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 - 1

- 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
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

<table>
<thead>
<tr>
<th>Proximal small bowel</th>
<th>Distal small bowel and colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Salmonella</em> spp.</td>
<td>• <em>Campylobacter</em> spp.</td>
</tr>
<tr>
<td>• Other <em>Escherichia coli</em></td>
<td>• <em>Shigella</em> spp.</td>
</tr>
<tr>
<td>• <em>Clostridium perfringens</em></td>
<td>• Enterohemorrhagic and enteroinvasive <em>Escherichia coli</em></td>
</tr>
<tr>
<td>• <em>Vibrio cholerae</em></td>
<td>• <em>Yersinia</em> spp.</td>
</tr>
<tr>
<td>• <em>Staphylococcus aureus</em></td>
<td>• <em>Vibrio parahaemolyticus</em></td>
</tr>
<tr>
<td>• <em>Bacillus cereus</em></td>
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</table>
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
- 2\textsuperscript{nd} to 3\textsuperscript{rd} 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 1\textsuperscript{st} 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$_3$C$_6$H$_5$O$_7$ (trisodium citrate) or 2.5 g NaHCO$_3$
    • 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

<table>
<thead>
<tr>
<th>Pathogen or Group</th>
<th>Recommended Antibiotics</th>
</tr>
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<tbody>
<tr>
<td>Empiric</td>
<td>Ciprofloxacin or azithromycin</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td>None or ciprofloxacin</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Azithromycin or ciprofloxacin</td>
</tr>
<tr>
<td>Staphylococcus aureus toxin</td>
<td>None</td>
</tr>
<tr>
<td><em>Bacillus cereus</em> toxin</td>
<td>None</td>
</tr>
<tr>
<td><em>Shigella</em> spp.</td>
<td>Ciprofloxacin or azithromycin</td>
</tr>
<tr>
<td><em>Yersinia</em> spp.</td>
<td>Ciprofloxacin or doxycycline</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Doxycycline or ciprofloxacin</td>
</tr>
<tr>
<td>Non-enterohemorrhagic <em>E. coli</em></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Alternative in many cases</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
</tbody>
</table>
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

Antibiotic use

↓ normal flora

↓ breakdown of carbohydrates

↑ luminal osmotic load

↑ luminal water

↑ growth of resistant bacteria
- *Clostridium difficile*
- *Klebsiella oxytoca*

Diarrhea
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

- Death of colonic cells caused by *C. difficile* \(\rightarrow\) 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
Pseudomembranous colitis

Normal

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*
- *Giardia lamblia*
- *Cryptosporidium parvum*
- *Isospora belli*
- Microsporidia

Scale: 10 μm
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

- 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**

- 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.
- All 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
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
Used references


Preparing the exam

- These slides