

# Evaluation of Acute Diarrhea

Luis S. Marsano, MD

Professor of Medicine

University of Louisville & Louisville VAMC

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# Definition

- **Normal stooling frequency:** 3 per day, to 3 per week. Increased frequency may be diarrhea, or pseudodiarrhea.
- **Abnormal increase of stool liquidity, in excess of:**
  - 200 gm/day for US children and adults, or
  - 10 gm/kg body-weight in infants, or
  - > 85% water content in either

# Classification

## Duration

- **Acute:** less than 3 weeks
- **Chronic:** more than 3 weeks
- **Recurrent:** repetitive short episodes (less than 3 weeks each) that occur for several months

# Normal Volumes and Compositions

Source	Contribution mL	TOTAL IN & OUT/day mL	Na mM/L	K mM/L	Ca, Mg, NH <sub>4</sub> mM/L	Cl mM/L	HCO <sub>3</sub> mM/L	Other Anions
PO	2,000	2,000 -0	variable	variable	variable	variable	variable	variable
Saliva	1,500	3,500 -0						
Gastric	2,500	6,000 -0						
Bile	500	6,500 -0						
Pancreas	1,500	8,000 -0						
Jejunum	1,000	9,000 -5,500	130	6	variable	90	30	0
Ileum	0	3,500 -2,000	140	8	10	60	70	0
Colon	0	1,500 -1,300						
Stool		200	40	90	20	15	30	80-180

## Fluid Entering (per day)

Oral intake 2 L

Salivary 1.5 L

Gastric 2.5 L

Biliary 0.5 L

Pancreatic 1L

Intestinal 1L

## Fluid Reabsorbed

Small intestine  
7.0 L (max 12 L)

Large intestine  
1.4 L (max 5 L)

100 ml



# Fluid Absorption

- Absorption of water is passive; depends on the absorption of solutes.
- Neurotransmitters & enteric hormones can modify net water balance.
- Maximal absorptive capacity:
  - **Small bowel: 12 liters**
  - **Colon: 4-5 liters.**
- Theoretical Maximal Continuous “Oral Rehydration Solution” rate:
  - **375-400 mL/hour (9-10 L/d)**

# Pathophysiologic Classification

## Osmotic Diarrhea

- The human bowel can not keep osmotic gradients; Stool osmolarity is equal to plasma osmolarity (280-310 mOsm)
- If malabsorbed nutrients or non-absorbable solutes are ingested, fluid will enter the intestine to reach iso-osmolarity.
- Normally, most of the stool osmolarity comes from its electrolytes (Na, K, corresponding organic anions)
- **Osmolar gap =  $290 - 2[\text{Na} + \text{K}]$**  ; Normal < 125 mOsm (usually < 50 mOsm)

# Pathophysiologic Classification

## Osmotic Diarrhea

- **Features of Osmotic Diarrhea:**
  - Osmolar gap  $> 125$  mOsm
  - Stool Na  $< 60$  mM/L
  - Fasting (food & drugs) stool output  $< 200$  g
  - Carbohydrate related: pH  $< 5.3$  ; reducing substances (+) [does not detect lactulose, sorbitol, mannitol, nor sucrose]
- **Examples:**
  - **a) Osmolar load:** PEG, Mg salts, Na Phosphate, sorbitol, mannitol, lactulose, xylitol
  - **b) Malabsorption:** Mucosal damage (sprue, infections), disaccharidase deficiency, Olestra, bacterial overgrowth, pancreatic insufficiency, short bowel, IBD, lymphangiectasia, etc.



# Pathophysiologic Classification

## Osmotic Diarrhea

- In  $\text{SO}_4$  or  $\text{PO}_4$  diarrhea: they are  $> 10\text{mmol/L}$
- In diarrhea due to Mg salts:
  - Mg concentration  $> 45\text{ mM/L}$  (usually  $> 100\text{mM/L}$ )
  - 24 hours stool Mg  $> 15\text{ mmol}$ ; (7.3 g stool/ mmol Mg)
  - Stool output after 24 h fasting:
    - a) Innocent  $< 200\text{ g/d}$ ;
    - b) Surreptitious:  $> 200\text{ g/d}$  & gap  $> 100\text{ mOsm}$
- In diarrhea due to Na salts:
  - Stool Na  $> 90\text{ mM/L}$
  - Osmotic gap  $< 50\text{ mOsm}$
  - Stool  $\text{Cl}^- < 20\text{ mM/L}$

# Unusual Measured Stool Osmolalities

- If stool is stored for hours, even in deep freeze, Osm may exceed 350 due to degradation of carbohydrates: process immediately.
- **Stool Osm > 375 + Na > 150 mM/L:**
  - contamination with concentrated urine.
- **Stool Osm < 250:**
  - contaminated with diluted urine, or water was added.
- **Stool [Na] + [K] > 165 mM/L:**
  - concentrated urine in stool.

# Pathophysiologic Classification

## **Secretory Diarrhea**

- Due to:
  - Inhibition of ion (Na, K, Cl, HCO<sub>3</sub>) absorption,
  - Stimulation of ion secretion, or
  - Both.
- May affect small bowel, colon, or both;
  - in small bowel disease, the amount of fluid presented to the colon exceeds its maximal absorption capacity (5 L)

# Pathophysiologic Classification

## **Secretory Diarrhea**

- **Features of secretory diarrhea:**
  - Osmolar gap  $< 50$  mOsm
  - Na concentration  $> 90$  mM/L
  - 24 h fasting stool volume  $> 200$  g
  - pH  $> 5.6$ ; reducing substances (-)

# Pathophysiologic Classification

## Secretory Diarrhea

- **Classification:**
- **1) Exogenous:**
  - **a) Drugs:** Phenolphthalein, anthraquinones, bisacodyl, senna, aloe, ricinoleic acid, DOSS, furosemide, thiazides, theophylline, thyroid, misoprostol, 5-ASA, gold, colchicine, etc. (see PDR)
  - **b) Foods:** tea, coffee, cola, ethanol, MSG, seafood toxins (ciguatera, scombroid, paralytic or neurotoxic shellfish poisoning).
  - **c) Bacterial toxins:** *S. aureus*, *C. perfringens*, *C. botulinum*, *B. cereus*.
  - **d) Toxins:** Arsenic, Amanita phalloides, organophosphates,

# Pathophysiologic Classification

## Secretory Diarrhea

- **2) Endogenous:**

- **a) Bacterial:** *V. cholerae*, Toxigenic *E. coli*, *C. jejuni*, *Y. enterocolitica*, *K. pneumoniae*, *C. difficile*.
- **b) Endogenous laxatives:** bile acids, long-chain fatty acids.
- **c) Hormone-producing tumors:** VIPoma, ganglioneuromas, medullary carcinoma of thyroid, gastrinoma, carcinoid, glucagonoma, mastocytosis, villous adenoma.
- **d) Congenital:** chloridorrhea, Na diarrhea, enterocyte heparan sulphate defic., microvillous inclusion disease.

# Pathophysiologic Classification

## Inflammatory Diarrhea

- Enterocyte damage or death, with minimal or severe inflammation; can cause malabsorption or secretion.
  - **Classification:**
- **1) Minimal to mild inflammation:**
  - **a) Infections:** enteroadherent or enteropathogenic E. coli, rotavirus, Norwalk, HIV, giardia, cryptosporidium, isospora, cyclospora, ascariis, trichinella, bacterial overgrowth, tropical sprue.
  - **b) Cytostatics:** chemotherapy, radiation.
  - **c) Hypersensitivity:** food allergy, nematodes.
  - **d) Autoimmune/ idiopathic:** microscopic colitis, collagenous colitis, Canada-Cronkhite, graft-vs-host.

# Pathophysiologic Classification

## Inflammatory Diarrhea

- **2) Moderate to severe inflammation with or without ulceration:**
  - **a) Destruction of enterocyte:** shigella, enteroinvasive E. coli, E. histolytica, hookworm.
  - **b) Penetration of mucosa:** salmonella, C. jejuni, Y. enterocolitica, M. avium complex, Whipple dz.
  - **c) Hypersensitivity:** Celiac sprue, milk or soybean hypersensitivity, eosinophilic gastroenteritis, gold, methyldopa, nematode infestation.
  - **d) Autoimmune/ idiopathic:** Ulcerative colitis, Crohn's disease, lymphoma



# Pathophysiologic Classification

## **Deranged Motility**

- Due to autonomic dysfunction, rapid small intestine transit, and/or colonic irritability.
- Examples:  
Sandhoff disease (hexosaminidase B deficiency), IBS.

# Pathophysiologic Classification

## **Mixed**

- Most diarrheal disorders have more than one pathophysiologic component.

# Helpful Questions to the Patient with Diarrhea

- **Stool volume:**

- a) Volume < 250 g + tenesmus, frequency, urgency, mucus or blood:
  - suggest recto-sigmoid involvement.
- b) Volume > 400 g, watery, minimal urgency, no tenesmus, little mucus:
  - suggest SB or proximal colon origin, secretory diarrhea.
- c) Volume > 400 g, foul smelling, greasy, minimal urgency, no tenesmus:
  - suggest SB origin with malabsorption.

# Helpful Questions to the Patient with Diarrhea

- **Pain:**
  - a) Periumbilical or RUQ, crampy, with borborigmi:
    - Small bowel or asc. Colon.
  - b) Hypogastric, RLQ, or LLQ, aching, with tenesmus:
    - rectosigmoid
- **Blood:**
  - mucosal invasion (salmonella, campylobacter),
  - IBD,
  - neoplasia,
  - ischemia,
  - cytotoxin (enterohemorrhagic E. coli [EHEC], C. difficile, Shigella, Klebsiella oxytoca)
- **Effect of fasting (48-72h):**
  - a) Stops: osmotic, or allergic.
  - b) Continues: secretory, or exudative /inflammatory.
- **Nocturnal Diarrhea:** suggest organicity

# Helpful Questions to the Patient with Acute Diarrhea

- **Food ingestion:**

- **Poultry:** salmonella, campylobacter, shigella.
- **Ground beef, unpasteurized juice:** Entero-Hemorrhagic 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 Acute Diarrhea

- **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. gonorrhoea, N. meningitidis, Chlamydia, syphilis, CMV, HSV
- **Anilingus:** all enteric bacteria, virus, and parasites.

# Infectious Doses of Enteric Pathogens

- *Cryptosporidium parvum* 1-10<sup>3</sup>
- *Entamoeba histolytica* 10-10<sup>2</sup>
- *Giardia lamblia* 10-10<sup>2</sup>
- *Shigella* 10-10<sup>2</sup>
- *Campylobacter jejuni* 10<sup>2</sup>-10<sup>6</sup>
- *Salmonella* 10<sup>5</sup>
- *Escherichia coli* 10<sup>8</sup>
- *Vibrio cholerae* 10<sup>8</sup>

# Infectious Etiologies

## Type & Site of Involvement

- **Noninflammatory**
  - *Watery diarrhea*
  - Proximal Small bowel
  - Enterotoxin/adherence/ superficial invasion
  - No fecal WBC
  - Minimal or no Lactoferrin
- **Inflammatory**
  - *Dysentery*
  - Colon
  - Invasion/cytotoxin
  - (+) fecal WBC
  - High Lactoferrin
- **Penetrating**
  - Enteric fever
  - Distal small bowel
  - Penetration
  - Fecal mononuclear leukocytes
- **Distal Small Bowel (Penetrating)**
  - **Salmonella typhi**
  - **Yersinia enterocolitica**
  - **Campylobacter fetus**



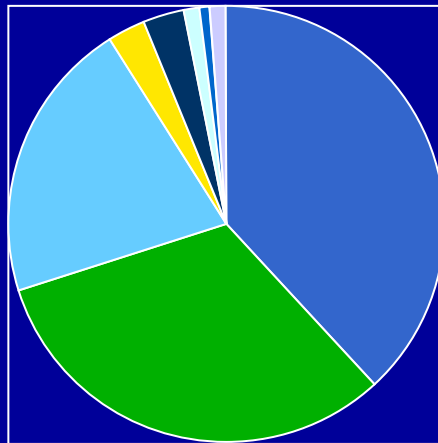
# Infectious Etiologies

## Site of Involvement

- | • Proximal Small Bowel<br>inflammatory)   | (Non- | • Colon  | (Inflammatory) |
|---|-------|--|----------------|
| <ul style="list-style-type: none"><li>• Salmonella (*)</li><li>• E. coli</li><li>• C. perfringens</li><li>• S. aureus</li><li>• Aeromonas hydrophila</li><li>• B. cereus</li><li>• V. cholerae</li><li>• Rotavirus</li><li>• Norwalk-like agents</li><li>• Cryptosporidium (*)</li><li>• Microsporidium (*)</li><li>• Giardia</li><li>• Cyclospora</li><li>• Isospora</li></ul> |       | <ul style="list-style-type: none"><li>• Campylobacter (*)</li><li>• Shigella</li><li>• C. difficile (WBC(+) in 30%)</li><li>• Yersinia</li><li>• V. parahemolyticus</li><li>• Enteroinvasive E. coli</li><li>• Plesiomonas shigelloides</li><li>• Klebsiella oxytoca</li><li>• CMV (*)</li><li>• Adenovirus</li><li>• HSV</li><li>• Entamoeba histolytica (WBC absent b/o destruction)<ul style="list-style-type: none"><li>– (*) Dominant involvement</li></ul></li></ul> |                |

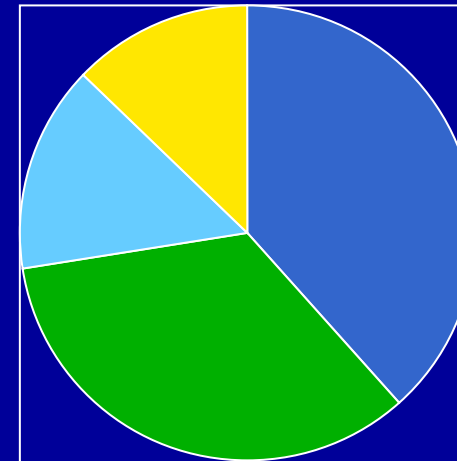
# Common Infectious Etiologies

**WATERY DIARRHEA**  
6% of Stool studies (+)



- Salmonella
- Campylobacter
- Shigella
- EHEC
- Cryptosporidium
- Listeria
- Yersinia
- Vibrio

**BLOODY DIARRHEA**  
20-30% Stool studies (+)



- EHEC
- Shigella
- Campylobacter
- Salmonella

# Complications & Extraintestinal Manifestations of Acute Infectious Diarrhea

- **V. cholerae, E. coli:** volume depletion, shock & death
- **B. cereus:** Fulminant liver failure
- **V. vulnificus, V. parahemolyticus:** 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
- **Campylobacter:** Guillian-Barre syndrome
- **Shigella:** seizures and encephalopathy
- **Salmonella, shigella, campylobacter, yersinia:** Reiter syndrome
- **Yersinia:** Thyroiditis, pericarditis, glomerulonephritis, myocarditis, HUS, Guillian-Barre

# Diagnostic Workup

# Initial Diagnostic Tests

## Acute Diarrhea

- **Patients with high priority for investigation:**
  - Severe volume depletion
  - Impaired host (immunodeficiency, age >70, malnutrition)
  - Bloody diarrhea, dysentery.
  - Toxicity, or fever > 38.5 °C (101.3 °F)
  - Severe abdominal pain
  - Recent antibiotic use, or onset in the hospital (C. diff)
  - Inflammatory Bowel Disease
  - Duration > 3 days.
  - WBC's or Lactoferrin > 1:50 in stool (using these markers to guide further diagnostic studies has been proven to be imprecise and probably unnecessary)
  - Community outbreak, or food handlers.

# Initial Diagnostic Tests

- **Calprotectin:** Elevated fecal calprotectin indicates the migration of neutrophils to the intestinal mucosa, which occurs during intestinal inflammation (In IBD: Sensitivity 93%; Specificity 96%)
  - Calprotectin is a 24 kDa dimer of calcium binding proteins S100A8 and S100A9. The complex accounts for up to 60% of the soluble protein content of the neutrophil cytosol.
  - Increased in inflammatory bowel diseases, celiac disease, infectious colitis, necrotizing enterocolitis, intestinal cystic fibrosis, use of NSAIDs and colorectal cancer.
- **Fecal Lactoferrin:** indicates inflammatory diarrhea (sensitivity=90%, specificity=95%); if (+); send stool culture.
  - *C. difficile* colitis, 64-77% are FL(+) @ titer >1:50. (Steiner et al. Clin Diag Lab Immun 1997,719-722)
  - *Cryptosporidium*: 7% adults & 70-83% malnourished children are LF(+) (Alcantara et al. Am J Trop Med Hyg 2003; 68:325-328)
  - *Shigella*, 95% are FL(+) @ titer > 1:200. (Guerrant et al. J Clin Microbiol, 1992; 30:1238-42)
- **Fecal Leukocytes:** indicates inflammatory diarrhea (sensitivity=42-73%, specificity=84%); if (+); send stool culture.
  - In *C. difficile* colitis, has sensitivity of 30% & specificity of 75% (Reddy et al. Ann Clin Microbiol Antimicrob 2006, 5:9)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- Diagnostic evaluation using **stool culture and culture-independent methods** if available should be used in situations where the individual patient is **at high risk of spreading disease** to others, and during **known or suspected outbreaks**. (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 of the patient's illness and enable specific directed therapy. (Strong recommendation, very low level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- 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 of cases of acute diarrheal infection.
- If available, the use of **FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct** to traditional methods. (Strong recommendation, low level of evidence)



# Initial Diagnostic Tests

- **Molecular Stool Testing for Enteric Pathogens.**
  - If available is first line Test
  - May detect potential pathogens that are “not guilty”.
- **Stool culture:** send only in “**high priority**” patients, or if stool lactoferrin, calprotectin or leukocytes is (+).
  - Stool should be fresh, and processed immediately.
  - Routine culture includes salmonella, shigella, and campylobacter; all other suspected pathogens should be “ordered by name”.
  - In hospital acquired diarrhea, only c. difficile toxin A&B studies are cost effective.
  - If hemorrhagic: E. coli O157:H7 & O26:H11; also Klebsiella Oxytoca (post antibiotics)

# FDA Approved Molecular Tests For Enteric Pathogens

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

can detect microbes at non-pathogenic levels

# Molecular Diagnostic Testing xTAG GPP (Luminex)

- **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
- Rotavirus A

# FilmArray Gastrointestinal (GI) Panel

Reverse transcription PCR with detection of 23 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**
- Enteraggregative 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

# 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

# Initial Diagnostic Tests

- **Stool for Ova & Parasites:**
  - Routine O&P *does not include* studies for cryptosporidium, isospora, cyclospora, nor microsporidium; giardia Ag is done in some labs. You should order the test by name.
  - O&P is not helpful in hospital acquired diarrhea.
  - Because of intermittent shedding, O&P studies should be done in stools of 3 different days.

# Initial Diagnostic Tests

- Stool for Ova & Parasites:
  - **Indications:**
    - AIDS, man having sex with men
    - Immunodeficiency (post-transplant, IgA deficiency, common variable immunodeficiency, chemotherapy)
    - Persistent diarrhea (> 10 days).
    - Weight loss.
    - Community waterborne outbreak (from drinking water, or from swimming pool)
    - Bloody diarrhea with few or no leukocytes (ameba)
    - Exposure in day-care center
    - Ingestion of fresh berries
    - Practice of oral sex
    - Pets & farm animals.

# Test done when Stool Test ordered

	O&P	Comprehensive O&P	C. Difficile toxin	Only on Special order
U of L	Giardia Ag, Cryptosporidium immunoassay	Giardia Ag & Regular O&P	EIA (Toxin A & B) and GDH PCR (toxin B) for discrepancy Interval: 3/wk	Isospora Cyclospora Microsporidia
VA	Lactoferrin: (+) stool examined; (-) "negative"		PCR for toxin B Interval: 1/wk	Cryptosporidium Isospora Cyclospora Microsporidia
Jewish	Giardia Ag	Giardia Ag & Regular O&P	EIA (Toxin A&B) Interval: 1/day	Cryptosporidium Isospora Cyclospora Microsporidia
Norton	Regular O&P		EIA (Toxin A & B) and GDH PCR (toxin B) for discrepancy Interval: 1/wk	Cryptosporidium Isospora Cyclospora Microsporidia



# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of Travelers Diarrhea (TD) where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. (Strong recommendation, high level of evidence)
- Use of **antibiotics for community-acquired diarrhea should be discouraged** as epidemiological studies suggest that most community-acquired diarrhea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics. (Strong recommendation, very low-level evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- In patients receiving **antibiotics for traveler's diarrhea**, adjunctive **loperamide therapy should be administered** to decrease duration of diarrhea and increase chance for a cure. (Strong recommendation, moderate level of evidence)
- The usage of **balanced electrolyte rehydration (ORS)** over other oral rehydration options in the **elderly with severe diarrhea** or any **traveler with cholera-like watery diarrhea** is recommended.
- 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. (Strong recommendation, moderate level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- **Antibiotic sensitivity** testing for management of the individual with acute diarrheal infection is currently **not recommended**. (Strong recommendation, very low level of evidence)
- The use of **probiotics or prebiotics** for the treatment of acute diarrhea in adults is **not recommended**, except in cases of post-antibiotic-associated illness. (Strong recommendation, moderate level of evidence)
- **Bismuth subsalicylates** can be administered to control rates of passage of stool and may help **travelers** function better during bouts of **mild-to-moderate illness**. (Strong recommendation, high level of evidence)

# ACG Guidelines for Acute Diarrheal Infections in Adults 2016

- After the initial stool tests are done, Serological and clinical lab testing in individuals with persistent diarrheal symptoms (between 14 and 30 days) are not recommended. (Strong recommendation, very low level of evidence)
- Endoscopic evaluation is not recommended in individuals with persisting symptoms (between 14 and 30 days) and negative stool work-up. (Strong recommendation, very low level of evidence)

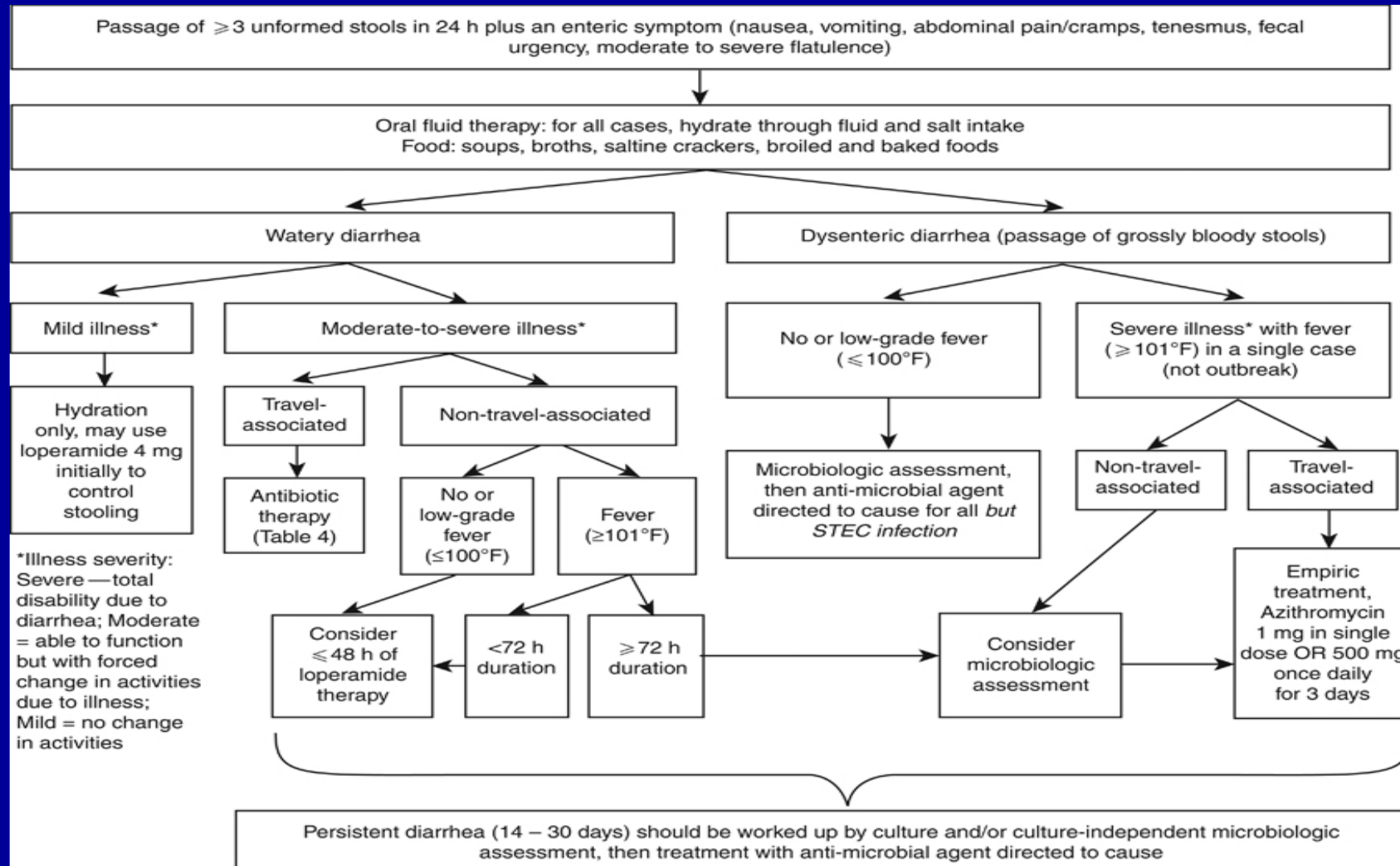
## Preventive Interventions

- Individuals **SHOULD** undergo pre-travel counseling regarding high-risk food/beverage avoidance to prevent traveler's diarrhea. (Conditional, very low level of evidence)
- Probiotics, prebiotics, and synbiotics are **NOT** recommended for prevention of TD. (Conditional recommendation, low level of evidence)
- Patient level counseling on prevention of acute enteric infection is **NOT** routinely recommended but:
  - may be considered in the individual or close contacts of the individual who is at high risk for complications. (Conditional, very low level of evidence)

# Preventive Interventions

- Frequent and effective hand washing and alcohol-based hand sanitizers are of limited value in preventing most forms of traveler's diarrhea but:
  - may be useful where low-dose pathogens are responsible for the illness as for an example during a cruise ship outbreak of norovirus infection, institutional outbreak, or in endemic diarrhea prevention. (Conditional recommendation, low level of evidence)
- Bismuth subsalicylates have moderate effectiveness and may be considered for travelers who do not have any contraindications to use and can adhere to the frequent dosing requirements. (Strong recommendation, high level of evidence)
- Antibiotic chemoprophylaxis has moderate to good effectiveness and may be considered in high-risk groups for short-term use. (Strong recommendation, high level of evidence)

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



# Second Line Diagnostic Tests

- **Flexible sigmoidoscopy:** Indicated in:
  - Dysentery with negative stool studies.
  - History of rectal intercourse.
  - Suspect IBD
  - Immunocompromised patient when CMV, C. difficile, or opportunistic infections are suspected but stool studies are negative.
  - When ischemic colitis is suspected but radiology is equivocal.
  - Suspected pseudomembranous colitis with negative stool studies.
  - Persistent diarrhea with (-) stool studies



# Second Line Diagnostic Tests

- **Special cultures:** with history of rectal intercourse, consider the following,
  - Rectal swab culture for *N. gonorrhoea*, and *N. meningitidis*.
  - Rectal swab for syphilis (dark field or immuno-fluorescence)
  - Rectal swab for chlamydia (culture & immuno-fluorescence)
  - Rectal/colonic Bx for CMV & HSV culture.

# Studies for Acute Diarrhea Evolving to Chronic ( $\geq$ 3 weeks)

# Second Line Diagnostic Tests

- **EGD with SB Bx & Aspirate:**
  - Excellent for SB mucosal disease, but can have false (-) in patchy disease.
  - Fairly good for detection of giardia, cryptosporidium, isospora, cyclospora, microspora & strongyloides (patchy); aspirate & Bx.
  - Quantitative culture of  $> 10^5$  colonies/mL is indicative of bacterial overgrowth.

# Second Line Diagnostic Tests

- **Serologic studies:**
  - Quantitative serum IgG, IgA, & IgM: to evaluate for “common variable immunodeficiency” & IgA deficiency; also for proper interpretation of Celiac Sprue serology
  - Anti-tissue transglutaminase (IgA & IgG), for Celiac Sprue.
  - Ameba serology
  - Anti-HIV serology

# Second Line Diagnostic Tests

- **Stool Electrolytes:**
  - Na, K, Cl
  - Phosphorus, Magnesium, Sulphate, PEG.
  - pH and Reducing Substances.
- **Laxative analysis in stool & urine.**
  - Stool water can be tested for phenolphthalein, emetine (ipecac syrup), & bisacodyl.
  - Urine can be tested for anthraquinone.

# Initial Treatment

- **Oral Rehydration Solution (ORS):**

- Best way to treat fluid loss from diarrhea (unless vomiting)
- WHO: 1 L water + 3.5 g NaCl (3/4 tsp)+ 2.5 g Na bicarbonate (1/2 tsp) + 1.5 g KCl (20 mEq) + [40 g sucrose (3 tbsp), or 20 g glucose, or 50-80 gm rice powder cooked x 3 minutes]. [Na=90 mEq, K=20 mEq, Cl=80 mEq, HCO<sub>3</sub>=30 mEq, glucose=111 mMol]
- WHO: Water 1 liter +  $\frac{3}{4}$  tsp salt +  $\frac{1}{2}$  tsp baking soda + 1 cup orange juice + 4 Tbs of sugar.
- Ceralyte-70 1 liter +  $\frac{1}{4}$  tsp salt or 11 Zesta crackers
- Pedialyte 1 liter + 1 Tbs sugar +  $\frac{1}{2}$  tsp salt, or 22 Zesta crackers
- Gatorade 3 glasses + 1 glass orange juice + {[ $\frac{1}{2}$  tsp salt +  $\frac{1}{2}$  tsp baking soda], or [37 Zesta crackers]}

$\frac{1}{2}$  tsp salt = 22 Zesta crackers

$\frac{1}{2}$  tsp baking soda = 15 Zesta crackers

# Initial Treatment

- **Racecadotril:** reduces output & duration of diarrhea in children and adults; is taken in addition to ORS
- **Zn supplements:** Decrease duration & need of antibiotics; taken in addition to ORS.
- **Crofelemer (Fulyzac):** 125 mg BID. For non-infectious diarrhea in HIV/AIDS.

# Antisecretory Drugs

- **BSS** will reduce the stools passed by ~40%.
- **Crofelemer:**
  - 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,**
  - 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 is production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption.
  - Secondary effect appears to be inhibition of calmodulin leading to reduced mucosal secretion



# Antibiotic Therapy in Diarrhea

- **Risk of Empiric antibiotic therapy:**
  - Increases risk of HUS in EHEC, and
  - Prolongs shedding of salmonella,
  - Do not give when you suspect:
    - c. difficile colitis (targeted therapy is OK), or
    - EHEC, or
    - salmonella
- **Consider antibiotics for:**
  - Travelers Diarrhea\*\* with > 4 BM/d, fever, blood, pus in stool, or
  - Severe diarrhea (> 8 BM/d, or volume depletion), or
  - Diarrhea longer than 7 d, or
  - Diarrhea in immunocompromised

\*\*In Traveler Diarrhea add Loperamide to Antibiotic Regimen

# 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
Azithromycin <sup>c,d</sup>	1,000 mg by mouth or 500 mg by mouth	Single dose <sup>b</sup> 3-day course <sup>d</sup>
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.

# Initial Treatment

- **Symptomatic therapy:** Loperamide, diphenoxylate, Pepto-Bismol
- May be used only in patients without fever nor bloody stool. Pepto-Bismol most helpful for nausea & vomiting.
- **Loperamide:** 4 mg, followed by 2 mg q BM, not to exceed 16 mg/d, x 2 days.
  - Used together with antibiotics in Traveler Diarrhea.
- **Diphenoxylate:** 4 mg QID x 2 days
- **Pepto-Bismol:** 2 tab, or 30 mL q 30 min. x 8 doses

# Viral Foodborne Infections

## Specific Causes of Foodborne Diarrhea - Viral

# Norwalk & Norwalk-like Virus

- 40-60% of acute viral gastroenteritis epidemics in older children & adults
- 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
- **Diagnosis:** Serology, or E/M for stool virus
- **Immunity:** weeks to months
- **Treatment:** ORS, supportive.

# Specific Causes of Foodborne Diarrhea - Viral

## Rotavirus

- 60% of diarrhea in children < 2 years-old
- 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)
- **Treatment:** ORS, supportive.

# Foodborne Bacterial Infections with Diarrhea due to Mucosal Invasion

## Specific Causes of Foodborne Diarrhea – 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  $< 102^{\circ}\text{F}$ , watery diarrhea; sometimes severe dysentery. May cause osteomyelitis, septic or reactive arthritis, sepsis, peritonitis, cholecystitis, pancreatitis, mycotic aneurism, intraabdominal abscess.
- **Treatment:** ORS & support. Antibiotics prolong disease.
  - Treat only 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, than improves and then worsens, with WBC's in stool.
- **Complications:** Endocarditis, meningitis, Guillian-Barre, cholecystitis, pancreatitis, septic abortion, glomerulonephritis, reactive arthritis (HLA-B27)
- **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.
- **Children < 5y:** fever, abdominal cramps, diarrhea for 1 or more weeks.
- **Children > 5 y:** mesenteric adenitis, or ileitis; sometimes ileal perforation.
- **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.
- **Treatment:** only in severe or prolonged disease; 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 L/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

- After salmonella, second cause of food-borne diarrhea in USA
- **Spread:** contaminated food with preformed cytotoxic, heat-stable, enterotoxin A. No WBC in stool. 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.
- **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 (one heat-labile, and two heat-stable), activate adenylate & 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.
- **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, with shiga-like verotoxin I & II; cytotoxic to endothelial cells and enterocyte. (After antibiotics, Klebsiella Oxytoca gives similar clinical picture).
- Sporadic and epidemic illness.
- **Spread:** ingestion of contaminated ground beef, unpasteurized milk or apple cider. 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 cpe**]
- Heat-labile cytotoxic enterotoxin.
- **Incubation:** 8-24 hours.
- **Duration:** 24 hours.
- **Symptoms:** severe watery diarrhea, with intense abdominal cramps. Can cause antibiotic associated diarrhea without pseudomembranes (**plasmid cpe**).
- **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.
- Cytotoxic toxin A&B
- **Symptoms**: watery diarrhea (sometimes bloody), abdominal pain, fever, leukocytosis; may have hypoalbuminemia. (*K. oxytoca* gives severe hemorrhagic antibiotic-related diarrhea)
- **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%.

# 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

## Antibiotic Related Diarrhea (ARD)

# Clostridium difficile

- **Complications**: protein losing enteropathy, ascites, toxic megacolon requiring colectomy; risk high in >64y/o, immunosuppression & hospital acquisition.
- **Risk Factors for complicated nosocomial PMC:**
  - WBC > 20K,
  - Creat > 2 mg/dL
  - (Risk: 0=10%; 1=28%; 2=60%)
- Mortality due to “hypervirulent strain” PMC with “binary toxin” & “deletion in tcdC”: 16% over expected by Dx.
- Mortality due to “Fulminant” PMC: 53% (most within initial 48h)

## Antibiotic Related Diarrhea (ARD)

# Clostridium difficile

- **Treatment:**

- **Initial:**

- **Severe disease or IBD:** Vancomycin 125 mg po or rectal QID x 14d (failure 4%, recurrence 20%, \$600) , or
    - **Mild to Moderate disease:** Metronidazole 500 mg po QID x 14 d (failure 13%, recurrence 20%, \$20) ).

- **First relapse:** treat as above

- **Ileus or Fulminant Colitis:**

- Vanco 500 mg po, or 500 mg in 100 mL 0.9% NaCl 1h-retention enema QID, **plus**
    - Metronidazol 500 mg IV q8h or 500 mg IV q6h.

- **Critically ill:**

- IVIG 400 mg/kg IV +/-
    - total colectomy if persistent hypotension, lack of response to medical therapy, megacolon or perforation.

- **Multiple Relapses:** See Surawicz protocol later.

# Updated Infectious Diseases Society of America guidelines for the treatment of CDI (2010)

Clinical classification	Clinical features	Recommended treatment
Mild or moderate disease	-Leukocytosis with a WBC count $\leq 15 \times 10^9/l$ and -Serum creatinine level $< 1.5$ times baseline level	Metronidazole administered orally at a dose of 500 mg three times daily for 14 days
Severe disease or with IBD	-Leukocytosis with a WBC count $\geq 15 \times 10^9/l$ and/or -Serum creatinine level $\geq 1.5$ times baseline level	Vancomycin administered orally at a dose of 125 mg four times daily for 14 days
Complicated disease	Hypotension, ileus, megacolon	-Vancomycin administered either orally or by nasogastric tube at a dose of 500 mg four times daily, plus -Metronidazole administered intravenously at a dose of 500 mg every 8 h. -If complete ileus is present, consider adding a rectal instillation of vancomycin (500 mg in 100mL of 0.9% NaCl, 1 hour retention enema) QID. -All treatments to be continued until the patient improves

## Treatment options for refractory and recurrent CDI

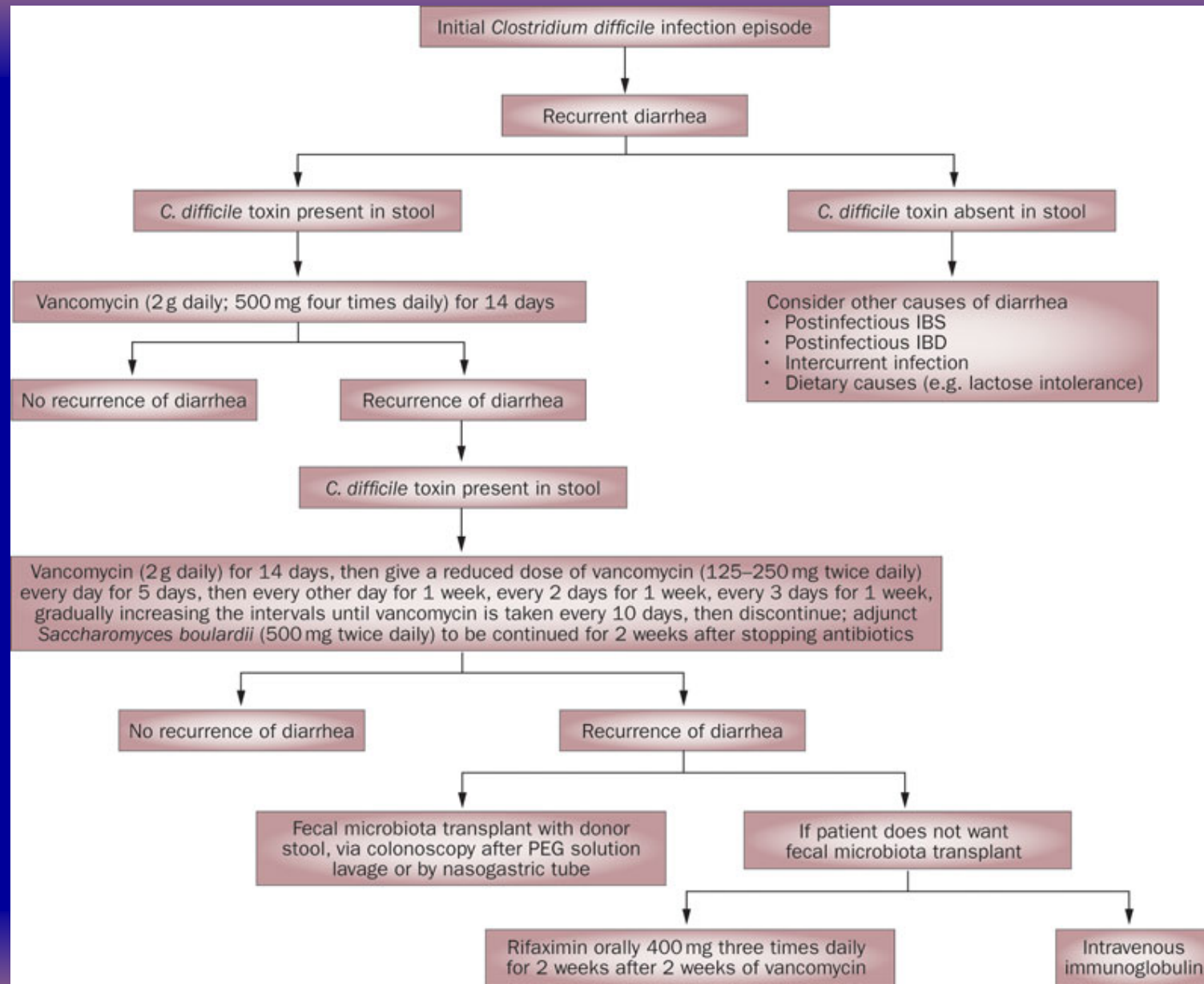
**Table 1** | Treatment options for refractory and recurrent CDI

Type of therapy	Currently available agents	Agents under development
Antimicrobial agents	Vancomycin, metronidazole, nitazoxanide*, tigecycline*	Fidaxomicin, ramoplanin, CB-183315
Nonantimicrobial agents	<i>Saccharomyces boulardii</i> , <i>Lactobacillus plantarum</i>	NA
Biotherapeutic agents	Fecal microbiota transplant	Nontoxigenic <i>Clostridium difficile</i>
Intraluminal toxin-neutralizing agents	NA	Bovine whey protein, tolevamer
Systemic antibody approaches	Intravenous immunoglobulin	Monoclonal antibodies, active vaccines

Data obtained from Gerding & Johnson (2010).<sup>103</sup> \*The efficacy of these drugs in the treatment of refractory CDI has been shown in case reports. Abbreviations: CDI, *Clostridium difficile* infection; NA, not applicable.

Surawicz, C. M. & Alexander, J. (2011) Treatment of refractory and recurrent *Clostridium difficile* infection  
*Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2011.59

# Treatment algorithm for recurrent *Clostridium difficile* infection



# Fecal Flora Reconstitution (FFR) or Fecal Microbiota Transplant

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)

- **Donors:**

- **Inclusion** in this order;

- 1. intimate domestic partners,
    - 2. family members or those living in the same household,
    - 3. close friends

- **Exclusion** of donors:

- recent antibiotic use,
    - current or recent diarrheal illness,
    - hospital or health care worker, and
    - at-risk sexual behaviors

- **Screening for illness:**

- Donor stool screened for *C. difficile*, and enteric pathogens;
    - Serology for HIV and viral hepatitis.

- Stool is spontaneously passed or prompted with an small dose of Mg Citrate.



# 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 polyethylene glycol purge taken the evening before their procedure

# 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 and delivery of donated stool:**
  - In a room separate from the procedure area donated stool is suspended in 350 mL of **nonbacteriostatic saline**, with manual shaking in a large suction canister.
  - To prevent clogging of the colonoscope channel, the suspension is then poured once or twice through a filter. The filter is made of multiple 4×4 gauze sheets opened up, and draped over another suction canister, and then held in place by rubber bands. This process presumably does not significantly affect the bacterial content.
  - Stool is infused through the colonoscope channel into the TI or cecum, with the help of 60 cc syringes.
  - Immodium 2 tablets after procedure and 2 tablets 6 hours later.
  - Recipients are instructed to remain at bed rest for several hours after the colonoscopy, or the remainder of the day of infusion, as much as possible.
  - A bland diet is advanced slowly.

# NIH Recommended Testing

## Donor Stool Testing

- *C. difficile* toxin,
- Enteric bacterial pathogens (including specifically *Listeria monocytogenes*, *Vibrio cholera* and *Vibrio parahaemolyticus*),
- Parasites such as Giardia (Giardia antigen test) Cryptosporidium (Cryptosporidium antigen test), and Isospora (acid-fast stain),
- Rotavirus;
- H. Pylori stool Ag

## Donor & Recipient Blood Testing

- **Donor blood** must be screened for hepatitis A (IgM), B (HBsAg, anti-HBc (IgG and IgM), and anti-HBsAg) and C (HCV antibody) viruses, HIV types 1 and 2, and syphilis.
- **Recipients blood** is tested for HIV 1 and 2, Hepatitis A, C, and syphilis.

# RePOOPulate

Petrof EO et al. *Microbiome* 2013, 1:3

- Synthetic stool made with 33 of 62 bacterial isolates from the stool of a healthy 41 years old woman.
- Isolates were chosen because they were “commensal”, susceptible to multiple antibiotics, and easy to culture.
- Bacterial ratios were derived from those observed in healthy population.
- Presentation: 100 ml pre-reduced sterile 0.9% normal saline with an estimated concentration of  $3.5 \times 10^9$  colony-forming units/ml. The bacterial suspension was placed in a reduced atmosphere in a double-sealed container at 4° C, and used within 24 hours

## Antibiotic Related Diarrhea (ARD)

# Clostridium perfringens Type A

- Proliferation of C. perfringens type A 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)
- **Colonoscopy**: 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

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

# 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; Duodenal aspirate, string-test, or Bx.
- **Treatment:** Metronidazole 250 mg po TID x 5-7 days; Quinacrine 100 mg TID x 5 days. Patients with IgA or IgM deficiency need 6-8 weeks of therapy. Nitazoxanide (Alinia) 500 mg TID x 3 days.

# 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; 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

- **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. 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} + {Diloxanide 500 mg TID x 10 d, or Iodoquinol 650 mg TID x 20 d or Paramomycin 25-35 mg/k 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. 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:**
  - a) Enterocytozoan bienusi: fumagillin 60 mg/d x 14 days.
  - b) Encephalitozoon intestinalis: albendazole 400 mg BID x 3-4 weeks.

# Diarrhea due to Fish & Shellfish associated Toxins



## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Ciguatera

- Ciguatoxin accumulates in large-fish muscles after eating smaller fish; is heat-stable
- 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. Atropine for bradycardia. Gastric lavage and cathartics. May need respiratory support. Amitryptiline for chronic neuropathy.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Scombroid

- Formation of histamine & saurine in flesh of fish by action of marine bacteria
- Fish tastes sharp and peppery.
- 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; cathartics & gastric lavage.

## Specific Causes of Foodborne Diarrhea – Toxin Mediated

# Paralytic Shellfish Poisoning

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

## Specific Causes of Foodborne Diarrhea – Toxin Mediated Neurotoxic Shellfish Poisoning

- Dinoflagellate with brevetoxin, concentrated by mollusks. Associated to "red tide".
- Heat-stable toxin
- Gulf Coast, North Carolina, and Florida
- **Onset:** few hours
- **Duration:** hours to days.
- **Symptoms:** paresthesias, reversal of hot-cold sensation, nausea, vomiting, diarrhea, ataxia. Respiratory symptoms after aerolization.
- **Treatment:** symptomatic

## Specific Causes of Foodborne Diarrhea – Toxin Mediated Diarrheic Shellfish Poisoning

- From eating mussels, scallops, or clams who have okadaic acid or dinophysistoxin-1
- 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

- From eating shellfish (Razor clams, Dungeness crabs), and anchovies who have domoic acid.
- 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



## Specific Causes of Acute Diarrhea - Viral

### Other Virus

- HSV & CMV: may cause proctitis and diarrhea after anal sex. Colitis and diarrhea in immunocompromised patients.
- Adenovirus, coronavirus, astrovirus, and calicivirus.



# Common Infectious Etiologies

## • WATERY DIARRHEA

- **6% of stool studies (+):**
- Salmonella 38%
- Campylobacter 32%
- Shigella 21%
- E. coli O157:H7 3%
- Cryptosporidium 3%
- Listeria 1%
- Yersinia 1%
- Vibrio 1%

## • BLOODY DIARRHEA

- **20-30% of stool studies (+):**
- E. coli O157:H7 39%
- Shigella 35%
- Campylobacter 15%
- Salmonella 13%
- K. oxytoca