Infectious Diseases

Lesson 7

GASTROINTESTINAL AND HEPATOBILIARY INFECTIONS

Part A – Infectious Diarrhea

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Objectives and learning goal

Objective

To review all clinically relevant knowledge on infectious diarrhea, including the diverse etiology and the principles of treatment in the different clinical scenarios

Learning goal

To know how to properly manage a patient with infectious diarrhea in the different epidemiological and clinical settings

Contents

- Epidemiology an classification of infectious diarrhea
- Bacterial diarrhea: etiology, epidemiology and pathogenesis
- Bacterial diarrhea: clinical manifestations
- Bacterial diarrhea: diagnosis
- Bacterial diarrhea: treatment and prevention
- Antibiotic-associated diarrhea
- Viral diarrhea
- Chronic infectious diarrhea
- Infectious diarrhea in immunocompromised hosts
- Key messages
- Further reading

Epidemiology and classification of infectious diarrhea

Definitions

- Diarrhea, depending on duration:
  - **Acute**: lasts < 14 days
  - **Persistent**: lasts > 14 and < 30 days
  - **Chronic** : lasts > 30 days
- Diarrhea, depending on affected region:
  - Gastroenteritis – stomach and small intestine
  - Enteritis – small intestine
  - Colitis – large intestine or colon

Epidemiologic features - I

- Second most common infection, after respiratory infections
- More than **2 million deaths** annually worldwide, almost all of them in developing countries
- Estimated incidence in developed countries, 1 episode per person per year

Epidemiologic features - II

- Generally a benign condition in developed countries, but life-threatening cases exist, especially in:
  - Infants and young children
  - Elderly people or debilitated people
- Transmitted through:
  - **Food**
  - Water
  - Person-to-person
  - Animal-to-person

Epidemiologic features - III

- Condition that favors infectious diarrhea: lack of basic **hygiene**
- Persons at special risk:
  - Children, especially in daycare centers
  - Institutionalized individuals, particularly those mentally ill

Classification of infectious diarrhea

- Acute:
  - Bacterial
  - Antibiotic-related
  - Viral
- Chronic:
  - Parasitic related
  - Diarrhea in the immunocompromised host

Bacterial diarrhea: etiology, epidemiology and pathogenesis

Concept and overall etiology

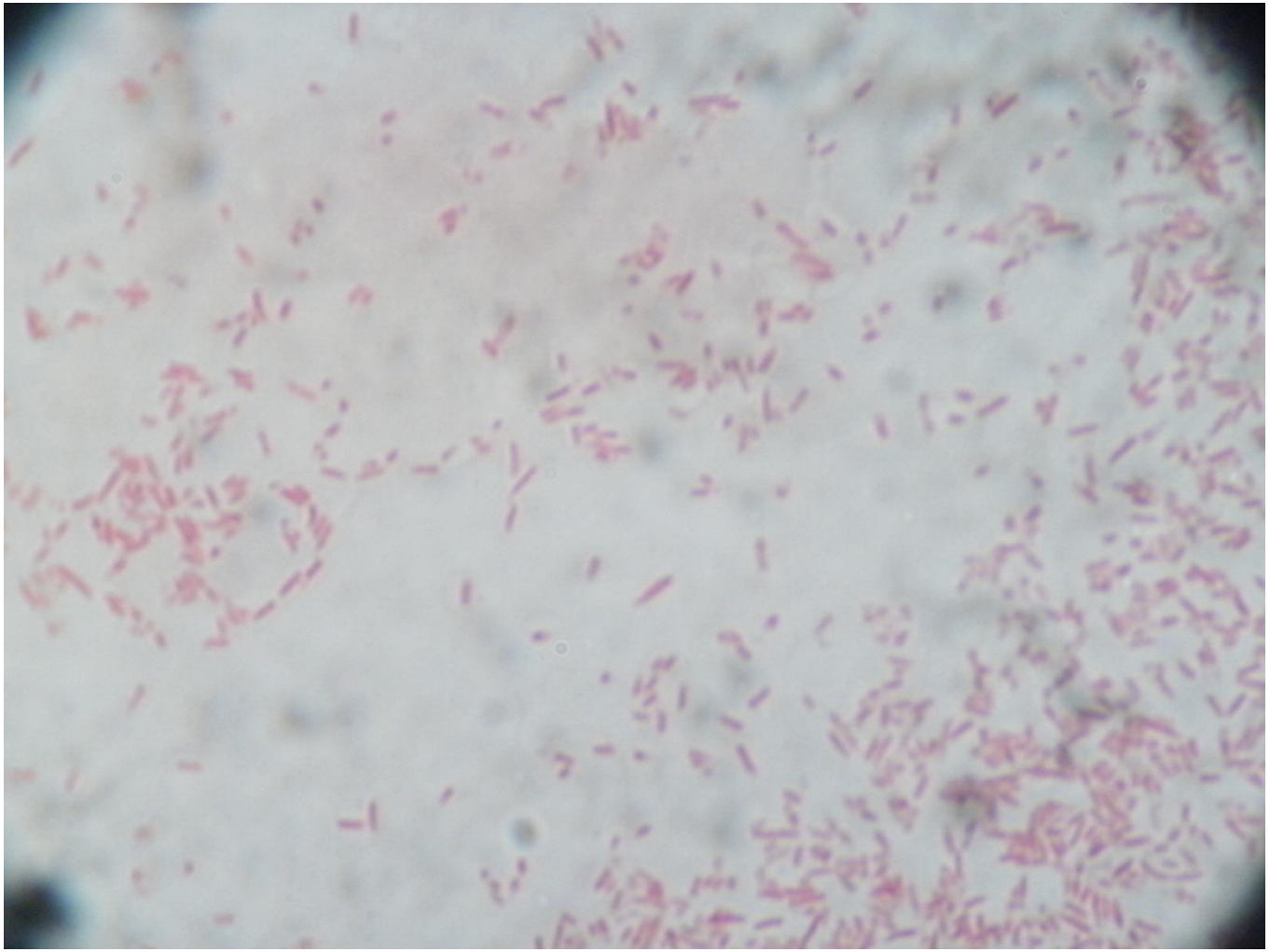
- Acute and generally self-limiting
- The three most common causes:
  - ***Salmonella* spp**
  - *Shigella* spp
  - ***Campylobacter* spp**
- Other: *Escherichia coli*, *Vibrio parahaemolyticus*, and *Yersinia enterocolitica*

General characteristics of etiologic agents

- Each pathogen:
  - Has a unique life cycle and virulence characteristics
  - Survive in a distinct environment
  - Has his own mode of transmission
  - Require a different inoculum size to cause disease
- The various causes of acute bacterial diarrhea are usually not distinguishable clinically
- Diagnosis requires isolation of the organism on stool culture

Salmonella spp. – Microbiology and epidemiology

- Aerobic gram-negative bacillus, readily grows on simple culture media, motile, and most strains do not ferment lactose
- Clinical classifications of *Salmonella* spp.:
  - **Typhoidal**: *S. typhi* and *S. paratyphi*
  - **Nontyphoidal**: *S. enteritidis*, *S. typhimurium*, and *S. choleraesuis*
- *S. typhi* rarely infects animals
- The other species infect both wild and domestic animals



Salmonella spp.

Salmonella spp. – Pathogenesis I

- Attach to intestine epithelial cells, and inject the cells specific proteins that favor their entry → replication → **cell lysis** and invasion of **lymph nodes** and **blood** → endovascular and other local infections
- *S. typhi* is particularly adept at surviving within cells, causes little intestinal epithelial damage, and primarily enters the lymph nodes and bloodstream
- *S. choleraesuis* is the nontyphoidal species more adept at invading the bloodstream

Salmonella spp. – Pathogenesis II

- 10^4 to 10^8 organisms required to produce disease in healthy volunteers
- Stomach **acidity kills** many *Salmonella* → risk of infections increased in:
  - Gastrectomy patients
  - Those who use antacids
- Antibiotic treatment → ↓ intestinal flora → ↓ **competition for nutrients** and *Salmonella* spp. more readily multiply

Salmonella spp. – Pathogenesis III

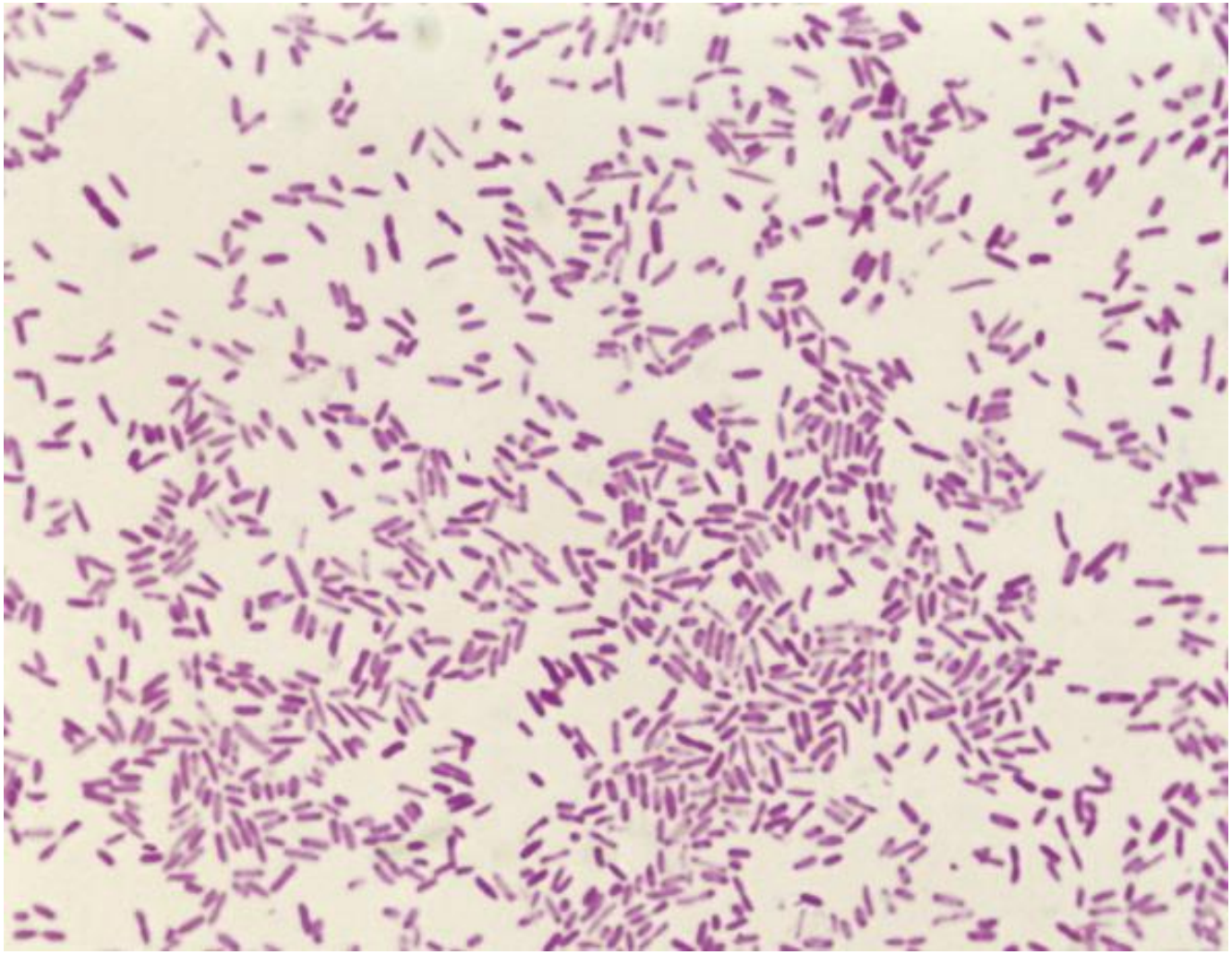
- Depressed immune function increases the risk, as in:
  - AIDS
  - Lymphoma and other neoplasms
  - Sickle cell disease → osteomyelitis
- **Chickens** often excrete *Salmonella* spp. in their stools and eggs → undercooked chicken and egg products are frequent source of infections
- Many other foods, contaminated from human or animal feces

Salmonella spp. – Pathogenesis IV

- Water, outbreaks in developing countries
- More common in summer months, as warmer temperatures allow the organism to multiply more rapidly on contaminated foods

Shigella spp. – Microbiology

- Facultative anaerobe, gram-negative bacillus, readily grows on simple culture media, nonmotile, and does not ferment lactose
- Major serologic groups, A through D, and major species:
  - **Group B *Shigella flexneri***
  - **Group D *S. sonnei***
  - Group A *S. dysenteriae*
  - Group D *S. boydii*



Shigella spp.

Shigella spp. – Pathogenesis I

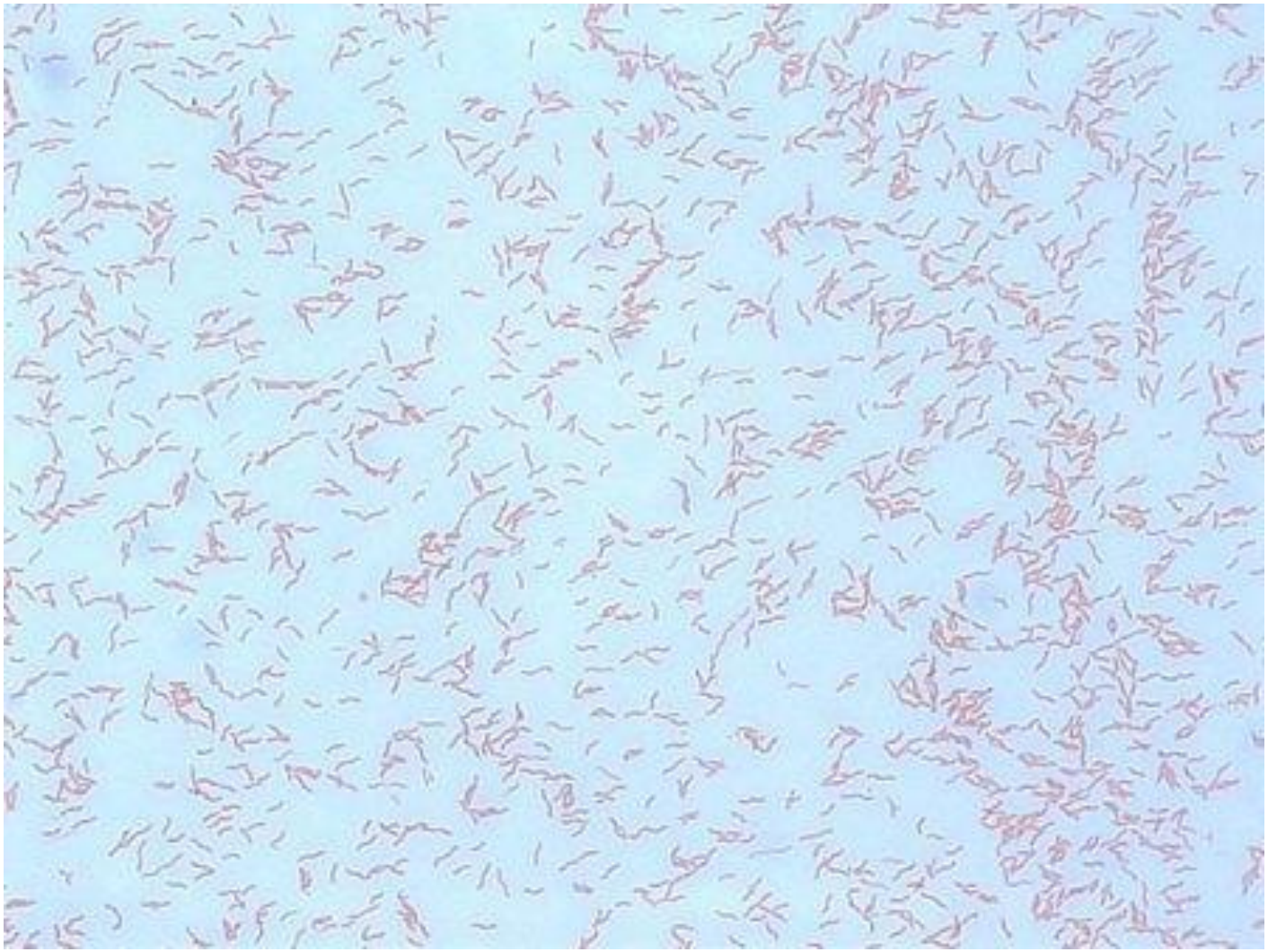
- *Shigella* surface proteins favors its entrance into intestinal epithelial cells and M cells
- Also injects the epithelial cells specific proteins that facilitates its entry
- A surface **hemolysin** and other properties allow an efficient spread from cell to cell
- Cytotoxic **Shiga** toxin → premature cell death → superficial ulcers in the bowel mucosa and extensive inflammation that usually prevents bloodstream entry

Shigella spp. – Pathogenesis II

- As few as 200 bacteria can cause disease
- Shigella can survive in the stomach for several hours
- The first few days reside in the small intestine, then invade de colon, where cause intense inflammation, microabscesses and mucosal ulcerations
- Reside only in the intestine of humans
- Seizures, leukemoid reactions, reactive arthritis, and hemolytic uremic syndrome
- **Person to person, anal-oral**, food, water, flies

Campylobacter spp. – Microbiology

- Comma-shaped, gram-negative rod, paired in a distinctive seagull shape, microaerophilic
- Other bowel floras often overgrow on routine medium, so selective Campy–BAP medium is recommended
- ***C. jejuni*** the strain that most commonly causes diarrhea
- *C. fetus*



Campylobacter spp.

Campylobacter spp. – Pathogenesis I

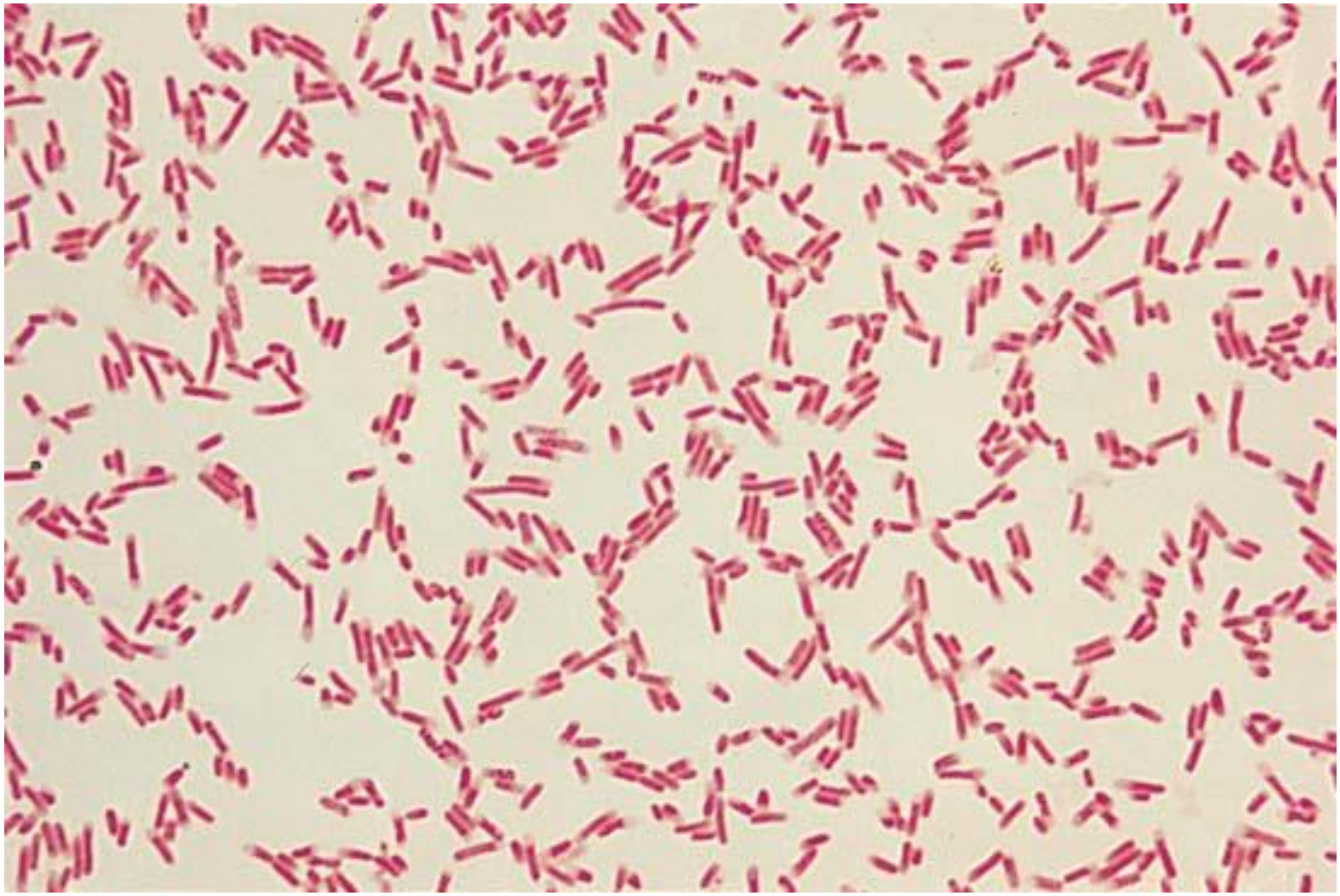
- **Fibronectin-binding protein CadE** and other proteins important for adherence to host cells
- Intestinal epithelial cells ingest *Campylobacter* utilizing **pseudopods** enriched in microtubules
- Inflammation through protein NOD1
- **Cytolethal distending toxin** (Cdt) that acts as a DNAse cleaving nuclear DNA
- ***C. fetus* subspecies *fetus***: little diarrhea, but resistant to the bactericidal activity of serum → bacteremia → vascular infections, soft tissue abscesses, and meningitis

Campylobacter spp. – Pathogenesis II

- Sensitive to acid, large numbers of organisms (more than 10^4) required to cause disease
- *C. jejuni* frequently contaminates **poultry**, can also be carried in water, raw milk, sheep and other animals
- More common in the summer months, as *C. jejuni* grows best at high temperatures
- Reactive arthritis and Guillain-Barré syndrome after *C. jejuni* infection

Escherichia coli – Microbiology

- Facultative, gram-negative, rod-shaped bacterium
- **Nonpathogenic** strains of *Escherichia coli* normally **colonize** the bowel
- Pathogenic strains of *E. coli* that cause diarrhea:
  - Cannot easily be distinguished from nonpathogenic
  - Have antigens with pathogenic roles:
    - O, lipopolysaccharide
    - H, flagellar
  - Five classes based on their mechanisms of virulence



Escherichia coli

Escherichia coli – Enterotoxigenic strains

- Colonize the **small bowel** and produce a cholera-like or heat-stable **toxin** that stimulates secretion of chloride, causing watery diarrhea
- Contracted from water contaminated with human sewage
- Most common in developing countries
- A major cause of traveler's diarrhea

Escherichia coli – Enteroaggregative strains

- Adhere in large **aggregates** to human **colonic** mucosa
- Produce a low-molecular-weight **enterotoxin** that causes watery diarrhea, often prolonged
- Contracted by ingesting contaminated water or food
- In developing countries and is the second most common cause of traveler's diarrhea

Escherichia coli – Enteropathogenic strains

- Adhere to the **small bowel**
- Induce the polymerization of actin filaments to form a **pedestal** directly beneath the site of attachment
- Mild inflammation
- Usually causes watery diarrhea
- Transmitted by contaminated **food** or **water** and by **person-to-person** spread in nurseries
- More common in developing countries

Escherichia coli – Enterohemorrhagic strains

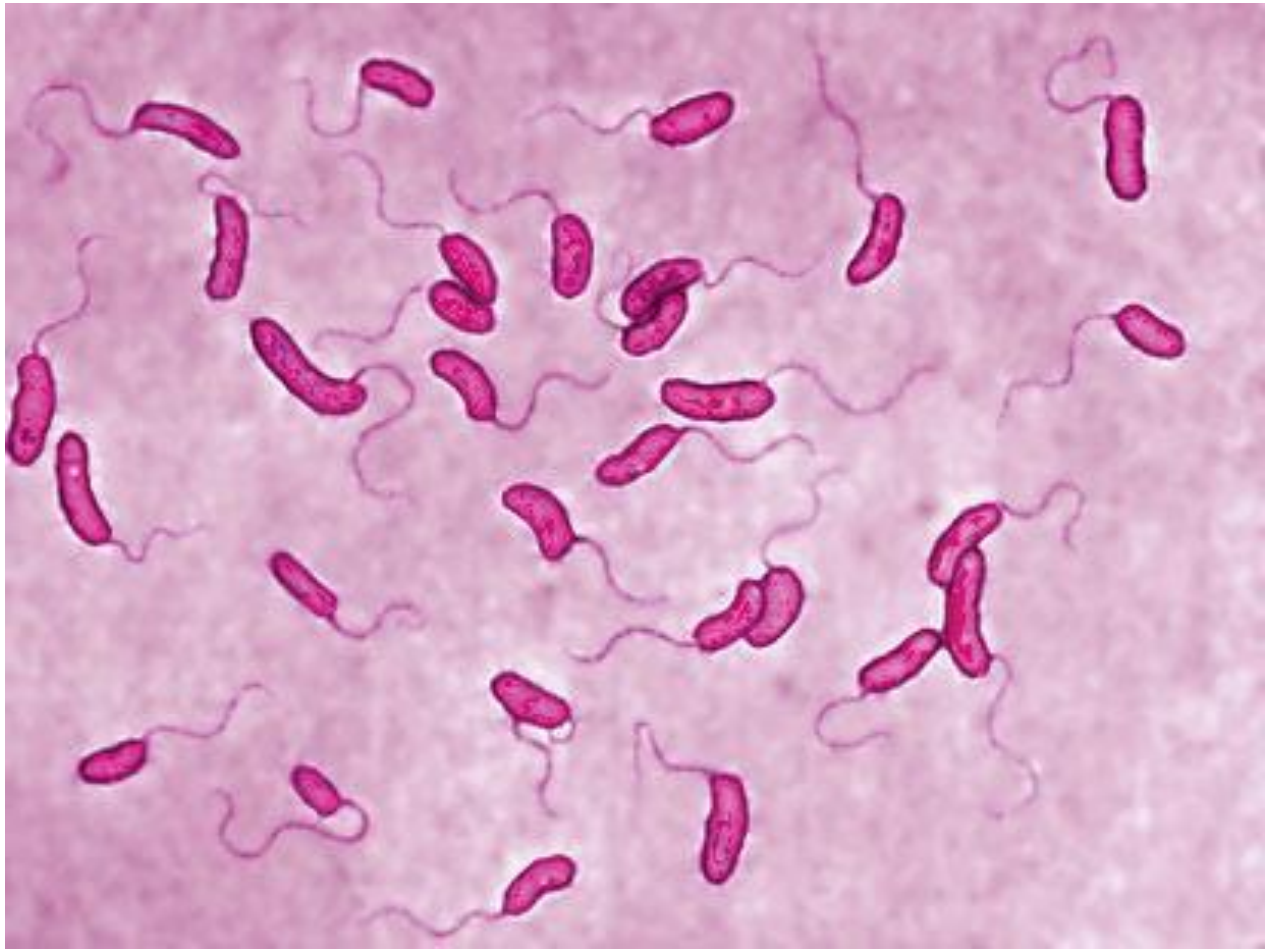
- Strains that produce **Shiga-like cytotoxins**:
  - Inhibit protein synthesis and cause **cell death**
  - Damage vascular **endothelium** of **bowel** and **glomeruli**, causing **hemorrhagic inflammatory colitis** and the **hemolytic uremic syndrome**, strains O157:H7 and others
- Most commonly associated with ingestion of undercooked contaminated ground beef
- Less commonly, unpasteurized milk, spinach, lettuce, mayonnaise, etc.
- In industrialized nations, during the summer months

Escherichia coli – Enteroinvasive strains

- **Invade** colonic epithelial cells by the same mechanisms that *Shigella* spp. uses
- Do not produce toxins, but cause an inflammatory colitis indistinguishable from that caused by *Shigella* spp.
- A large inoculum (10^8 organisms) needed to cause disease
- Associated with contaminated foods in developing countries

Vibrio cholerae – Microbiology

- Small, slightly curved gram-negative rod
- A single flagellum at one end causes the bacterium to move erratically under the microscope
- Present in contaminated **water** or food
- Neutralization of stomach acid favors infection
- Dormant state that impedes to be cultured
- Can form a “rugose”, aggregate of bacteria surrounded by a biofilm that blocks killing by disinfectants



Vibrio cholerae

Vibrio cholerae – Pathogenesis

- Attaches to the small intestine wall, where it produces **cholera toxin** → specific receptor in the mucosa → activates adenylate cyclase → ↑ cyclic adenosine monophosphate → secretion of chloride and water → voluminous watery diarrhea → shock and death
- Non- cholera toxin strains → mild gastroenteritis
- Large epidemics or pandemics
- During the hot seasons of the year

Vibrio parahaemolyticus

- Halophilic ("salt loving"), grows in marine environments
- **Enterotoxin** and causes moderate bowel **inflammation**
- **Hemolytic** strains → mild to moderately severe diarrhea
- Nonhemolytic strains are almost always avirulent
- Raw shellfish is the primary cause of human disease

Yersinia enterocolitica

- Aerobic, gram-negative bacillus
- Large numbers must be ingested to cause disease (10^9)
- Primarily invades the mucosa of the terminal ileum → **painful enlargement of the mesenteric nodes**
- Usually occurs in children
- From contaminated meat or milk; can **grow at 4 °C**, so refrigerated meats are a particular concern
- Most cases during **winter** months

Other bacteria

- *Staphylococcus aureus*, toxin related gastroenteritis
- *Bacillus cereus*, toxin related gastroenteritis

Bacterial diarrhea: clinical manifestations

Concept and incubation

- The most common clinical picture is **enterocolitis**, that consist of diarrhea, abdominal pain, vomits
- Approximate incubation period
  - *Staphylococcus aureus*, toxin: a few hours
  - *Salmonella* spp.: 8–24 hours
  - *Shigella* spp.: 36-72 hours
  - Enterohemorrhagic *Escherichia coli*: 4 days

Physical examination

- Fever common, usually in the 38 °C - 39 °C, but patients with **enterohemorrhagic *E. coli* are often afebrile**
- Hyperactive bowel sounds, increased peristalsis
- Diffuse tenderness, but not guarding or rebound in most cases
- Fluid loss can be profound, leading to hypotension

Blood analyses

- Leukocyte count normal, or moderate leukocytosis
- Electrolyte abnormalities
- Positive blood cultures are common in *Salmonella* spp. infection, but are rare in *Shigella* spp. or *C. jejuni* infections

Main determinants of clinical manifestations

- Causing microorganism
- Region del intestine predominantly affected
  - Small bowel
  - Distal small bowel and large bowel or colon

Small bowel infections

- Region with secretory functions → profuse watery diarrhea and vomits
- Enterotoxins play an important role
- Colicky pain, meteorism
- Low grade or no fever
- Stool: no blood cells

Distal small bowel and colon infections (dysentery)

- Region with absorptive functions → small stool volume
- Mucosal inflammation generally present
- Important role of invasive properties and cytotoxins of bacteria
- Tenesmus and marked pain on defecation
- Fever is very common
- Stool: red blood cells and white blood cells

Bowel regions predominantly affected by every bacterium

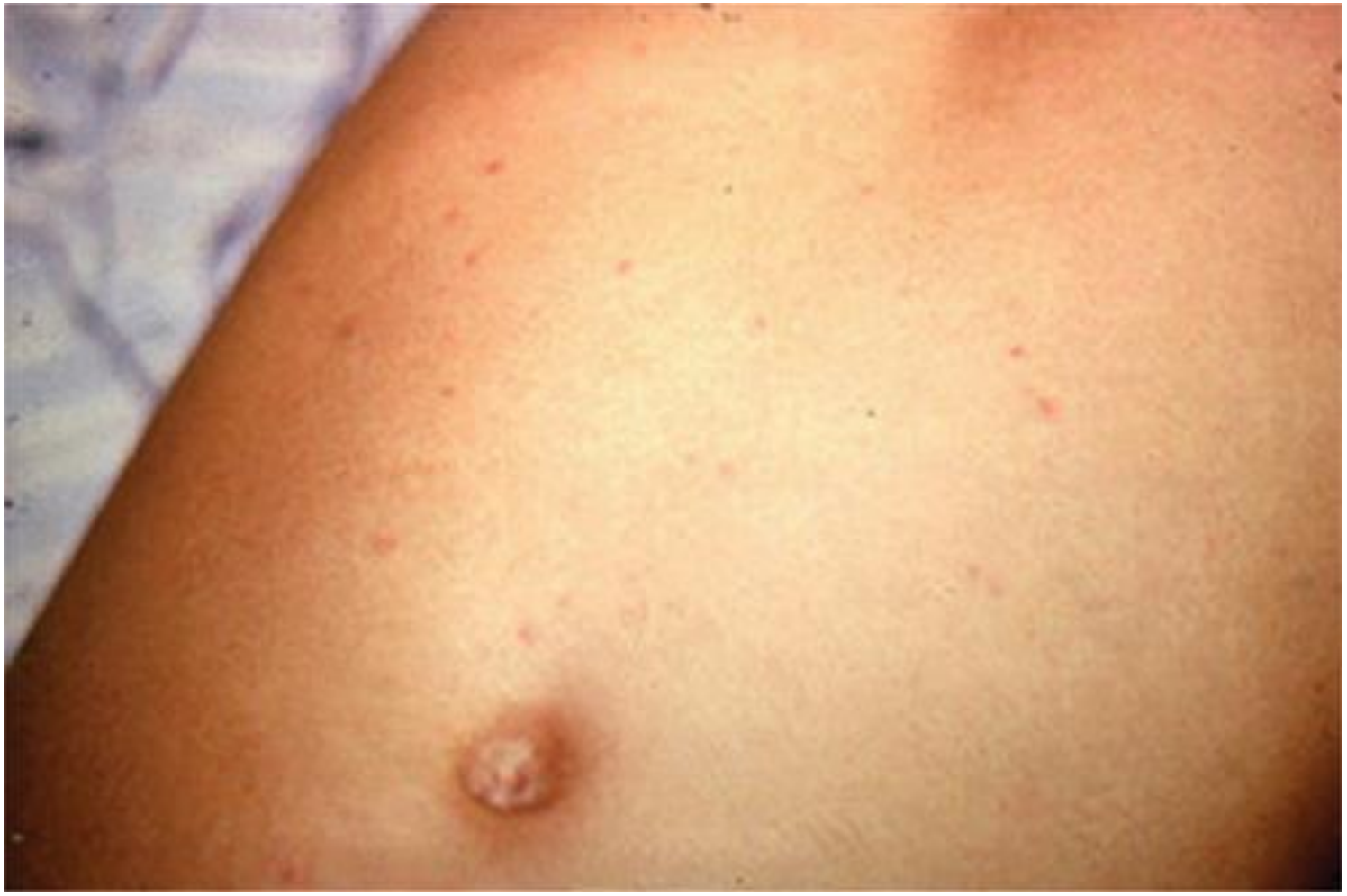
Proximal small bowel	**Distal small bowel and colon**
•***Salmonella* spp.** •Other *Escherichia coli* •*Clostridium perfringens* •*Vibrio cholerae* •*Staphylococcus aureus* •*Bacillus cereus*	•***Campylobacter* spp.** •***Shigella* spp.** •**Enterohemorrhagic and enteroinvasive *Escherichia coli*** •*Yersinia* spp. •*Vibrio parahaemolyticus*

Enteric fever or typhoid fever - Symptoms

- ***S. typhi,*** *S. paratyphi, C. fetus* & *Y. enterocolitica*
- Incubation 8–14 days, longer with low inoculum
- 1st week: fever, flu-like symptoms, constipation
- 2nd week: high fever, bloody diarrhea, abdominal pain and distension, mental status may dull
- 3rd week: in the absence of antibiotic treatment, most patients recover, but 10% die of septic shock or bowel perforation

Enteric fever or typhoid fever - Physical exam

- Pulse may inappropriately slow despite the high fever (temperature–pulse dissociation)
- Abdomen often markedly distended and tender during the later phases of the disease
- Splenomegaly in a significant percentage
- 2nd to 3rd week: 2-5 mm rose-spots on the upper abdomen and chest; persist for 2-4 days



Rose spots in typhoid fever

Enteric fever or typhoid fever – Laboratory and treatment

- Normochromic normocytic anemia
- Leukopenia
- Blood cultures positive, especially 1st week
- Stool cultures positive for many weeks

- Treatment: ciprofloxacin or ceftriaxone

Bacterial diarrhea: diagnosis

Direct examination of stool I

- Using **methylene blue** stain, presence of polymorphonuclears suggests:
  - Bacterial enterocolitis
  - Amoebic dysentery
  - Antibiotic-associated pseudomembranous colitis
- **Abundant** polymorphonuclears are seen in *Shigella* spp., *Campylobacter* spp., and enteroinvasive *E. coli*
- *S. typhi* may demonstrate increased numbers of fecal monocytes

Direct examination of stool II

- Determination of fecal **lactoferrin**, a protein of polymorphonuclears, is more sensitive and specific for diagnosis of acute bacterial enterocolitis and differentiate the disease from viral gastroenteritis
- Gram stain: seagull-shaped gram-negative forms highly suggestive of *Campylobacter* spp., etc.

Culture of stool

- Positive only in 5% of cases, indicated in:
  - Severe disease in which hospitalization is being considered
  - Patients with bloody diarrhea
  - When an outbreak is suspected
- Stool sample should be planted immediately
- *Campylobacter* spp., special selective media required
- Pathogenic strains of *E. coli* cannot be readily identified by culture; immunologic and molecular biologic methods are required

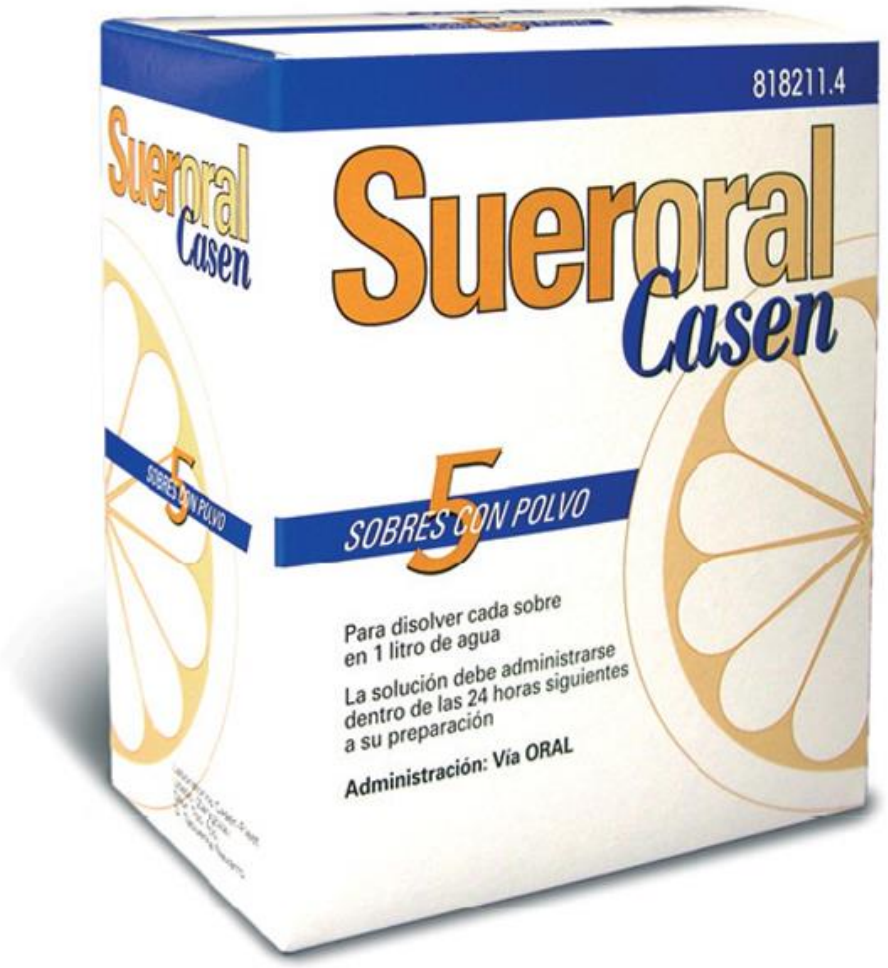
Other tests of stool

- Slide agglutination using specific antiserum
- Polymerase chain reaction tests
- DNA hybridization tests
- Important: **inform the Microbiology laboratory if an etiologic suspicion exists**

Bacterial diarrhea: treatment and prevention

Treatment principles

- Most cases self-limiting, usually lasting 3-7 days, and only require symptomatic treatment
- **Fluid and electrolyte replacement** is the most important supportive measure
  - Oral rout if possible, WHO recommended solution:
    - 1 L water
    - 3.5 g ClNa
    - 2.9 g $Na_3C_6H_5O_7$ (trisodium citrate) or 2.5 g NaHCO3
    - 1.5 g ClK
    - 20 g glucose or 40 g sacarose
- Intravenous route if patient is vomiting



WHO recommended oral rehydration solution

Antibiotic use

- Generally not recommended
- *Salmonella* spp. enterocolitis: they prolong carriage in the stool, but generally recommended in:
  - Traveler's diarrhea
  - Neonates
  - Elderly and immune-compromised
  - Patients with prosthetic valves or synthetic vascular grafts
- **Contraindicated in enterohemorrhagic *E. coli* infection**, because they may exacerbate the hemolytic uremic syndrome

Antibiotic election

Empiric	Ciprofloxacin or azithromycin
Salmonella spp.	None or ciprofloxacin
Campylobacter jejuni	Azithromycin or ciprofloxacin
Staphylococcus aureus toxin	None
Bacillus cereus toxin	None
Shigella spp.	Ciprofloxacin or azithromycin
Yersinia spp.	Ciprofloxacin or doxycycline
Vibrio cholerae	Doxycycline or ciprofloxacin
Non-enterohemorrhagic *E. coli*	Ciprofloxacin
Alternative in many cases	Trimethoprim-sulfamethoxazole

Other recommendations

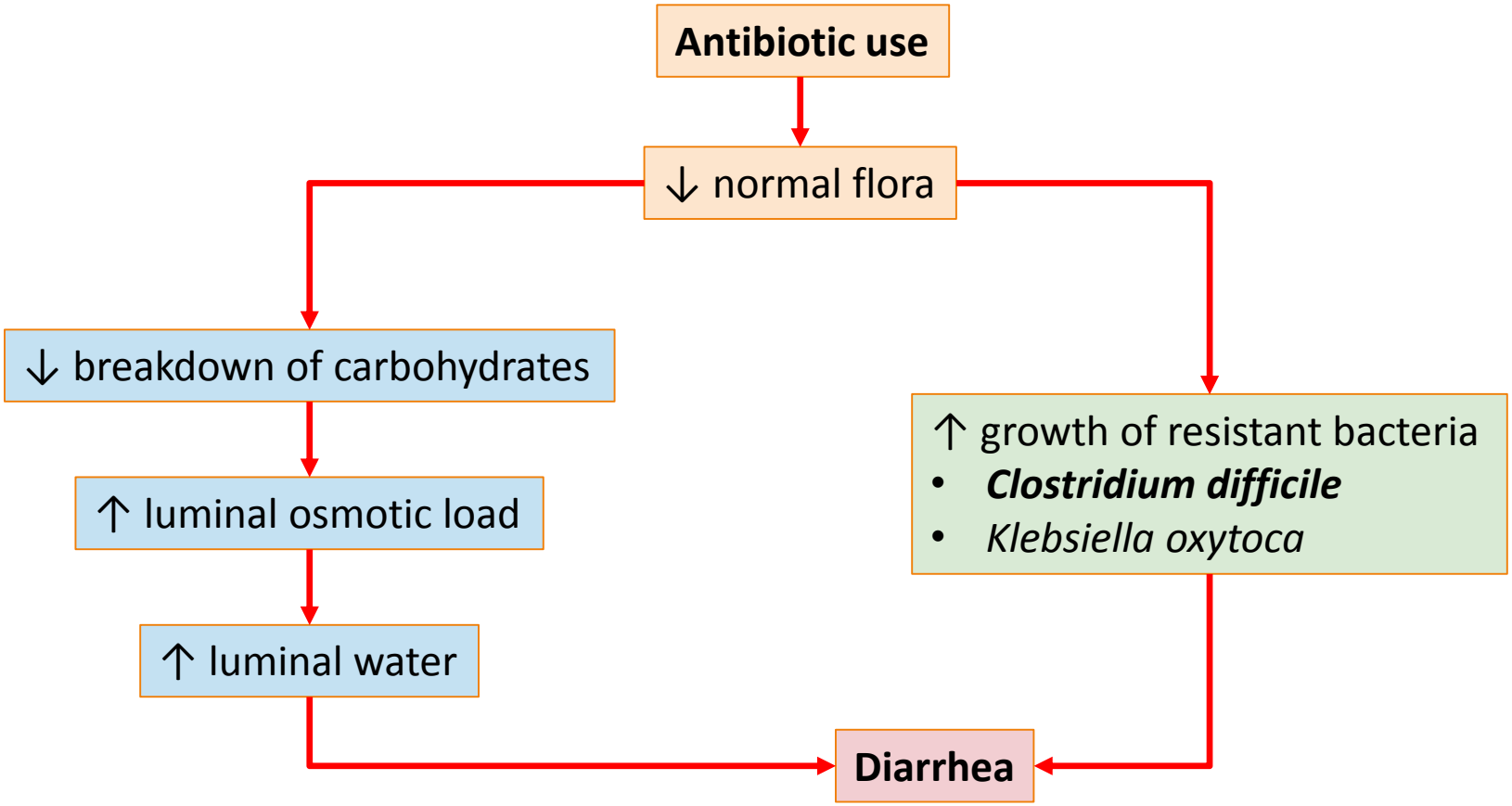
- Agents that slow peristalsis:
  - Are contraindicated in patients with fever or bloody stools
  - May prolong fever, increase the risk of bacteremia, lead to toxic megacolon, and prolong fecal excretion of the pathogen
- On recovery
  - Easily digestible diet (non-elaborated food)
  - Avoid lactose-containing food

Prevention

- Public health measures are the most efficient and cost-effective way of reducing these diseases
- *Salmonella* spp. fecal carriage may continue for long, particularly if antibiotics used; health hazard for food handlers; amoxicillin or fluoroquinolone for 4-6 weeks can eradicate; gallstones difficult carrier state elimination
- To prevent (and treat) traveler's diarrhea: rifaximin

Antibiotic-associated diarrhea

General concept



Epidemiology

- Antibiotic-associated diarrhea develops in up to 30% of hospitalized patients
- The most frequent cause is **osmotic** diarrhea
- The 2nd most frequent cause is ***C. difficile***:
  - Causes diarrhea in 10% of patients hospitalized > 2 days
  - Is implicated in
    - 20-30% of antibiotic-associated cases of diarrheas
    - 50-75% of antibiotic-associated cases of colitis
  - Rarely cause of diarrhea in outpatients

Microbiology

- ***Clostridium difficile***, anaerobe, spore-forming, gram-positive rod
- Difficult to isolate on routine media
- Toxins A and **B**, bind to and kill cells in the bowel wall
- Both toxins affect the actin cytoskeleton and weaken intracellular cell–cell tight junctions
- Hyper-virulent strain, resistant to fluoroquinolones, **NAP1**, → high quantities of toxins A and B and an additional binary toxin
- *Klebsiella oxytoca* → cytotoxin → hemorrhagic colitis

Pathogenesis of *C. difficile* diarrhea I

- Death of colonic cells caused by *C. difficile* → shallow ulcers, acute inflammation, and **pseudomembranes**
- Factors that favor the disease:
  - Old age
  - Severe underlying diseases
  - Gastrointestinal surgery
  - Use of broad-spectrum **antibiotics**, anticancer **chemotherapy**, bowel **enemas** or **stimulants**, **enteral feedings**, and close proximity to another **patient with C. difficile diarrhea**

Pathogenesis of *C. difficile* diarrhea II

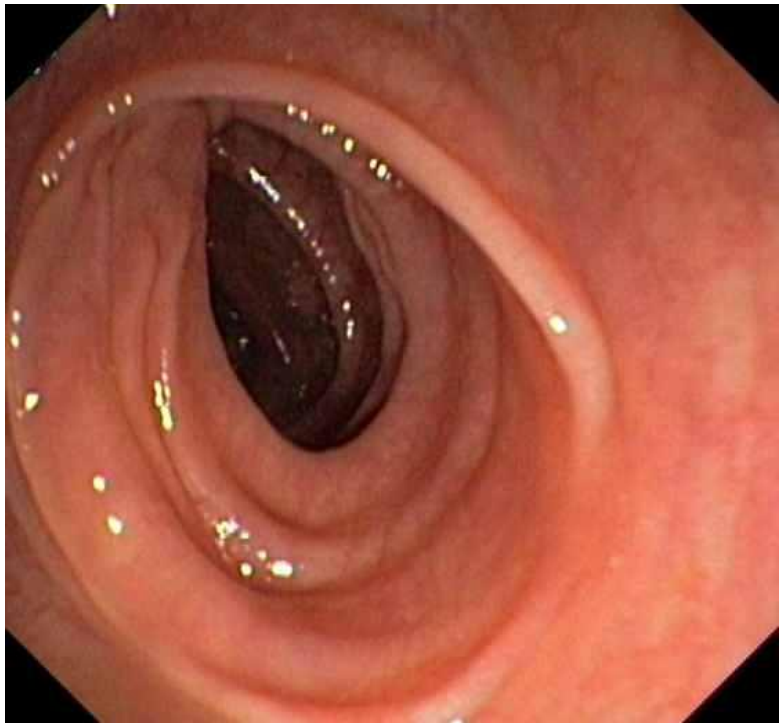
- Spreads from patient to patient by **hospital personnel**
- Spores can be readily carried on hands, clothes, or stethoscopes
- Hospital outbreaks, more commonly on wards where **clindamycin** is frequently used

Clinical manifestations of *C. difficile* diarrhea I

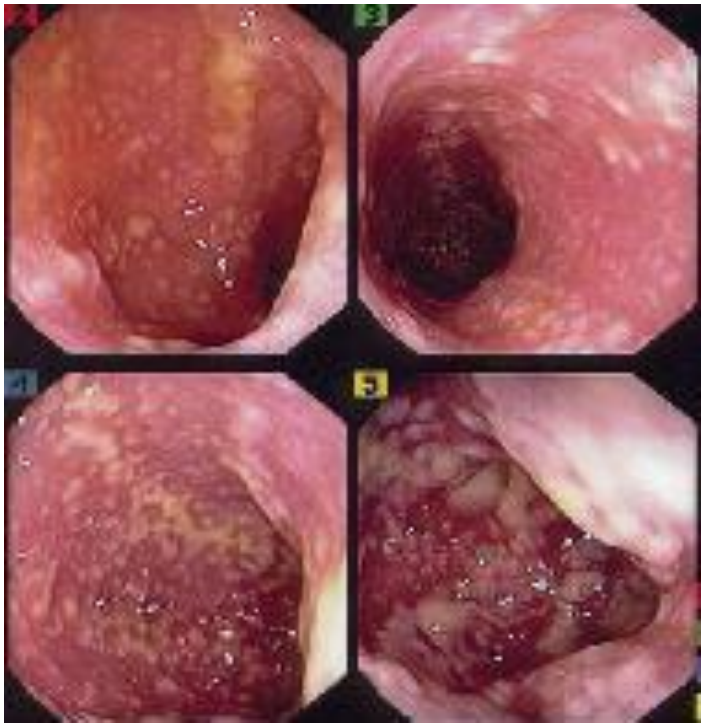
- From an **asymptomatic** carrier state to **fulminant** colitis
- Severity may relate to the number of toxin receptors in the host's bowel
- High titers of IgG against toxin A appear to be protective

Clinical manifestations of *C. difficile* diarrhea I

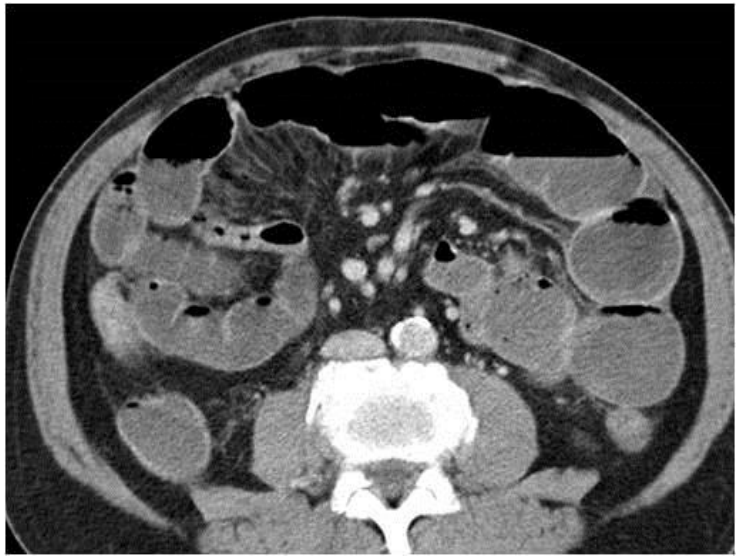
- **Diarrhea without colitis**: the most common symptomatic form:
  - Usually begins 5-10 days after the initiation of antibiotics, but can develop up to 10 weeks later
  - 5-15 watery bowel movements daily
  - Crampy, low abdomen pain, decreases after bowel movements
  - Low-grade fever, mild peripheral blood leukocytosis
- **Pseudomembranous colitis**: the same symptoms and findings, but **pseudomembranes** are seen on colonoscopy and **marked thickening of the colonic bowel wall** is seen on computed tomography scan



Normal



Pseudomembranous colitis



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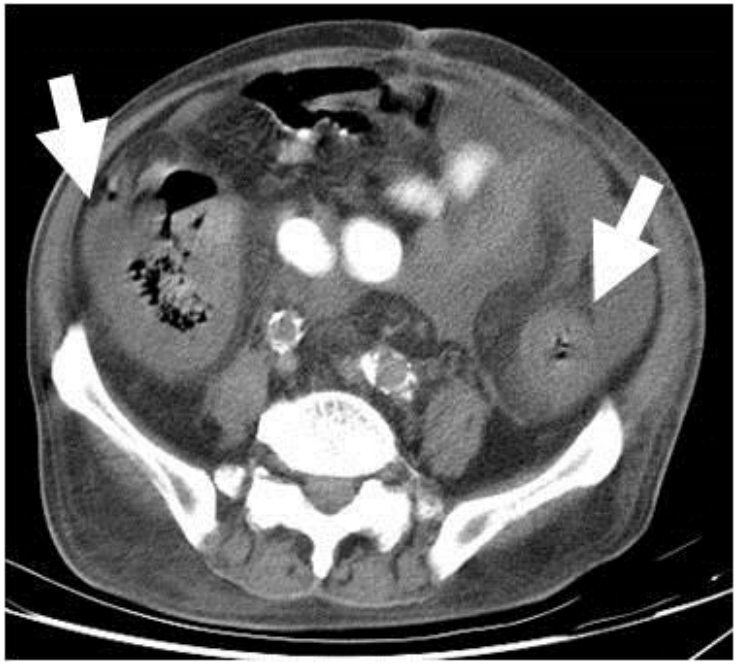
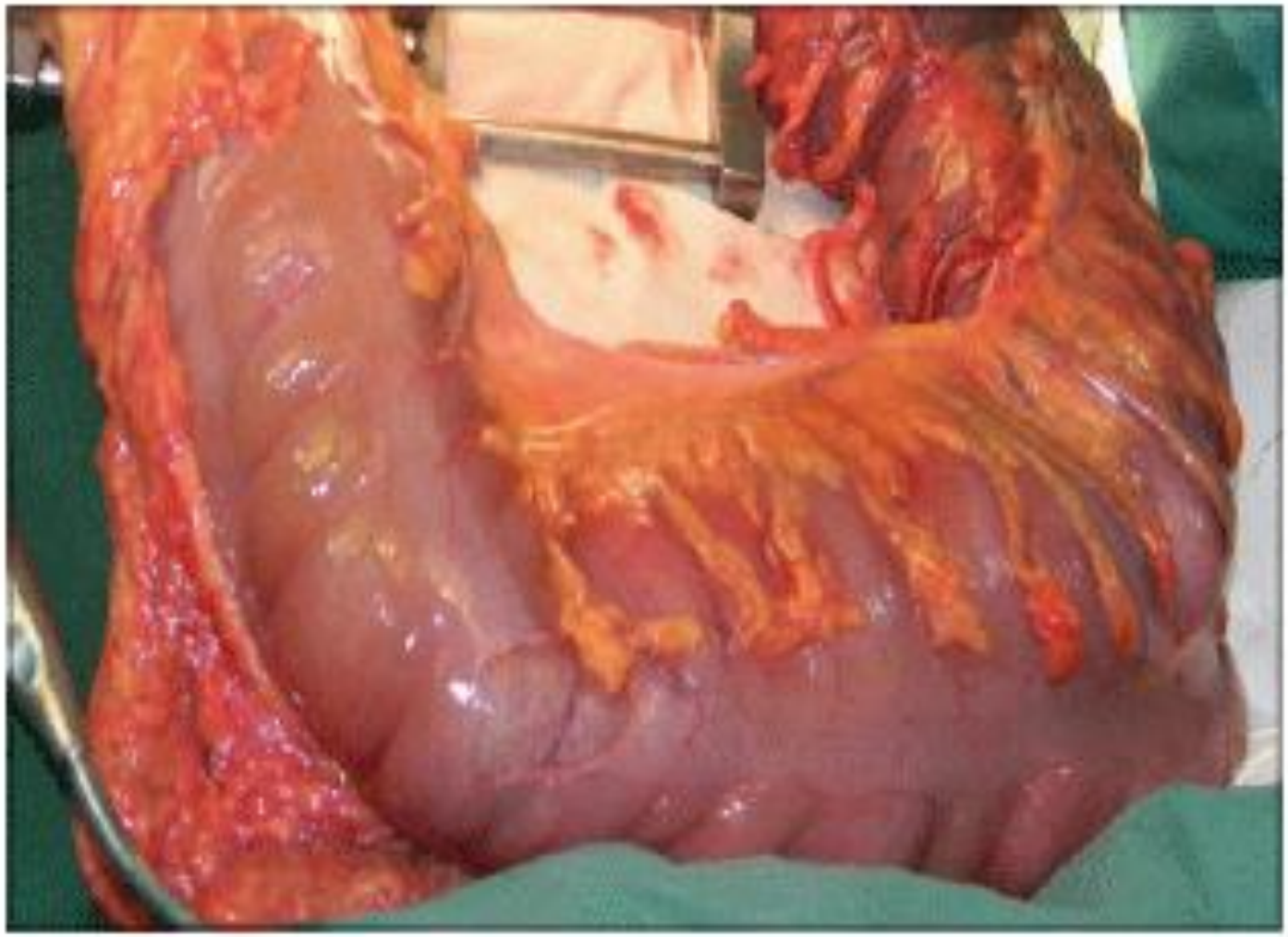


Pseudomembranous colitis

Clinical manifestations of *C. difficile* diarrhea II

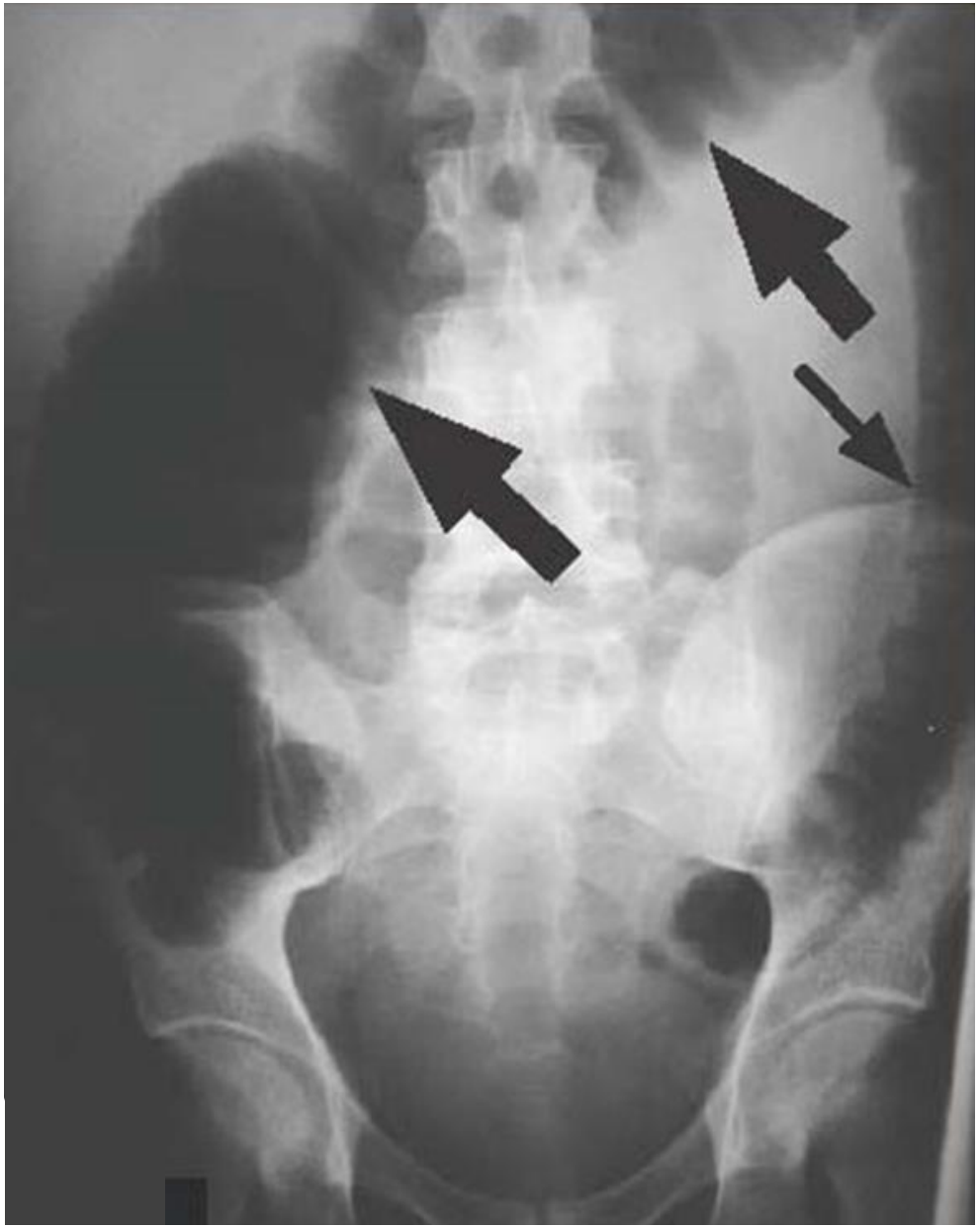
- **Fulminant colitis**:
  - In 2-3% of patients infected with *C. difficile*
  - Severe morbidity and high mortality
  - Diarrhea is usually present; however constipation is possible
  - Abdominal pain usually diffuse and severe
  - Hypoactive bowel sounds, abdominal distension, and guarding
  - Bowel perforation and peritonitis may occur
  - **Toxic megacolon** (bowel dilated > 7 cm), a feared complication



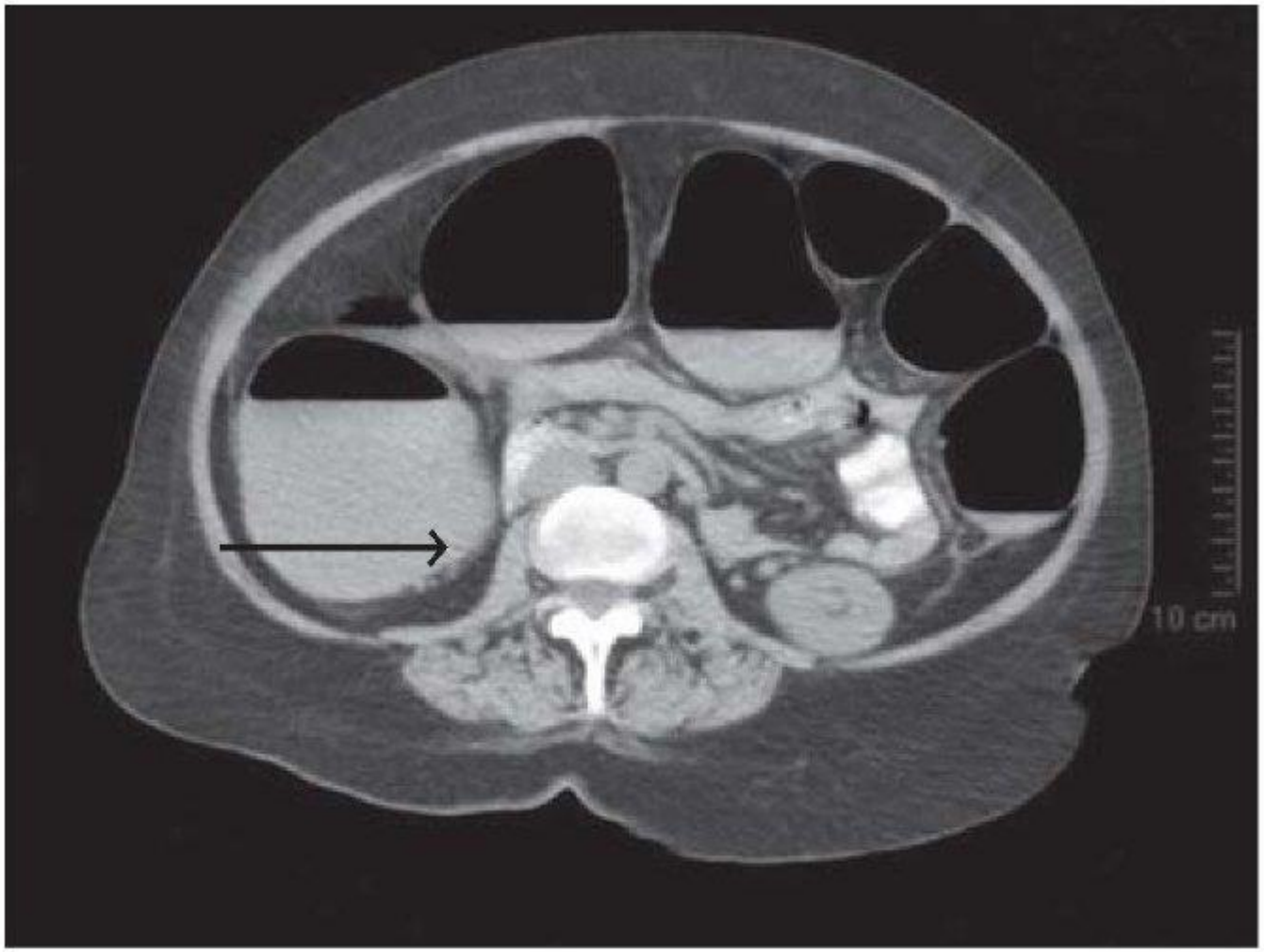
Toxic megacolon

Clinical manifestations of *C. difficile* diarrhea III

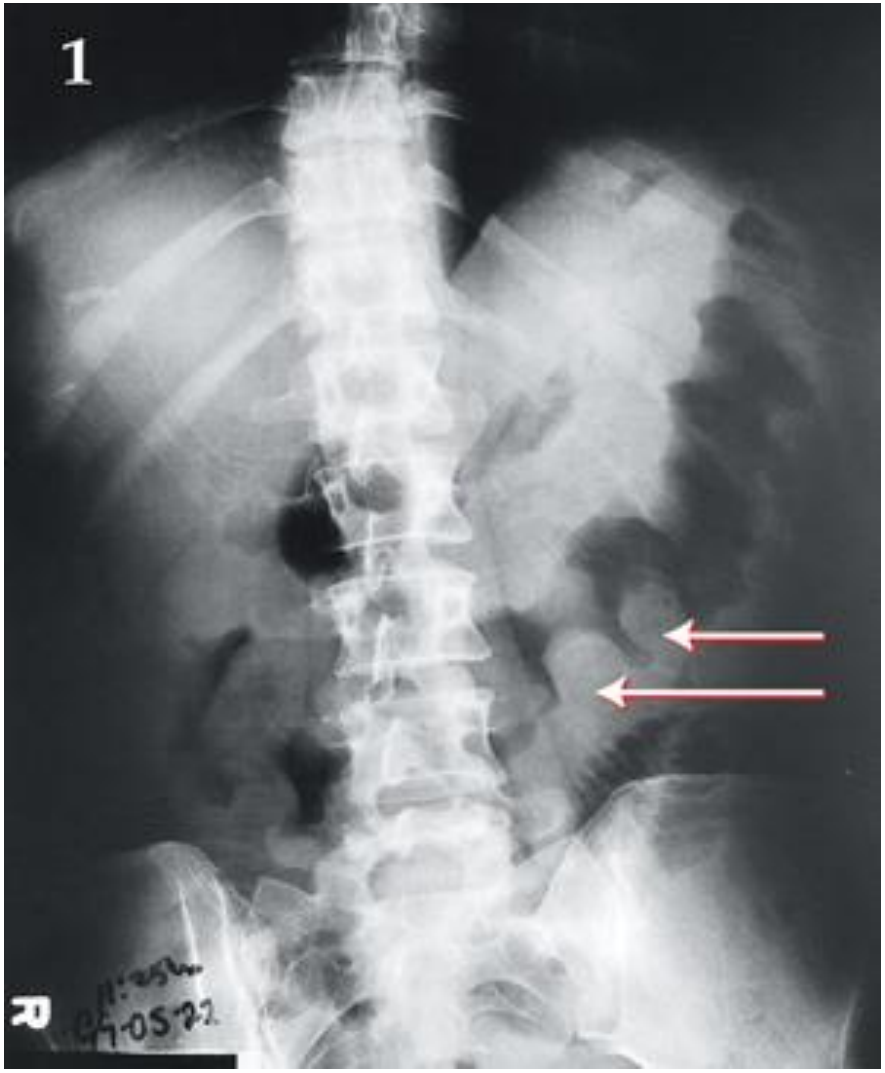
- **Fulminant colitis (continued)**:
  - Full-thickness involvement of the bowel → bowel distension and air-fluid levels visible on abdominal CT scan or X-ray
  - Thumbprinting, reflecting submucosal edema, mimic bowel ischemia
  - Sigmoidoscopy performed cautiously, high risk of perforation
  - ↑↑ peripheral leukocyte count (25,000-35,000/mm^3)
  - Lactic acidosis may indicate impending bowel perforation and irreversible bowel damage that requires immediate surgical intervention
  - Stool smear: polymorphonuclears, blood



Toxic megacolon



Toxic megacolon, pneumatosis intestinalis (arrow)



Thumbprinting

Diagnosis of *C. difficile* diarrhea

- Stool culture: difficult and many false positive results
- Cytotoxicity assay, sensitivity 94-100% and specificity 99%, expensive and requires 2-3 days
- ELISA detection of toxins A and B, comparable specificity and sensitivity 70-90%
- PCR detection of the **genes** for both toxins is now preferred, sensitivity nearly 100% and specificity 97%, assays that detect both toxins preferred
- Sigmoidoscopy is usually not required

Differential diagnosis of *C. difficile* diarrhea III

- Antibiotics associated osmotic diarrhea, characteristics:
  - Lack of fever or leukocytosis
  - Absence of polymorphonuclears in the stool
  - Improvement when oral intake is reduced
- Other causes of diarrhea
  - Parasites
  - Bacteria
  - Inflammatory bowel disease
  - Etc.

Treatment of *C. difficile* diarrhea

- Whenever possible **discontinue the offending antibiotic**
- Avoid antiperistaltic agents → ↑ risk of toxic megacolon
- Fluids and electrolytes replaced
- **Oral** (or IV) **metronidazole** → oral vancomycin
- Asymptomatic patients colonized with *C. difficile* should not be treated
- Recurrent disease is common as a consequence of residual spores that are not killed by the antibiotics, treatment: fidaxomicin → rifaximin

Prognosis and prevention of *C. difficile* diarrhea

- Toxic megacolon and bowel perforation arise in 0.4-4 % of patients, but have a mortality rate of 30-50 %; surgery is frequently needed
- Standard infection control measures must be scrupulously followed to prevent hospital personnel from spreading *C. difficile* spores from patient to patient
  - Physical hand washing
  - Prolonged broad-spectrum antibiotics avoided if possible
  - Limit the use of clindamycin

Viral diarrhea

General characteristics

- Viruses cause **most cases of acute diarrhea**
- Viral diarrhea is usually watery, mild, and self-limited
- The viruses most commonly associated with viral diarrhea are:
  - **Noroviruses**
  - Rotaviruses
  - Enteric adenoviruses
  - Astroviruses

Norovirus

- Single-stranded RNA, belonging to the **calicivirus** family
- **Blunting of villi** and **polymorphonuclear infiltration** of the lamina propria in the jejunum
- Shed in vomitus and stool in high concentrations
- Ingestion of as few as 18 viral particles can cause disease
- Transmitted by water, food and person-to-person
- Relatively resistant to chlorine and heat resistant
- Outbreaks in **winter** months

Rotavirus

- Double-stranded RNA, member of the **reovirus** family
- Replicate in villous epithelial cells of small intestine →:
  - Loss of absorption by epithelial villi
  - **Lactase** and other disaccharidases deficiency
  - Increase chloride secretion
- The most common cause of infant diarrhea
- Fecal–oral transmission
- Resistant to hand washing and to many disinfectants, but inactivated by chlorine
- Most common during **winter** months

Other virus

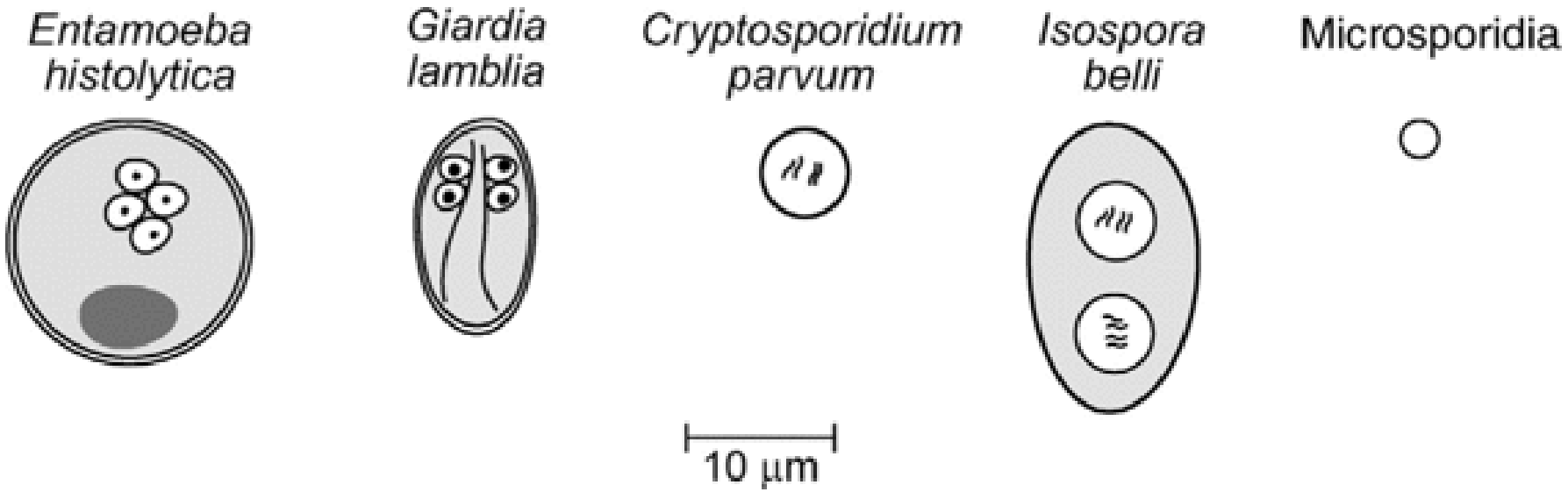
- Enteric adenoviruses
  - Double-stranded DNA, two serotypes, 40 and 41
  - Second most frequent cause of nonbacterial gastroenteritis in infants and young children
  - Most commonly during summer months
- Astrovirus
  - Single-stranded RNA
  - Outbreaks of gastroenteritis in children on pediatric wards and in elderly patients in nursing homes

Clinical features, diagnosis, prevention and treatment

- From mild watery diarrhea with minimal symptoms to severe nausea, vomiting, abdominal cramps, headache, myalgias, and fevers of 39 °C
- Stool smear reveals no leukocytes, and cultures are negative for bacteria
- Identification of the specific viral agent is usually not possible, requires electron microscopy, etc.
- PCR to identify norovirus, ELISA assays for rotavirus
- Maintaining hydration is the primary goal of therapy
- A rotavirus vaccine exists

Chronic infectious diarrhea

Causative agents of chronic infectious diarrhea



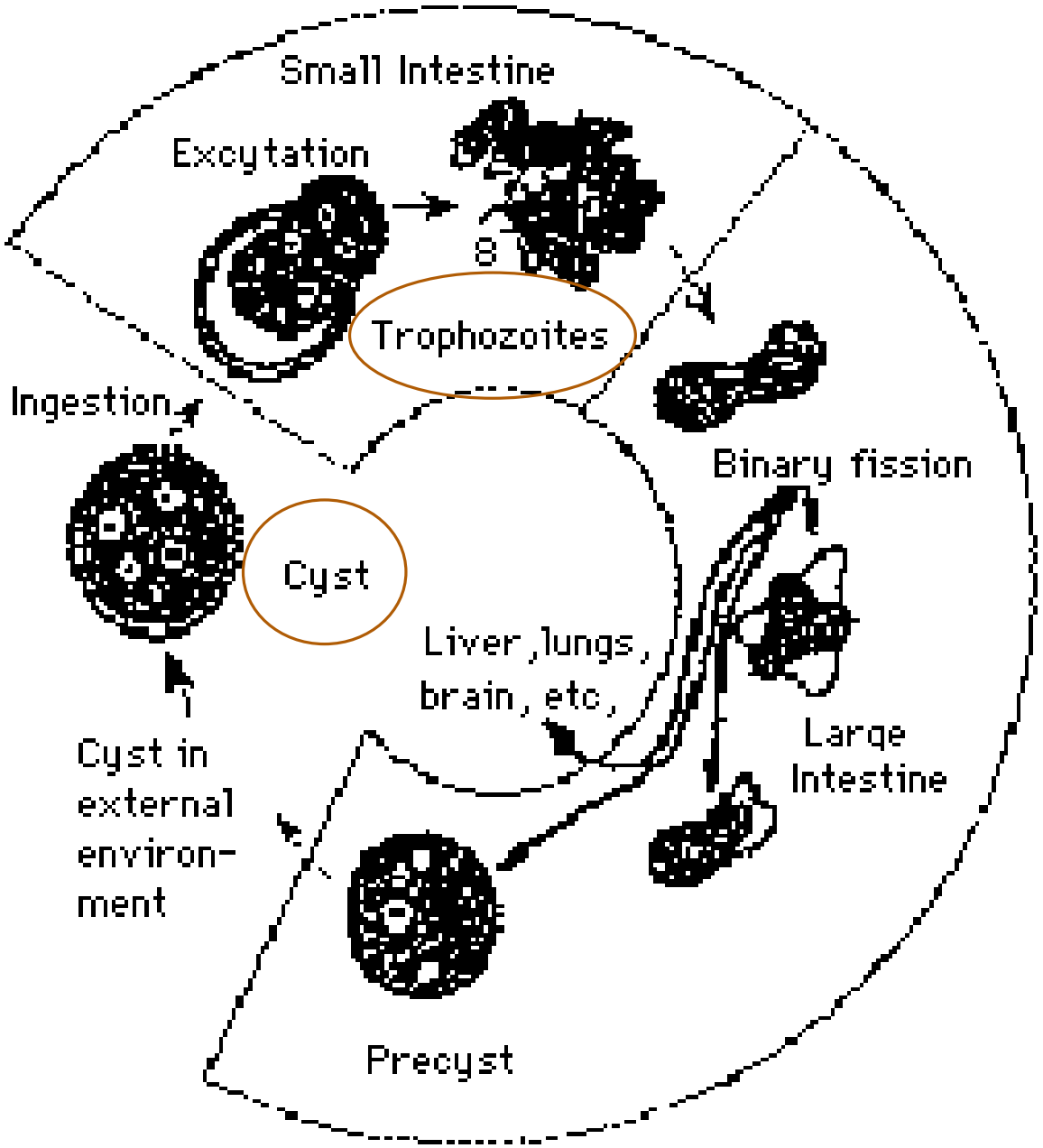
Entamoeba histolytica (amoebiasis) – Pathogenesis I

- Enteric anaerobic protozoan, trophozoite and cyst
- Other *Entamoeba* spp. do not cause disease
- *E. histolytica* trophozoite attaches to host cells, and rapidly kill them by releasing **proteolytic enzymes**
- Ulcers → submucosa → bloodstream → portal vein → liver abscesses
- *E. histolytica* **lyse host neutrophils**, and acute inflammatory cells are rarely seen in regions of infection
- IgA antibodies and cell-mediated immune response

Entamoeba histolytica (amoebiasis) – Pathogenesis II

- **Trophozoites** are very sensitive to acid
- **Cysts** can remain viable for months outside the host, and survive the gastric environment
- A single cyst can cause active infection
- Cysts can spread by fecal–oral route, food and water
- Infected individuals usually carry the parasite in their stool for 12 months
- In **developing countries**, also in developed countries: institutionalized, promiscuous homosexual males, etc.

Life cycle of *Entamoeba histolytica*

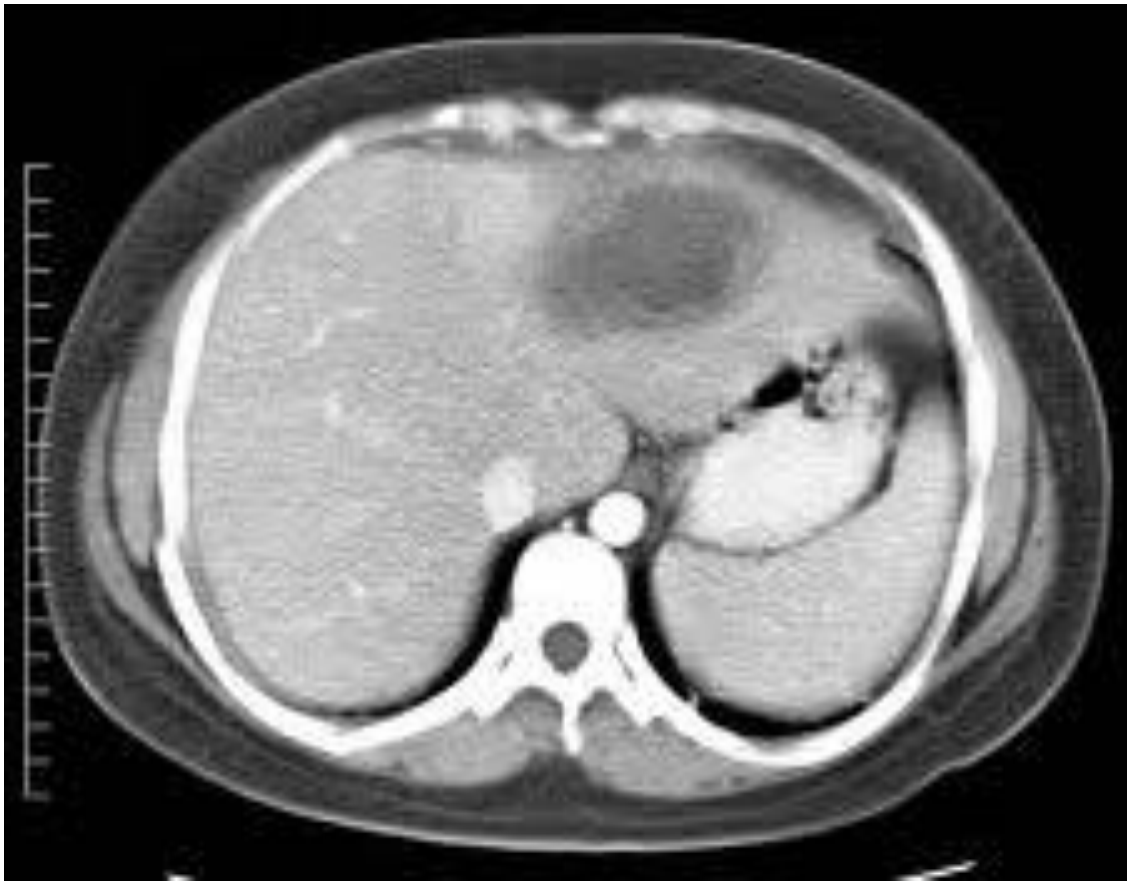


Entamoeba histolytica (amoebiasis) – Clinical manifestations

- **Superficial** bowel infection: watery diarrhea and nonspecific gastrointestinal complaints
- **Invasive** intestinal disease: abdominal pain, bloody diarrhea, tenesmus, fever; if mistaken for ulcerative colitis, corticosteroids → toxic megacolon
- Amoebic **liver abscess**: right upper quadrant pain, may radiate to right shoulder; hepatomegaly; in conjunction with colitis or not

Entamoeba histolytica (amoebiasis) – Diagnosis

- Stool smears: blood-positive, polymorphonuclears present but numbers low because trophozoites destroy them
- In acute hepatic disease, alkaline phosphatase may not be elevated, but it rises in chronic hepatic infection
- Fecal *E. histolytica* **antigen** or PCR tests
- Serum antiamoebic IgA antibody: + after 1 week of symptomatic disease, persist for life
- Abdominal CT scan



Amebic liver abscess

Entamoeba histolytica (amoebiasis) – Treatment

- **Aspiration** of the abscess: sterile, odorless, brownish liquid without polymorphonuclears; amoebae are not generally seen, and are only **rarely cultured** because the parasite concentrates in the walls of the abscess; antigen is detected in hepatic fluid in only 40%
- Invasive enterocolitis and hepatic abscess: oral metronidazole or **tinidazole**, followed by paromomycin or iodoquinol to kill intraluminal parasites' cysts

Giardia lamblia I

- Enteric flagellated protozoan, trophozoite and cyst
- Trophozoites adhere to gastrointestinal endothelial cells, disrupt the brush border, cause **disaccharidase deficiency**, and induce **inflammation** → watery diarrhea and malabsorption
- Cell-mediated and humoral immunity defend the host
- X-linked agammaglobulinemia → increased risk
- Dormant cysts excreted in stool
- Spreads by **water**, food and person to person

Giardia lamblia II

- Throughout the world; most common in children
- Asymptomatic or mild symptoms: abdominal cramps, bloating, belching, diarrhea, anorexia, nausea, etc.
- Usually resolves spontaneously in 4-6 weeks
- Chronic disease is less common and results in malabsorption, chronic diarrhea, and weight loss
- Stool smears: no polymorphonuclears
- ELISA or immunofluorescence antigen tests
- Oral metronidazole, tinidazole, or nitazoxanide

Other parasites

- *Cryptosporidium* spp., *Isospora belli*, and *Microsporidium* spp
- Al of them often present with complaints that mimic viral gastroenteritis, however, in most instances, these parasitic infections **persist** for prolonged periods

Infectious diarrhea in immunocompromised hosts

Cryptosporidium spp.

- Intestinal coccidian protozoan that survives and replicates within the intestinal microvilli
- Generate oocysts, excreted in the stool
- Ingestion of small numbers of oocysts can cause severe, persistent infection in the immunocompromised host
- Loss of cell-mediated immunity (AIDS) increases risk
- Affects intestinal **ion transport** and causes **inflammatory damage** to **intestinal microvilli** → malabsorption
- Resistant to chlorination, transmitted by **water**, etc.

Other parasites and viruses

- *Microsporidium* spp., obligate intracellular, much **smaller** than the other parasites that cause diarrhea:
  - Significant diarrhea only in AIDS and other immunocompromised
  - Villous atrophy and cholangitis
  - Diagnosis by finding the organisms in stool or intestinal biopsy
- *Cystoisospora belli* (previously *Isospora belli*) a cause of watery diarrhea in patients with AIDS
- *Cyclospora* spp., obligate intracellular, infects patients with AIDS as well as travelers
- Citomegalovirus, herpes simplex virus, etc.

Clinical manifestations, diagnosis, and treatment

- Chronic watery diarrhea, often with abdominal cramps
- Fatigue, headaches, eye, and joint pains may happen
- Patients may appear malnourished and be dehydrated
- Diagnosis by stool smear: Giemsa, gram, modified acid-fast, modified trichrome, and fluorescence stains
- *Cryptosporidium* spp.: treated with oral nitazoxanide
- *Microsporidium*: albendazole or fumagillin, but relapses
- *Cystoisospora belli*: trimethoprim-sulfamethoxazole, or pyrimethamine
- *Cyclospora* spp.: also trimethoprim-sulfamethoxazole

Key messages

To remember…

- In most cases of infectious diarrhea, in the immunocompetent host, fluid and electrolyte replacement is the only treatment needed
- Antibiotics and antiperistaltic agents are generally unnecessary and may cause serious complications in infectious diarrhea

Further reading

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