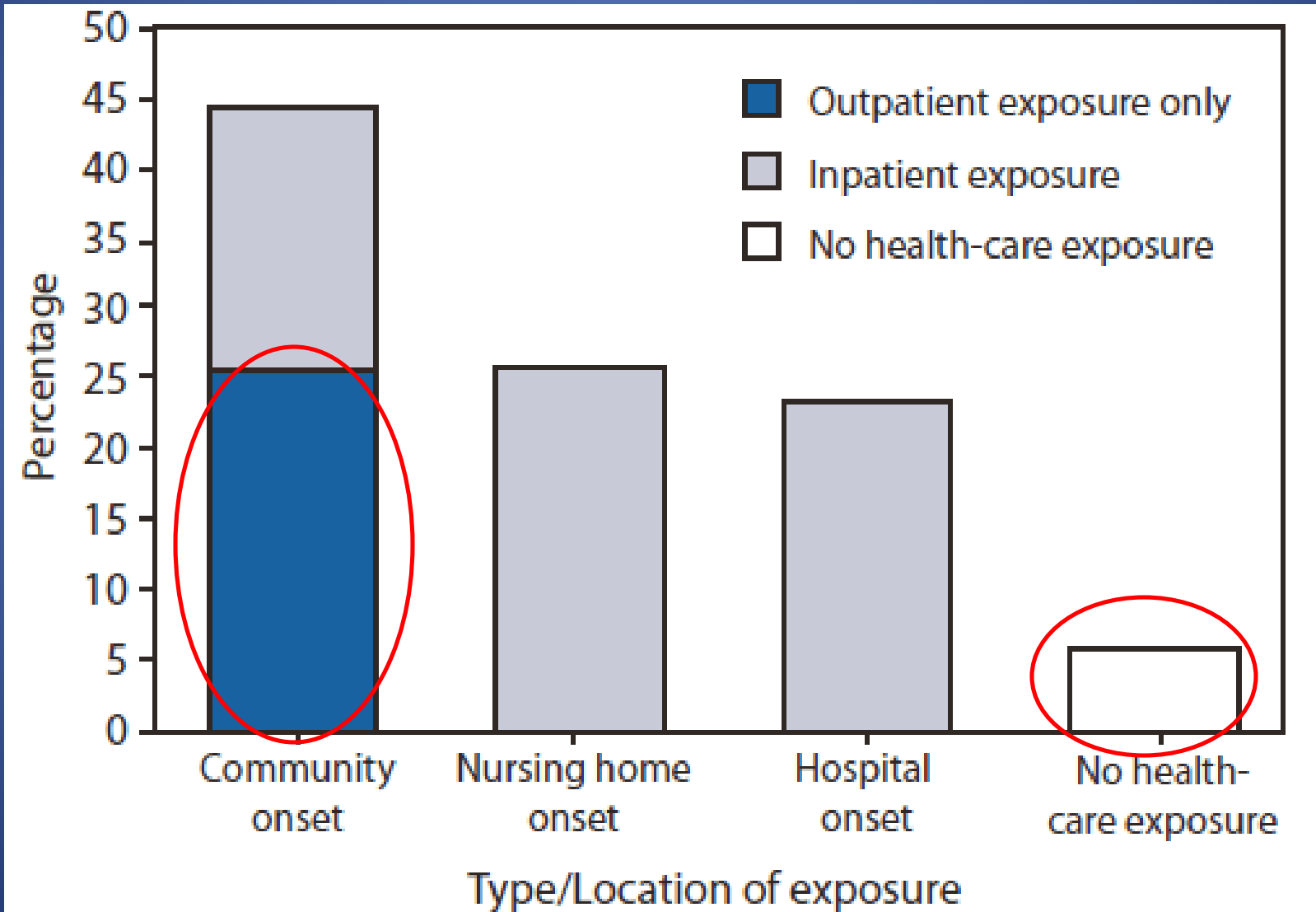
- Overgrowth of C. difficile during or up to 6 weeks after antibiotics, or MTX, cyclophosphamide, 5-FU.
  - Causes 20% of ARD.
  - 500,000 cases/y with 30,000 deaths/y;
  - 5 billion excess cost/y.
  - Cytotoxic toxin A&B
- **Symptoms:**
  - watery diarrhea (sometimes bloody), abdominal pain, fever, leukocytosis;
  - may have hypoalbuminemia (protein losing enteropathy).
- **Diagnosis:**
  - Toxin B(+) in stool (EIA, PCR, or cytotoxicity);
  - Flex. Sigm. with typical findings +/- Bx.;
  - WBC in stool may be (-); Stool lactoferrin (+) in 64-77%.

# Healthcare vs Community Associated CDI

## Site of Onset



# Infection by Site of Exposure



# Detection of C. difficile

## Toxin Assays

Test	Pro	Con
<b>Cytotoxicity</b> (Gold Standard; tests cytopathic effect)	Very sensitive (10 pg Toxin B) Very specific	Expensive Takes 2 days
<b>EIA</b> toxin A&B	Very specific (>95%) Cheap Takes < 24 h	Low sensitivity (60-90%) (100-1000 pg toxin B)
<b>PCR</b> (tests gene for toxin B)	Rapid (< 4h) Very sensitive Very specific (80-99%)	Expensive Does not differentiate colonization from infection

## Bacteria Detection

Test	Pro	Con
<b>GDH</b> (common antigen testing for glutamate dehydrogenase)	High sensitivity Rapid Cheap	Intermediate specificity Does not differentiate colonization from infection
<b>Stool culture</b> (anaerobic stool culture)	Extremely sensitive	Turn over: 3 days Does not differentiate colonization from infection

Use stool toxin test as part of a multistep algorithm rather than NAAT alone:

- Glutamate dehydrogenase [GDH] plus toxin (EIA);
- **GDH plus toxin (EIA), arbitrated by nucleic acid amplification test [NAAT];**
- NAAT plus toxin (EIA)

## Antibiotic Related Diarrhea (ARD)

# Clostridium difficile

- **Complications:**
  - protein losing enteropathy, ascites,
  - toxic megacolon requiring colectomy;
  - risk high in > 64 y/o, immunosuppression & hospital acquisition.
- **Risk Factors for complicated nosocomial PMC:**
  - WBC > 15 K,
  - Creat > 2 mg/dL (> 1.5 times baseline)
  - (Risk: 0=10%; 1=28%; 2=60%)
- Mortality 16% over expected, due to due to “hypervirulent strain” PMC with “binary toxin” & “deletion in tcdC”.
- Mortality due to “Fulminant” PMC: 53% (most within initial 48h)

# Updated Infectious Diseases Society of America guidelines for the treatment of CDI (2018)

Clinical classification	Clinical features	Recommended treatment
Mild or moderate disease	-Diarrhea without evidence of Severe nor Complicated CDI	-Vancomycin 125 mg four times a day x 10 days -FDX 200 mg given twice daily for 10 days -Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days
Severe disease or with IBD	-Creatinine > 1.5 mg/dL, or -Leukocytosis with a WBC count $\geq 15 \times 10^9/l$ , or -Abdominal tenderness	-Vancomycin administered orally at a dose of 125 mg four times daily for 10-14 days -FDX 200 mg given twice daily for 10 days
Complicated disease	Any of the following attributable to CDI: -Admission to ICU for CDI -Hypotension +/- vasopressors -Fever $\geq 38.5^\circ\text{C}$ -Ileus or significant abdominal distention -Mental status changes -WBC $\geq 35,000$ cells/mm <sup>3</sup> or $< 2,000$ cells/mm <sup>3</sup> -Serum lactate levels $> 2.2$ mmol/l -End organ failure (mechanical ventilation, renal failure, etc.)	-VAN, 500 mg 4 times per day by mouth or by nasogastric tube. -If ileus, consider adding rectal instillation of VAN (500 mg in 100 mL of 0.9% NaCl QID). -Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN (500 mg in 100 mL of 0.9% NaCl QID), particularly if ileus is present

# Surgical Management for Severe CDI

- If surgical management is necessary for severely ill patients:
  - Subtotal colectomy with preservation of the rectum (Strong recommendation, moderate quality of evidence).
  - Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes (Weak recommendation, low quality of evidence)

# Treatment of Recurrent CDI

Recurrence Number	Regimen
<b>First Recurrence</b>	<ul style="list-style-type: none"><li>-VAN 125 mg given 4 times daily for 10 days, if metronidazole was used for the initial episode.</li><li>-Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR</li><li>-FDX 200 mg given twice daily for 10 days, if VAN was used for the initial episode</li></ul>
<b>Second, or Subsequent Recurrence</b>	<ul style="list-style-type: none"><li>-VAN in a tapered and pulsed regimen, OR</li><li>-VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR</li><li>-FDX 200 mg given twice daily for 10 days, OR</li><li>-Fecal microbiota transplantation</li></ul>



# Fecal Flora Reconstitution (FFR)

Rohlke, F., Surawicz, C. M. & Stollman, N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J. Clin. Gastroenterol.* **44**, 567–570 (2010)

- **Preparation of recipient:**
  - Informed consent
  - The patients' prior treatment regimens (generally vancomycin) is stopped 1 to 3 days before the FFR procedure.
  - Patient is prepped for the FFR with a standard 4.0 liter polyethelyne glycol purge taken the evening before their procedure

# Commercial Fecal Microbiota

- **Vendor:** OpenBiome
- **Cost:** \$ 250/each
- **Recommend purchase:** 5 doses to decrease shipping cost
- **Shipping:** 5 days
- **Storage:** stored in a -20° C (-4° F) freezer, and should only be thawed immediately before treatment
- <http://www.openbiome.org/work-with-us/>

## Antibiotic Related Diarrhea (ARD)

# Clostridium perfringens Type A

- Proliferation of C. perfringens type A with **plasmid cpe gene**, after antibiotics
- Causes 5-15% of cases of pseudomembranous colitis.
- **Symptoms:**
  - Watery diarrhea after antibiotics, abdominal pain.
  - May give fever & leukocytosis.
- **Dx:** culture of c. perfringens in stool (plasmid cpe (+)); have to order specifically.
- **Treatment:**
  - discontinue antibiotics.

## Antibiotic Related Diarrhea (ARD)

# Klebsiella Oxytoca

- Proliferation of K. oxytoca in the colon (downstream from cecum) after antibiotics (usually penicillin derivate +/- clavulanate); toxin mediated.
- **Symptoms:**
  - sudden onset of hemorrhagic diarrhea 3 to 7 days after antibiotics;
  - abdominal cramps, leukocytosis and high CRP.
- **Diagnosis:**
  - Culture of K. oxytoca (have to order specifically)
  - Suggested in colonoscopy by: segmental hemorrhagic colitis (edema + petechiae +/- erosions or linear ulcers; no pseudomembranes), more severe in right side of colon, with rectal sparing.
- **Treatment:**
  - discontinue antibiotics and NSAIDs;
  - resolution in 4 days.

## Antibiotic Related Diarrhea (ARD)

### Others

- *Staphylococcus aureus*:
  - *(Need to give specific order to culture for S. aureus).*
  - *treat with Vancomycin 500 mg po QID x 10 days.*
- *Salmonella species*:
  - treat with cipro 500 mg po QID x 5-7 days

# Diarrhea due to Protozoa

# Giardia lamblia

- **Prevalence:**
  - healthy adults < 2%; homosexuals 4-18%.
- **Symptoms:**
  - Intermittent bloating and abdominal cramps, with watery and low grade steatorrhea; “sulfuric belching”.
  - Rare fever.
- **Diagnosis:**
  - Giardia Ag in stool; stool PCR
  - Duodenal aspirate, string-test, or Bx.
- **Treatment:**
  - Metronidazole 250 mg po TID x 5-7 days; Quinacrine 100 mg TID x 5 days; Nitazoxanide (Alinia) 500 mg TID x 3 days.
  - Patients with IgA or IgM deficiency need 6-8 weeks of therapy.

# Cryptosporidium parvum

- **Transmission:**

- usually person-to-person; domestic animal reservoir.
- causes 4% of acute diarrhea in small children;
- frequent in AIDS.

- **Symptoms:**

- a) **Immunocompetent host:** explosive, profuse watery diarrhea, with abdominal cramps; lasts 5-11 days.
- b) **Immunocompromised host:** extremely severe diarrhea (up to 17 L/day), which may persist for months. Fever in 30%.

- **Diagnosis:**

- AFB stain or fluorescent Ab in stool; Stool PCR
- Small bowel Bx.

- **Treatment:**

- a) Immunocompetent: Nitazoxanide (Alinia) 500 mg TID x 3 days
- b) Immunosuppressed: Paramomycin 500 mg with food, TID x 2-4 weeks + HAART



# Amebiasis

## Entamoeba histolytica

- **Prevalence:**
  - 1-5% of US population;
  - 20-30% in male homosexuals.
  - Only Zymodemes II & XI are invasive.
- **Symptoms:**
  - Usually asymptomatic.
  - Bloody diarrhea, fever, abdominal cramps, malaise, and tenesmus.
  - Cecal involvement more common than rectal disease.
  - Infrequent toxic megacolon or perforation.
- **Diagnosis:**
  - Stool Ag. - O&P x 4-6 samples. - Stool PCR.
  - Colonoscopy or Flex. Sigm with Bx (non-specific colitis).
  - Serology (+) in 88% of colitis (99% in liver abscess).
  - Stool WBC usually (-) due to destruction.
- **Treatment:**
  - Metronidazole 750 mg TID x 5-10 d, or Tinidazole 2 gm/d x 3 d, **PLUS**
  - Diloxanide 500 mg TID x 10 d, or Iodoquinol 650 mg TID x 20 d or Paramomycin 25-35 mg/kg per day, divided TID, x 7 days

# Balantidium coli

- **Source:**
  - ingestion of contaminated short stalk vegetables
- **Symptoms:**
  - frequently asymptomatic;
  - mild to moderate, acute or chronic recurrent diarrhea.
- **Treatment:**
  - Tetracycline 500 mg QID x 10 days

# Isospora belli

- **Transmission:**
  - fecal-oral
  - more common in children and male homosexuals.
- **Symptoms:**
  - fever, headache, abdominal cramps, diarrhea with mild malabsorption.
  - In normal host lasts a few weeks;
  - lasts months to years in immunocompromised host.
- **Diagnosis:**
  - duodenal aspirate & Bx.
  - Stool incubated at room temperature x 2 days; then Zn sulfate flotation & AFB stain.
- **Treatment:**
  - Bactrim

# Cyclospora cayetanensis

- **Source:**
  - contaminated fresh berries or water
- **Symptoms:**
  - Abrupt onset of watery diarrhea; fever in 30%.
  - Diarrhea improves in 3-4 days, and then relapses.
  - Anorexia, fatigue, nausea, malabsorption with 5-10% weight loss.
- **Duration:** 2-12 weeks, with abrupt end.
- **Pathology:** Acute & chronic inflammation in distal duodenum, with villous atrophy, and/or crypt hyperplasia.
- **Diagnosis:**
  - spherical 9-10 micron with red stain in AFB. - Stool PCR.
  - Duodenal aspirate (+) in 25%
- **Treatment:**
  - Bactrim DS BID x 7-10 days.

# Microsporidiosis

Enterocytozoan bienusi & Encephalitozoon intestinalis

- **Symptoms:**

- self limited diarrhea in immunocompetent.
- In immunocompromised gives chronic diarrhea for months.

- **Treatment:**

- Enterocytozoan bienusi:
  - fumagillin 60 mg/d x 14 days.
- Encephalitozoon intestinalis:
  - albendazole 400 mg BID x 3-4 weeks.

# Foodborne Diarrhea due to Fish & Shellfish associated Toxins

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Ciguatera

- **Cause:** heat-stable **Ciguatoxin** accumulated in large-fish muscles after eating smaller fish.
- **Geography:** Common in fish from Hawaii & Florida
- **Associated fish:**
  - Barracuda, red-snapper, amberjack, grouper, and goatfish.
- **Onset:** minutes to 30 hours
- **Duration:** 1-9 days; sensory disturbance for months.
- **Symptoms:**
  - nausea, vomiting, cramps, diarrhea, malaise, myalgia, arthralgia, blurred vision, pain in teeth, reversal of hot-cold sensation, sharp pain in extremities, bradycardia; respiratory paralysis in severe cases.
- **Treatment:**
  - Mannitol 20% solution; 1 g/kg IV over 45 min.
  - Gastric lavage and cathartics.
  - Atropine for bradycardia. May need respiratory support.
  - Amitryptiline, gabapentin for chronic neuropathy.
  - Amitryptiline or Fluoxetine for depression and fatigue.
  - Symptoms may recur after eating fish, nuts, caffeine or alcohol.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Scombroid

- **Cause:** histamine & saurine in flesh of fish by action of marine bacteria
  - Fish tastes sharp and peppery.
- **Geography:** Fish from Hawaii & California.
- **Associated fish:** tuna, mackerel, albacore, bonito, skip jack, mahi-mahi.
- **Onset:** minutes to 2 hours
- **Duration:** 4-10 hours.
- **Symptoms:**
  - flushing, headache, dizziness, burning in mouth, abdominal cramps, nausea, vomiting, diarrhea & bronchospasm.
- **Treatment:**
  - anti-histamines + H-2 blockers, bronchodilators & epinephrine for bronchospasm;
  - cathartics & gastric lavage.



## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Paralytic Shellfish Poisoning

- **Cause:** heat-stable **saxitoxins**, from dinoflagellates, concentrated in
  - bivalved mollusks,
    - worse in “red tide”.
    - outbreaks in summer.
- **Geography:** New England, West Coast, Alaska.
- **Onset:** 30 minutes - 3 hours; may be fatal in hours.
- **Duration:** hours to few days.
- **Symptoms:**
  - nausea, vomiting, diarrhea,
  - paresthesias in lips, mouth, face and extremities;
  - dysphonia, dysphagia, weakness, paralysis and respiratory insufficiency.
- **Treatment:**
  - respiratory support;
  - gastric lavage and cathartics.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Neurotoxic Shellfish Poisoning

- **Cause:** heat-stable **brevotoxin**, from dinoflagellates, concentrated in
  - Mollusks.
    - Associated to "red tide".
- **Geography:** Gulf Coast, North Carolina, and Florida
- **Onset:** few hours
- **Duration:** hours to days.
- **Symptoms:**
  - Nausea, vomiting, diarrhea,
  - Paresthesias, reversal of hot-cold sensation, ataxia.
  - Respiratory symptoms after aerolization.
- **Treatment:**
  - Symptomatic; IV fluids, cathartics, bronchodilators.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Diarrheic Shellfish Poisoning

- **Cause:** okadaic acid or dinophysistoxin-1 in
  - mussels, scallops, or clams.
- **Geography:** Described in Japan & Europe;
  - the organism has been found in U.S. coast.
- **Onset:** few hours
- **Duration:** hours to days.
- **Symptoms:**
  - nausea, vomiting, abdominal pain & diarrhea.
- **Treatment:**
  - symptomatic

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Amnestic Shellfish Poisoning

- **Cause:** domoic acid concentrated in
  - shellfish (Razor clams, Dungeness crabs), and
  - anchovies.
- **Geography:**
  - described in Canada;
  - toxin-producing blooms found in Maine & Texas
- **Onset:** few hours
- **Duration:** hours to days.
- **Symptoms:**
  - nausea, vomiting, abdominal cramps, headache, diarrhea, and loss of short-term memory.
  - Anterograde memory deficits may persist for months; neuronal necrosis in hippocampus and amygdala.
- **Treatment:**
  - Symptomatic; cathartics; benzodiazepines for seizures.