Clinical & Diagnostic Microbiology

GI, Skin, Soft Tissue & Wound

Gastrointestinal Infections & Food Poisoning - II

Acute Diarrheal Illness

- One of the most common problems evaluated by clinicians
  - Infectious agents transmitted via ingestion of contaminated food or beverage.
- Other names
  - Montezuma's revenge
  - Delhi belly
  - Greek gallop
  - Rome runs
  - Aztec two-step
  - Back door sprint

General Clinical Manifestations

- In healthy individuals
  - A self-limiting illness, lasting only a few days
- Some people experience chronic symptoms.
  - Bacteremia
  - Dehydration
  - Serious sequelae
    - Malnutrition, severe dehydration, death

What's Ahead?

- Review of host and pathogen factors that lead to illness
- A clinical and laboratory approach to making a diagnosis
- Discussion of common bacterial, viral, and parasitic pathogens
- Summarizes treatment and prevention strategies

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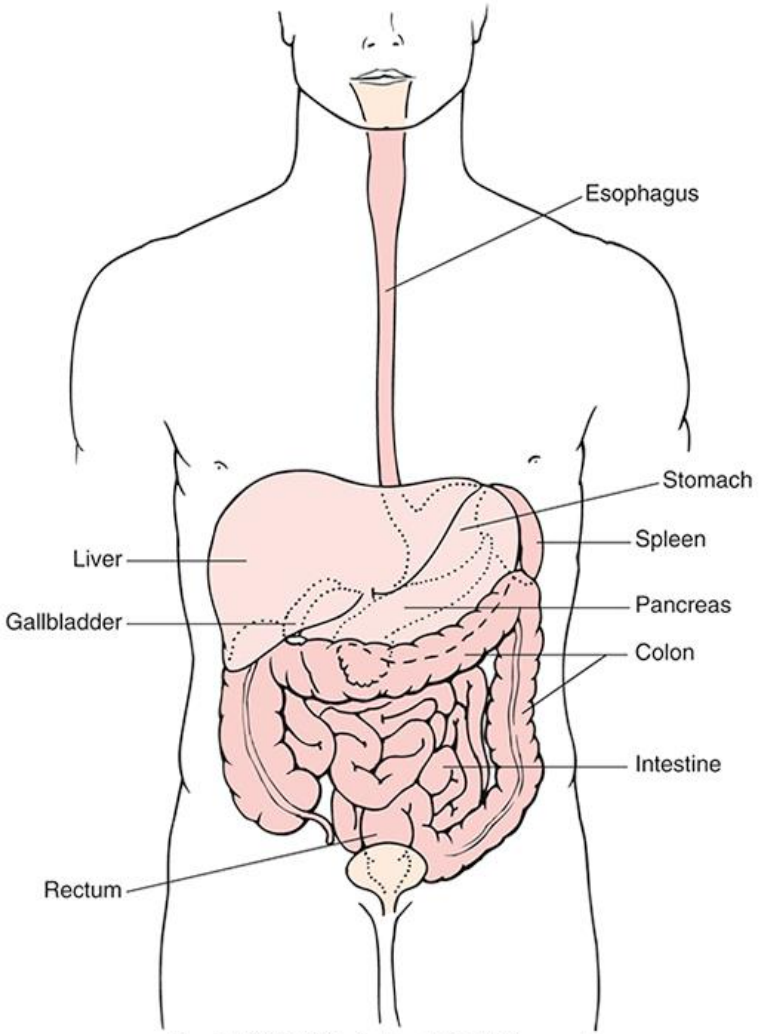
Anatomic Considerations

Anatomy of the GI Tract



Anatomic Considerations (Cont.)

- Host defenses
  - Stomach acidity (pH of lower than 4)
    - Kills more than 99.9% of coliform bacteria within 30 minutes
  - Some pathogens are resistant.
  - Small intestine
    - Peristalsis (constant motion)
  - Small intestine and colon
    - Possess lymphoid tissue that produces antibody, primarily IgA

Microbiota Found in the Large Intestine

TABLE 34.1 Microbiota Found in the Large Intestine

Bacterial Species[a]	Incidence (%)
Strict Anaerobes	
Gram-Negative	
Bacteroides fragilis	100
Bacteroides spp.	100
Fusobacterium spp.	100
Gram-Positive	
Lactobacilli	20–60
Clostridium perfringens	25–35
Clostridium spp.	1–35
Peptostreptococcus spp.	Common
Peptococcus spp.	Common
Facultative Anaerobes	
Gram-Positive Cocci	
Staphylococcus aureus	30–50
Enterococcus spp.	100
β-Hemolytic streptococci, groups B, C, F, and G	0–16
Gram-Negative Bacilli (Enterobacteriaceae)	
Escherichia coli	100
Klebsiella spp.	40–80
Enterobacter spp.	5–55
Proteus spp.	3–11
Pseudomonas aeruginosa	3–11
Candida albicans	15–30

[a]Strict anaerobes are present in ratio of 1000:1 with facultative aerobes.
Modified from Sommers HM: The indigenous microbiota of the human host. In Youmans GP, Paterson PY, Sommers HM, editors: *The biologic and clinical basis of infectious diseases,* ed 2, Philadelphia, 1980, WB Saunders, p. 83.

Differential Diagnosis Considerations

- Chronicity of disease may help narrow the differential.
- A variety of viral, bacterial and parasitic pathogens are involved.
- Causes of diarrhea
  - Toxin-mediated, invasion by infectious agent
  - Numerous noninfectious causes including but not limited to
    - Laxative use, tumor-related, malabsorption, inflammatory bowel disease

Risk Factors for GI Infection

- Number of ingested organisms
  - Median infectious dose (ID_{50})
    - Number of organisms ingested to cause disease in 50% of exposed individuals
- Achlorhydria (absence of hydrochloric acid in gastric secretion)
- Reduction in normal biota
  - Antibiotic exposure

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Approach To Diagnosis of the Patient w/Diarrhea

Determination of the Cause of Patient with Diarrhea

- Patient history
- Patient physical examination
- Laboratory analysis of a stool specimen

Common Pathogens Involved in Diarrhea

TABLE 34.2 Common Pathogens Involved in Diarrhea

Pathogen	Fever	Nausea, Vomiting	Bloody Stool	Fecal Inflammation
Campylobacter spp.	Common	Occurs	Occurs	Common
Salmonella spp.	Common	Occurs	Occurs	Common
Shigella spp.	Common	Common	Occurs	Common
Enterohemorrhagic *Escherichia coli*	Atypical	Occurs	Common	Often not found
Clostridioides difficile	Occurs	Not characteristic	Occurs	Common
Yersinia enterocolitica	Common	Occurs	Occurs	Occurs
Entamoeba histolytica	Occurs	Variable	Variable	Variable
Cryptosporidium spp.	Variable	Occurs	Not characteristic	None to mild
Cyclospora	Variable	Occurs	Not characteristic	Not characteristic
Giardia lamblia	Not characteristic	Occurs	Not characteristic	Not characteristic
Viruses	Variable	Common	Not characteristic	Not characteristic

Modified from Thielman NM, Guerrant RL: Clinical practice. Acute infectious diarrhea, *N Engl J Med* 350:38, 2004.

History

- Definition of diarrhea
  - An “alteration in normal bowel movement characterized by an increase in the water content, volume, or frequency of stools”
- Many epidemiologic investigations consider diarrhea as more than 3 bowel movements/day.
- Accurate travel and dietary history can point to causative diagnosis and direct microbiologic workup.

Key Questions to Ask Patients Suspected of GI Infections

- What is the duration of symptoms?
- Are there associated symptoms of inflammation?
- Does the patient have a history of previous GI symptoms?
- Does the patient have an underlying illness?
- Is the patient taking any medications?
  - A recent history of antimicrobial use may also suggest an infection with *Clostridioides difficile*.

History

- Food ingestion, travel, recreational activities
  - Traveler's diarrhea
    - Enterotoxigenic *Escherichia coli* (ETEC)
  - Parasitic infections
    - Giardiasis–*Giardia duodena*lis (a.k.a. *G lamblia* and *G. intestinalis*)
    - Entamebiasis–*Entamoeba histolytica*

Common Food Vehicles for Specific Pathogens or Toxins

TABLE 34.3 Common Food Vehicles for Specific Pathogens or Toxins

Vehicle	Pathogen or Toxin
Undercooked chicken	*Salmonella* spp., *Campylobacter* spp.
Eggs	*Salmonella* spp. (especially *S.* Enteritidis)
Unpasteurized milk	*Salmonella, Campylobacter* spp., *Yersinia* spp.
Water	*Giardia lamblia,* noroviruses, *Campylobacter* spp., *Cryptosporidium* spp., *Cyclospora*
Fried rice	*Bacillus cereus*
Fish	
Shellfish	*Vibrio cholerae, V. parahaemolyticus, V. vulnificus,* other *Vibrio* spp., neurotoxic shellfish poisoning, paralytic shellfish poisoning, Norwalk virus
Tuna, mackerel, mahi-mahi	Scombroid poisoning
Grouper, amberjack, snapper	Ciguatera
Sushi	*Anisakis* spp.
Beef, gravy	*Salmonella* spp., *Campylobacter* spp., *Clostridium perfringens*

Modified from Goodman LJ: Diagnosis, management, and prevention of diarrheal diseases, *Curr Opin Infect Dis* 6:88, 1993.

History (Cont.)

- Other Medical Conditions that may cause diarrhea
  - Inflammatory bowel disease
  - Malabsorption
  - Radiation therapy
- Consider opportunistic pathogens
  - Immunosuppressed from AIDS, chemotherapy, or organ transplantation

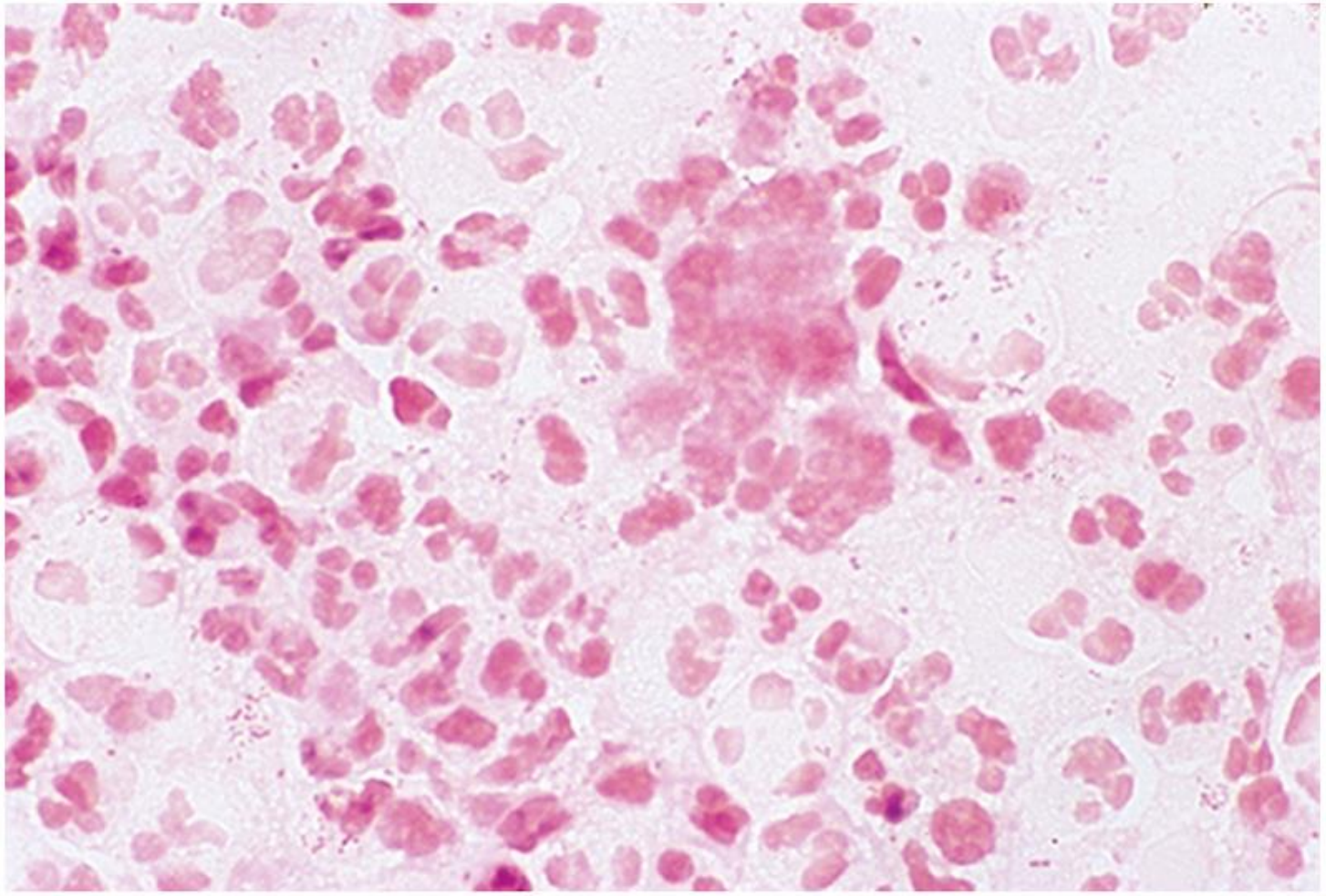
Physical Examination

- State of hydration
  - Sunken eyes
  - Dry oral membranes
  - Skin tenting
  - Orthostatic changes in blood pressure
- Examination of the abdomen
  - Hyperactive
  - Pain
    - Diffuse or localized can help determine disease process

Laboratory Studies

- Leukocytosis
- Anemia
- Thrombocytopenia
- Electrolyte abnormalities
- Fecal examination
  - Red blood cells (RBCs)
  - Fecal leukocytes
    - Help differentiate invasive from toxigenic disease
- Fecal lactoferrin testing
  - Neutrophil marker associated with inflammation

Gram Stain of Direct Fecal Smear



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Clinical Presentation & Pathogenic Mechanisms of Acute Diarrhea

Enterotoxin-Mediated Diarrhea Symptoms

- Abdominal cramps and vomiting
- Rapid onset of diarrhea
- Lack of fever
- Absence of blood or pus in stool
  - Point to enterotoxin-mediated illness
- Large number of nonbloody, watery stools
  - Sometimes more than 20 per day

Enterotoxin-Mediated Diarrhea Causative Agents

- Bacterial
  - ETEC
  - *Vibrio cholerae*
  - *Staphylococcus aureus*
  - *Clostridium perfringens*
  - *Bacillus cereus*
- Parasitic
  - *Cryptosporidium* spp.
  - *Cystoisospora belli*

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Diarrhea Mediated by Invasion of the Mucosal Surface

Symptoms and Causative Agents

- Symptoms
  - Fecal leukocytes
  - Fever
  - Leukocytosis
- Causative agents
  - *Salmonella enterica*
  - *Campylobacter* spp.
  - *Shigella* spp.
  - *E. coli*
  - *Entamoeba histolytica*

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Diarrhea Mediated by Invasion of Full-Bowel Thickness w/Lymphatic Spread

Causes, Incubation Time, and Stool Findings

- Most common causes
  - *Salmonella* Typhi
  - *Yersinia enterocolitis*
- Incubation time is about 1 to 3 days
- Findings in stool
  - RBCs present
  - WBCs present

Symptoms and Causative Agents

- Symptoms
  - Often diarrhea is not the presenting symptom.
    - Constipation
  - Fecal leukocytes and RBCs
  - Septicemia
  - Enteric lymphadenitis
  - Gross blood seen in the stool of 25% of patients with *Y. enterocolitis*
  - S. Typhi–infection become chronic, patients may become carriers and unknowingly spread infection to others.

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Common Viral, Bacterial & Parasitic Pathogens

Viral Pathogens

- Rotaviruses
  - Generally children under 5 years old
- Enteric adenoviruses
  - Serotypes 40 and 41 associated with infectious diarrhea
- Caliciviruses
  - Norovirus
    - Recent cruise ship outbreaks
  - Sapovirus
- Astroviruses
  - Older adults and very young

Other Viral Pathogens

- Diarrhea may be present as systematic manifestations of other viral infections
  - SARS-CoV-2

Bacterial Pathogens

- *Campylobacter jejuni*
  - Most common cause of gastroenteritis in the world
- *Salmonella* spp.
  - Gastroenteritis and food poisoning
  - Enteric fever of *S.* Typhi
- *Shigella* spp.
  - Gross blood and pus in the stool
  - Four species
  - Low inoculum (100 organisms)

Bacterial Pathogens
Escherichia coli

- Several diarrheagenic strains of *E. coli*
- Enterotoxigenic *E. coli* (ETEC)
  - Produces adhesins that bind to intestinal mucosa and enterotoxins
  - Patients have watery diarrhea that lacks RBCs and WBCs
  - Common cause of traveler's diarrhea

Bacterial Pathogens *E.coli* (Cont.)

- Enteroinvasive *E.coli* (EIEC)
  - Produces infection resembling *Shigella* infection
  - Patients have watery diarrhea then progress to an invasive-type diarrheal syndrome with fever, abdominal cramping, and bloody stools
  - Fecal leukocytes are abundant followed by
    - Increasing abdominal pain
    - Bloody stools

Bacterial Pathogens *E.coli* (Cont.)

- Enterohemorrhagic *E. coli* (EHEC)
  - This is also referred to as Shiga-toxin producing *E. coli* (STEC).
  - Produces Shiga toxin 1 and/or Shiga toxin 2
  - Produces a locus of enterocyte effacement that mediates attachment to enterocyte membrane and destruction of the brush border microvilli
  - Infection starts with watery diarrhea
  - *E. coli* 0157:H7 the principal causes of EIEC

Bacterial Pathogens
E.coli (Cont.)

- Enteropathogenic *E. coli* (EPEC)
  - Organisms seem to express various factors that facilitate their adherence to intestinal cells
    - Causes disruption and destruction of the brush border of cells and other intestinal cell derangements
    - Leads to electrolyte abnormalities and diarrhea
  - Most commonly affect children in nurseries and daycare centers
  - Symptoms: low-grade fever, vomiting, diarrhea

Bacterial Pathogens *E.coli* (Cont.)

- Enteroaggregative *E. coli* (EAEC)
  - Organism adheres to the intestinal surface but in a more clumped or aggregate fashion.
  - Appear to adhere to the intestinal wall first causing the production of mucus, then an inflammatory response
  - A recognized cause of traveler's diarrhea.
  - Symptoms can range from asymptomatic to chronic watery diarrhea.

Bacterial Pathogens
E.coli (Cont.)

- Diffusely adherent *E. coli*
  - Characterized by a diffuse adherence pattern on cultured HeLa or HEp-2 cells.
  - Strains can be part of the asymptomatic intestinal microbiota in older children and adults.
  - Symptoms in children include
    - Diarrhea
    - Abdominal pain
    - Vomiting

Diarrheagenic *E. coli*

TABLE 34.4 Diarrheagenic *Escherichia coli*

Group	Major Virulence Factors	Reported Food Sources
ETEC	Adhesins LT and ST toxins	Fresh fruits and vegetables, scallops, tuna paste, soft cheeses
EIEC	Invasion proteins	Cheese, guacamole
EHEC	Intimin (adherence to intestinal mucosa) Shiga toxins	Undercooked beef, sausage, chicken, lunch meats, deer jerky, lettuce, radishes, alfalfa sprouts, potatoes, milk, apple juice, cider, cheese curds
EPEC	Intimin (adherence to intestinal mucosa) Bundle-forming pili Surface-associated filaments Translocated intimin receptor	Fresh fruits and vegetables, likely infant formula
EAEC	Aggregative adherence fimbriae Dispersin Plasmid-encoded toxin	Likely foodborne, possibly fruits and vegetables, other food sources uncertain
DAEC	Adhesins	Likely contaminated food or water and also through person-to-person contact

DAEC, diffusely-adherent *E. coli; EAEC,* Enteroaggregative *Escherichia coli; EHEC,* enterohemorrhagic *E. coli; EIEC,* enteroinvasive *E. coli; EPEC,* enteropathogenic *E. coli; ETEC,* enterotoxigenic *E. coli; LT,* heat labile; *ST,* heat stable.

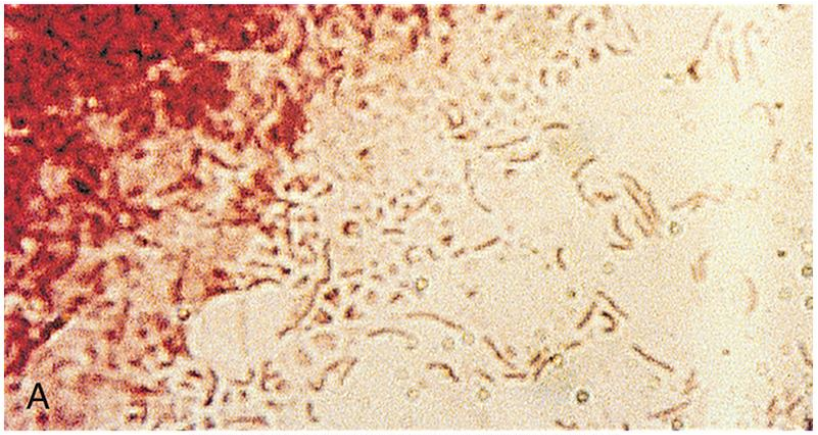
Bacterial Pathogens (Cont.)

- *Vibrio* spp.
  - Cholera
  - Noncholera *Vibrio* illness
- *Y. enterocolitica*
  - Self-limiting enteritis with possible invasion of the mesenteric lymph nodes
  - Sometimes mistaken for appendicitis
- *Clostridioides difficile*
  - Antibiotic-associated diarrhea
  - Pseudomembranous colitis
  - Mild to severe disease

Bacterial Pathogens (Cont.)

- *Listeria monocytogenes*
  - Of concern when isolated in stool of symptomatic patient
- *Helicobacter* spp.
  - Association with peptic ulcers: *H. pylori*
  - Diarrhea: *H. cinaedi* and *H. fennelliae*
- *Aeromonas* spp., *Plesiomonas shigelloides*
  - Watery diarrhea
- *Edwardsiella tarda*
  - Associated with fish and shellfish

Microscopic Morphology of *Helicobacter pylori*



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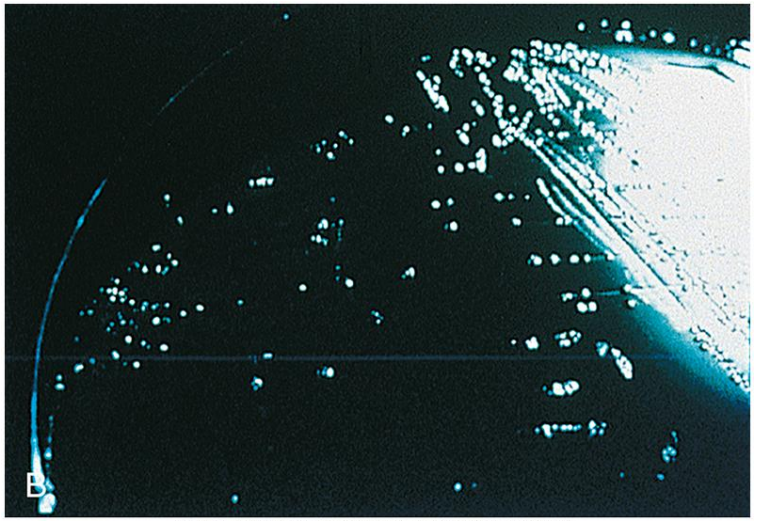

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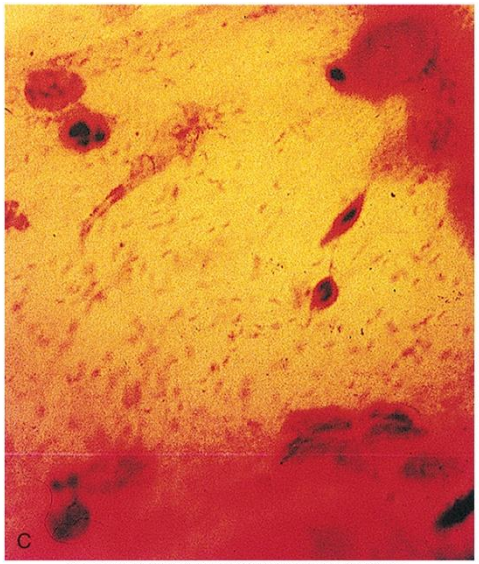

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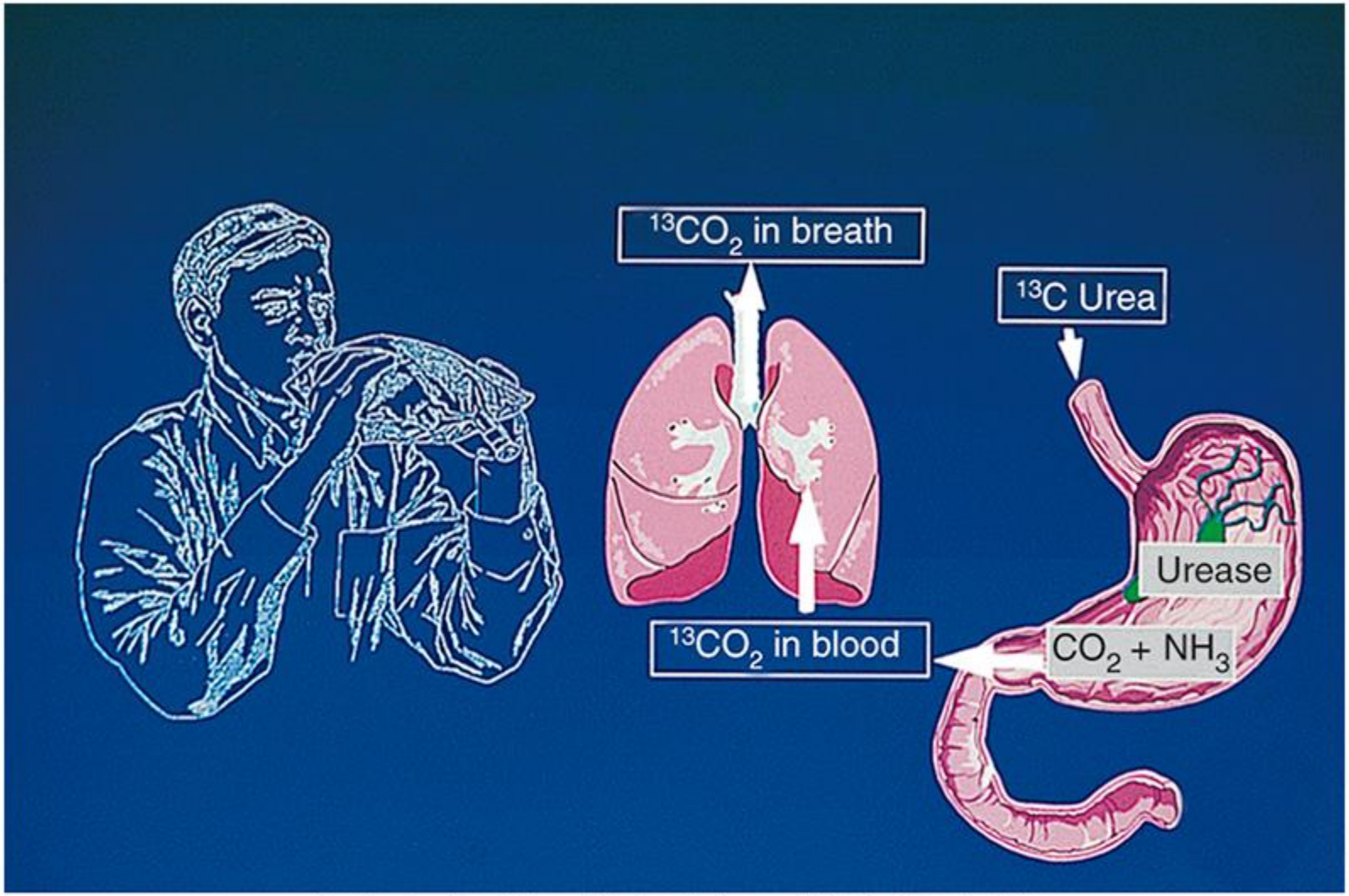
Urea Breath Test



Courtesy American College of Gastroenterology and DiaSorin, Stillwater, MN.

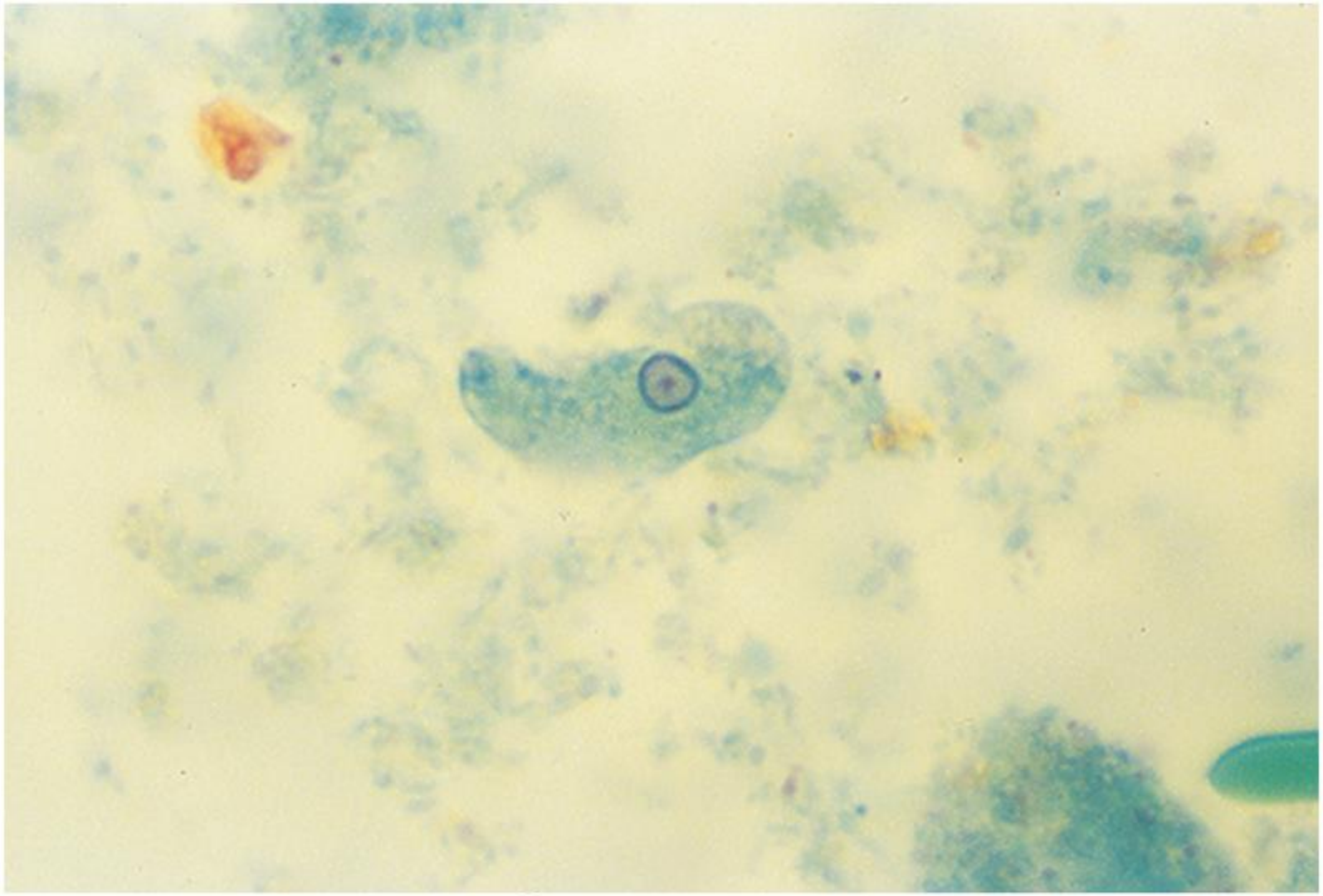
Bacterial Pathogens (Cont.)

- Sexually transmitted diseases causing GI disease
  - *Neisseria gonorrhoeae*
  - *Chlamydia trachomatis*
  - *Treponema pallidum*
  - Herpes simplex virus (HSV)
- All can cause proctitis with loose stools and pain on defecation
  - Most common in patients with receptive anal intercourse

Parasitic Pathogens

- *Giardia intestinalis*
  - Nausea, vomiting, flatulence, cramping, and diarrhea
- *E. histolytica*
  - Fever and bloody diarrhea
- *Cryptosporidium parvum* and *Cryptosporidium hominis*
  - Abdominal cramping, watery diarrhea, vomiting, fever, and anorexia
  - Stain of choice–acid fast

E. histolytica Trophozoites



Parasitic Pathogens (Cont.)

- *Cyclospora cayetanensis* and *Cystoisospora belli*
  - Watery diarrhea and abdominal cramps
  - Cramping, fever, profound fatigue, nausea, vomiting also possible
- Microsporidia
  - *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*
    - Asymptomatic to self-limiting diarrhea in healthy individuals

Other Parasitic Infections

- Representative parasitic agents
  - *Ascaris lumbricoides* (common roundworm)
  - *Strongyloides stercoralis* (threadworm)
  - *Ancylostoma* and *Necator* (hookworms)
  - *Trichuris trichiura* (whipworm)
  - *Enterobius vermicularis* (pinworm)
  - *Trichinella spiralis* (pork worm)

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Diarrhea in Special Circumstances

Toxic Agents of Food Poisoning

- Chemical intoxications
  - Scombroid
    - Flushing, headache, crampy abdominal pain, and diarrhea
      - Tissues of fish contain histamine and enzyme inhibitors, which are responsible for symptoms.
  - Ciguatera
    - Red tide toxin accumulates in fish
    - Diarrhea, abdominal pain, weakness, paresthesias, and headache
      - May progress to respiratory failure and hypotension
  - Paralytic shellfish poisoning
      - Toxin- tetrodotoxin

Compendium of Common Foodborne Diseases

TABLE 34.5 Compendium of Common Foodborne Diseases

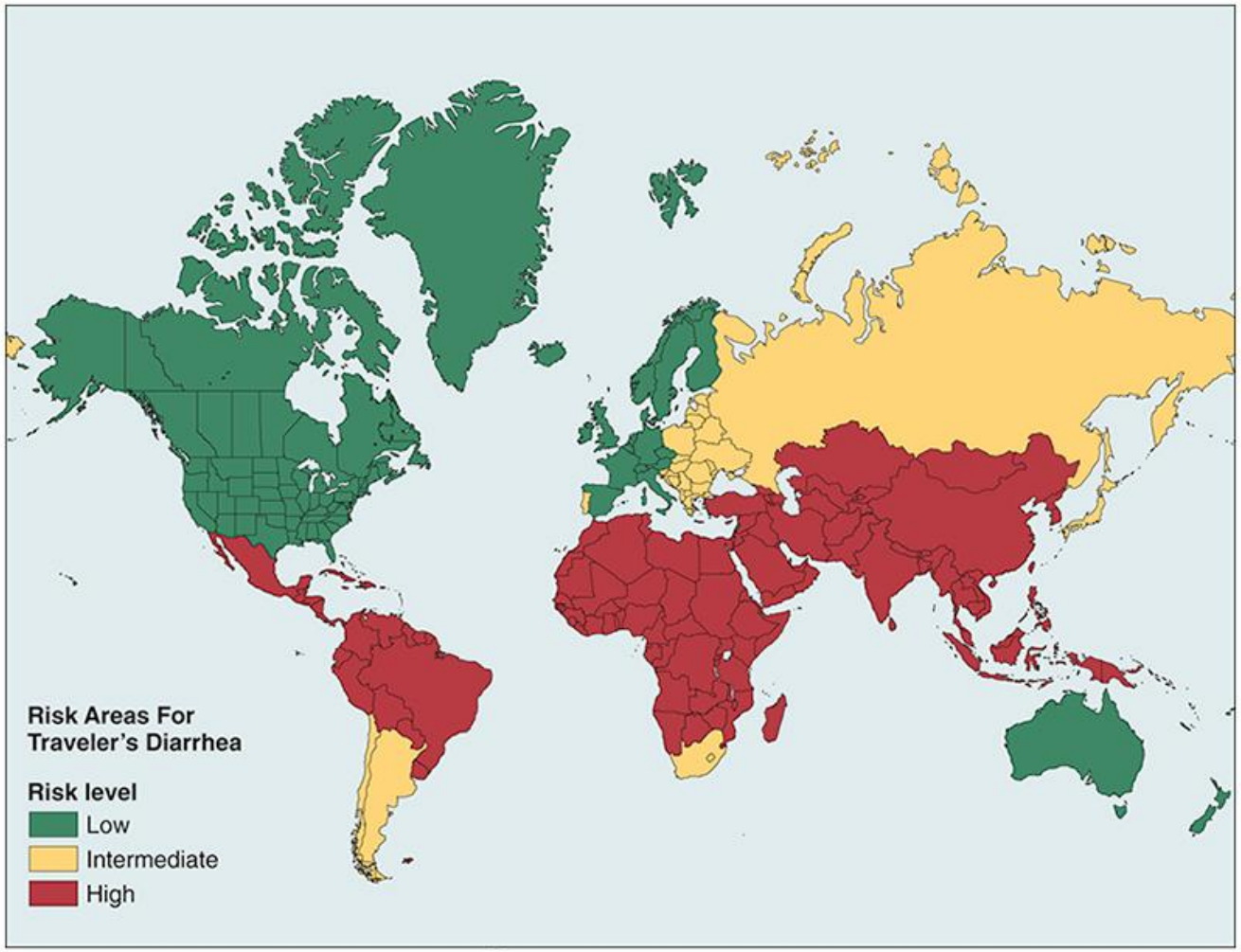
Average Incubation Period	Organism	Average Duration	Implicated Foods	Typical Symptoms	Comments
2–16 h	*Bacillus cereus*	1 day	Boiled and fried rice, meats, vegetables	Nausea, vomiting, (emetic) abdominal cramping, watery diarrhea	Produces two toxins, one emetic form that causes nausea and vomiting within hours, and one diarrheic form; common year-round; isolation of large numbers of bacteria from implicated foods and patient stool
6–72 h	*Vibrio parahaemolyticus*	3 days	Shellfish	Pain, vomiting, fever, watery diarrhea	Blood sometimes in stool; common in spring, summer, fall in coastal states; stool culture using TCBS medium recommended
6–72 h	*Vibrio cholerae*	3–7 days	Seafood, water	Rice water stools, severe diarrhea, no fever	No blood or mucus in stool; mechanism of action, in vivo enterotoxin production; no tissue invasion; stool culture using TCBS medium recommended
<8 h	*Staphylococcus aureus*	<1 day	Egg salad, meat, poultry, pastries	Abrupt onset of nausea, pain and projectile vomiting, infrequent diarrhea	Mechanism of action is preformed enterotoxin in foods; common in summer; ELISA or reverse passive latex agglutination enterotoxin test; gel electrophoresis in lieu of phage typing
8–22 h	*Clostridium perfringens*	1 day	Beef, poultry, gravy, fish	Abdominal cramping, watery diarrhea; vomiting and fever uncommon	In vivo enterotoxin production; unlike *Staphylococcus aureus*, viable organisms must be ingested for disease to occur; common in fall, winter, spring
12–48 h	*Salmonella* sp.	3 days	Eggs, dairy products, fowl, beef	Fever, abdominal cramping, diarrhea, mild vomiting	WBCs in stool; common in summer; culture and serologic identification
16–48 h	*Yersinia enterocolitica*	1 day to 4 weeks	Milk, pork	Fever, severe abdominal pain, diarrhea	WBCs and RBCs in stool; common in winter
18–36 h	*Clostridium botulinum*	Weeks-months	Vegetables, fruits (canned foods), fish, honey (infants)	Nausea, vomiting, diarrhea, paralysis	Mechanism of action is preformed neurotoxin; common in summer and fall
24–72 h	*Shigella* spp.	3 days	Egg and tuna salads, lettuce, milk	Fever, abdominal cramping, diarrhea, occasional vomiting	WBCs, RBCs, and mucus in stools; tissue invasion common mechanism of action; common in summer; culture and serologic identification
24–72 h	Enterotoxigenic *Escherichia coli*	3 days	Fruits, meats, pastries, salads	Abdominal cramping, watery diarrhea, no vomiting or fever	In vivo enterotoxin; major cause of traveler's diarrhea; year-round distribution; patient history includes travel to Mexico and other developing countries
24–72 h	Enterohemorrhagic *E. coli*	3 days	Undercooked ground beef, apple cider	Watery diarrhea progressing to bloody diarrhea, abdominal cramping, no fever or vomiting	Implicated shiga-toxin producing *E. coli*; organisms disappear rapidly from stool; culture of sorbitol-negative *E. coli* from stool using SMAC plate recommended

ELISA, Enzyme-linked immunosorbent assay; *RBCs*, red blood cells; *SMAC*, sorbitol MacConkey; *TCBS*, thiosulfate–citrate–bile salts–sucrose; *WBCs*, white blood cells.

Returning Travelers

- Common problem in patients visiting developing countries
- Most cases are often mild and self-limiting.
- Significant morbidity possible
- May disrupt traveler's itinerary
- Diarrhea usually occurs within the first 2 weeks of travel.
- Symptoms
  - Malaise, abdominal pain, fever, nausea, vomiting, and occasionally blood in the stool

Geographic Distribution of Risk for Traveler's Diarrhea



Immunocompromised Hosts

- Immunocompromised individuals increasing because of better treatments for chronic diseases
  - Lupus erythematosus
  - Crohn disease
- Other immunocompromising conditions
  - AIDS
  - Cancer patients
  - Transplantation recipients

Immunocompromised Hosts

- Higher risk for opportunistic pathogens causing disease
  - Bacteria
    - *Mycobacterium tuberculosis*, *Mycobacterium avium complex*
  - Virus
    - Cytomegalovirus (CMV)
  - GI histoplamosis
  - Parasites
    - *Cryptosporidium* (associated with HAART), *Cyclospora*, *Cystoisospora*, ~~and~~ *Microsporidia*, and *Strongyloides*

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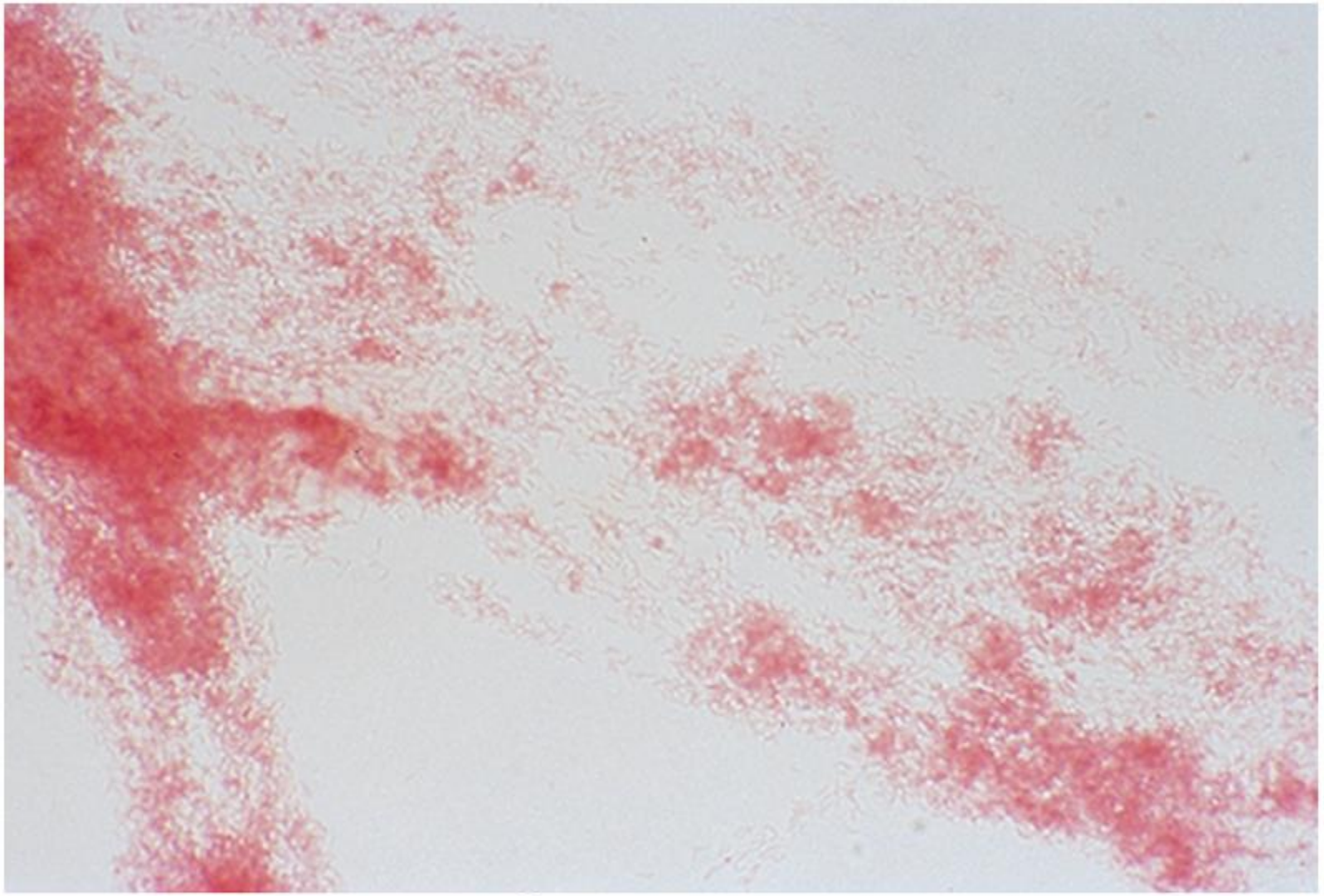
Gastrointestinal Infections & Food Poisoning – II

Laboratory Diagnosis of Gastrointestinal Pathogens

Specimen Collection and Handling/Direct Examination

- Fresh specimens are best for bacterial culture.
- Fresh or properly preserved for ova and parasite detection
- Direct microscopic examination
  - Fecal leukocytes
  - RBCs
  - Seagull-wing appearance suggests presence of
    - *Campylobacter* or *Vibrio*.

Gram Stain of *Campylobacter* Colony



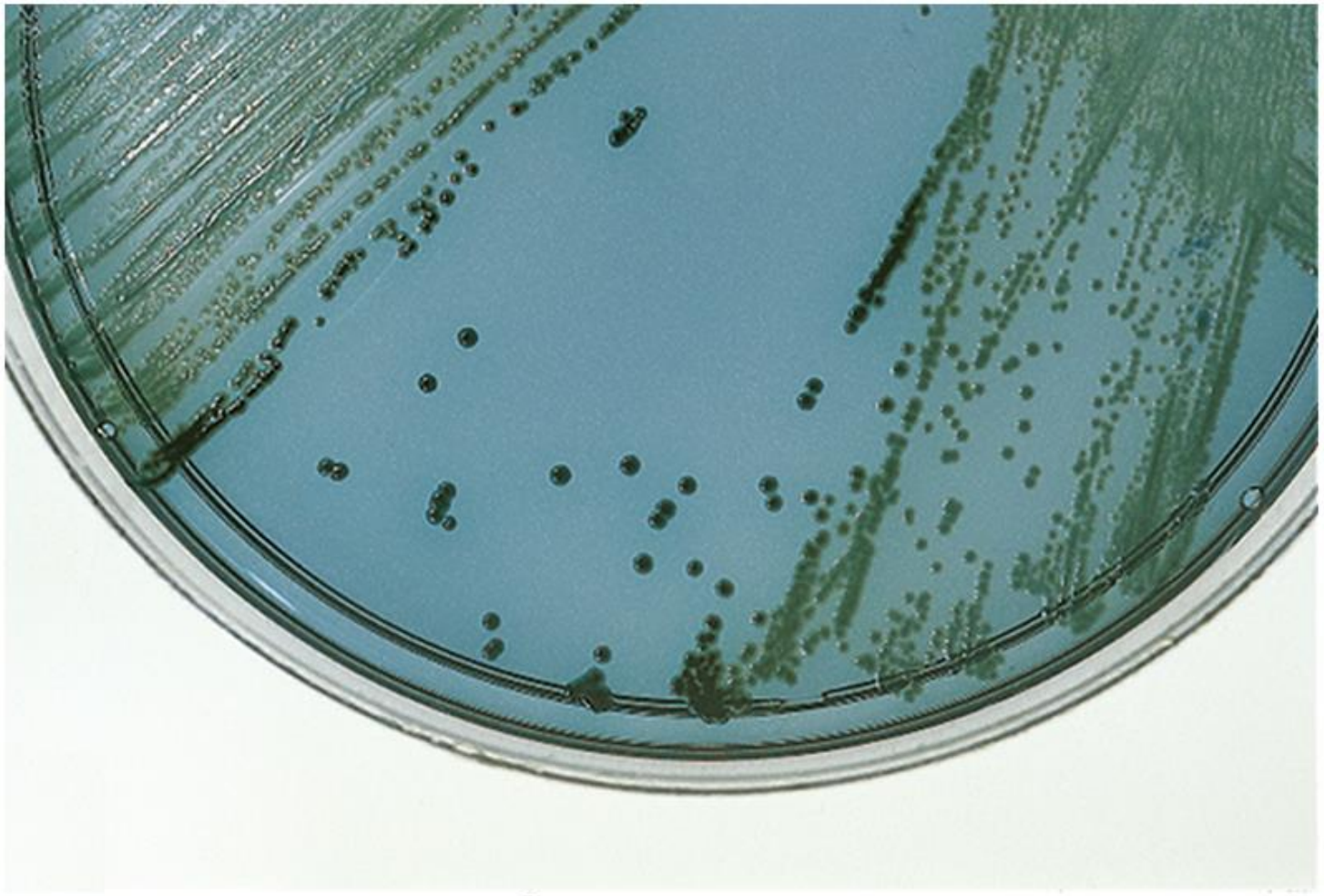
Culture

- Selective and differential culture media
  - Normal biota can mask pathogens; using appropriate media reduces normal biota.
  - Selective media
    - Contains antimicrobials or chemical
  - Differential media
    - Allows differentiation of bacterial species based on colony morphology
  - E.g., MacConkey (MAC), XLD, sorbitol MAC, Hektoen Enteric, and Salmonella-Shigella agars

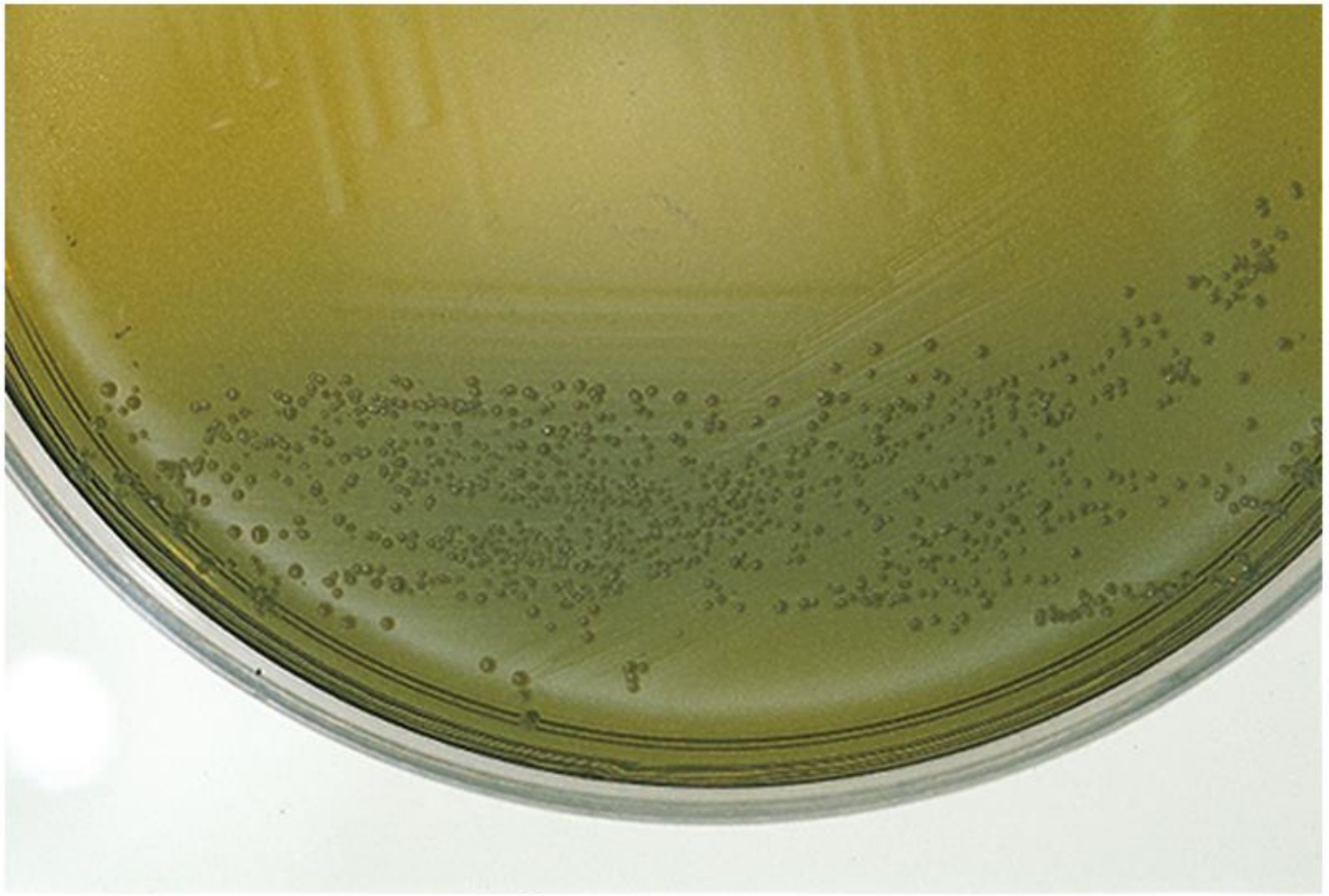
Organisms That Grow in Culture

- *Campylobacter jejuni*
- *Salmonella* spp.
- *Shigella* spp.
- *E. coli*
- *Yersinia* spp.
- *Vibrio* spp.
- *C. difficile*
  - Usually identified via toxin testing

Salmonella on Hektoen Enteric Agar

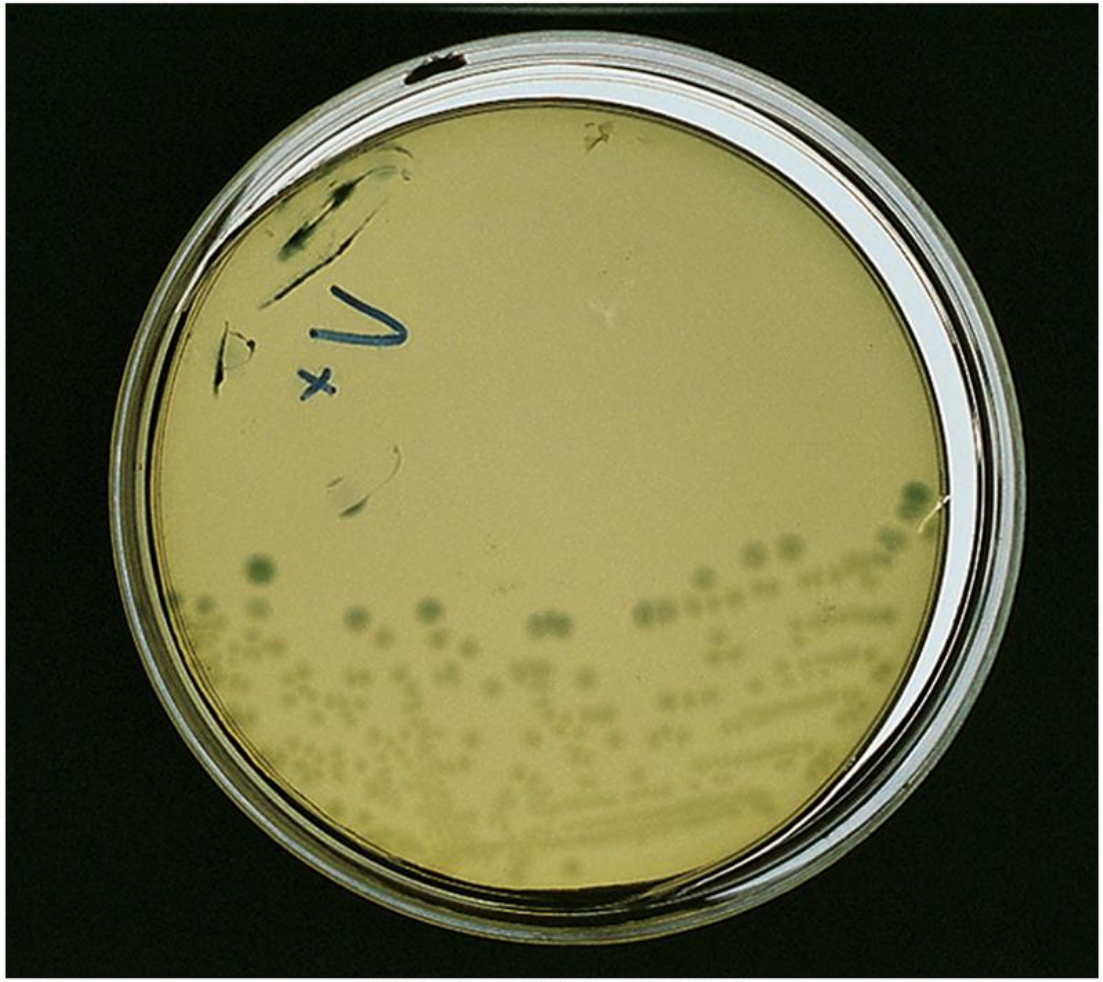


Shigella Growing on Hektoen Enteric Agar



E. coli O157:H7 on MAC and SMAC

Vibrio vulnificus on TCBS



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Gastrointestinal Infections & Food Poisoning – II

Treatment & Prevention for Diarrhea

Treatment Options

- Replenish electrolytes
  - Solution containing glucose and sodium
    - Occasionally intravenous fluids
- Antidiarrheal medications
  - Decrease symptoms
- Antimicrobial agents
  - Prophylaxis
  - May alleviate symptoms
- Bismuth subsalicylate (Pepto-Bismol)
  - May shorten disease course

Prevention Measures

- Prevention
  - Avoid high-risk foods and ice
  - Avoid foods prepared by another person and served undercooked or raw
  - Avoid dips and other foods left at room temperature
  - Properly cook foods such as poultry
  - Thoroughly wash all raw fruits and vegetables
- Vaccination
  - Rotavirus
  - *S.* Typhi

Points to Remember

- Factors that predispose patients to diarrheal illnesses include lack of clean drinking water, travel to endemic countries, history of GI disease, immunocompromised state, and medication intake.

Points to Remember (Cont.)

- Travel history and a detailed dietary history provide significant information when determining the cause of the diarrheal disease. Certain foods such as meat, shellfish, and poultry serve as vehicles of foodborne disease.
- Foodborne diseases are transmitted and acquired by ingestion of contaminated food and beverages.

Points to Remember (Cont.)

- Clinical presentations can be characterized as enterotoxin-mediated diarrhea, invasion of bowel mucosa, or invasion with lymphatic or metastatic spread of infection.
- Food poisoning may be caused by chemical intoxications from fish or shellfish consumption, as well as bacterial toxins.

Points to Remember (Cont.)

- Appropriate laboratory diagnosis may include the use of direct microscopy and selective culture media to recover and identify the suspected causative agent.