Chapter 136: Gastrointestinal Infections and Enterotoxigenic Poisonings

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 41, Gastrointestinal Infections.

KEY CONCEPTS

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1. Infectious diarrhea is a disease that causes significant morbidity and mortality worldwide. Its etiology includes various bacteria, viruses, and protozoans, with viral causes being most predominant globally.
2. Two types of infectious diarrhea include watery or enterotoxigenic diarrhea and dysentery or bloody diarrhea. Common pathogens responsible for watery diarrhea are viruses and enterotoxigenic *Escherichia coli*. Common pathogens responsible for dysentery diarrhea are *Shigella* spp., *Campylobacter jejuni*, nontyphoid *Salmonella*, and enterohemorrhagic *E. coli*.
3. Fluid and electrolyte replacement is the cornerstone of therapy for diarrheal illnesses. Oral rehydration therapy is preferred in most cases of mild and moderate diarrhea.
4. The use of antibacterial therapy for infectious diarrhea is not commonly indicated due to the mild and self-limited nature of the infection, or viral etiology. Antibiotic therapy is recommended in cases of severe diarrhea, moderate-to-severe cases of traveler's diarrhea, most cases of febrile dysenteric diarrhea, and culture-proven bacterial diarrhea in high-risk patients.
5. Loperamide and diphenoxylate/atropine may offer symptomatic relief in patients with moderate watery diarrhea; however, use of antimotility agents should be avoided in patients with watery and dysentery diarrhea.
6. Diarrheal illness can be largely prevented by procedures to prevent contaminated food or water supplies and with appropriate personal hygiene.
7. Oral vancomycin or fidaxomicin are recommended as the initial therapy for patients with *Clostridioides difficile* infection.
8. Common traveler's diarrheal pathogens include enterotoxigenic *E. coli*, *Shigella* spp., *Campylobacter* spp., *Salmonella* spp., and viruses.
9. Patient education on prevention strategies and appropriate self-treatment of traveler's diarrhea is preferred, and prophylaxis with antibacterials is not recommended.
10. Pathogens commonly responsible for food poisoning include *Staphylococcus* spp., *Salmonella* spp., *Shigella* spp., and *Clostridioides* spp.

BEYOND THE BOOK

BEYOND THE BOOK

Perform a literature search to identify investigational drugs and therapies for *Clostridioides difficile* infection (CDI) not addressed in the book chapter. Create a document that describes the proposed mechanism of action for each agent.

INTRODUCTION

Gastrointestinal (GI) infections and enterotoxigenic poisonings encompass a wide variety of medical conditions characterized by inflammation of the GI tract. Inflammation-induced vomiting and diarrhea are responsible for much of the morbidity and mortality of these conditions. Diarrhea is defined as a decrease in consistency of bowel movements (ie, unformed stool) and an increase in frequency of stools to three or more per day.[1,2] Acute diarrheal disease is commonly associated with diarrhea lasting less than 7 days, prolonged diarrhea lasts 7 to 13 days, persistent diarrhea lasts 14 to 29 days, and chronic diarrhea lasts 30 days or longer.

This chapter focuses on infectious etiologies of acute GI infections and enterotoxigenic poisonings. A wide variety of viral, bacterial, and parasitic pathogens are responsible for these infections. Chapter e138, "Parasitic Diseases," discusses the common protozoans that cause gastroenteritis. This chapter will focus on pathogenesis and management of common viral and bacterial etiologies. Because the clinical consequences of dysenteric diarrhea can be more severe compared with cases of watery diarrhea, the chapter is organized accordingly. Epidemiology, clinical presentation, diagnosis, treatment, and prevention strategies are discussed for all GI infections generally, and further elaborated in subsequent sections for specific diseases such as *Clostridioides difficile* infection, traveler's diarrhea, and foodborne illnesses.

EPIDEMIOLOGY

Dehydration resulting from acute infectious diarrhea is the second leading cause of mortality in children younger than 5 years, killing 525,000 annually.[2] Globally, 1.7 billion cases of infectious diarrhea occur yearly and cause over 1.39 million deaths.[2,3] The incidence of diarrhea for all children younger than age 5 years is 2.9 episodes per child per year. The incidence of diarrhea is higher in younger children, with 4.5 episodes per child per year among children aged 6 to 11 months, compared with 2.3 episodes per child per year among children aged 24 to 59 months.[2,3] Younger children also have a higher risk of death from acute dehydrating diarrhea, and diarrheal disease is still the leading global cause of malnutrition in children younger than 5 years.[2] Although the incidence of childhood diarrhea has been declining, diarrhea remains a major health problem in children, especially in those younger than 1 year.

In the United States, 179 million episodes of acute gastroenteritis occur each year, resulting in nearly 500,000 hospitalizations and more than 5,000 deaths.[4-7] The highest mortality risk from infectious diarrhea in the United States occurs in the elderly, which contrasts to the developing world where the risk of death is highest among young children.[4] Twenty-five percent of all hospitalizations and 85% of all mortality associated with diarrhea involved the elderly (age 60 years and older).[4] In addition to children and the elderly, other groups at risk for GI infections include travelers and campers, patients in chronic care facilities, military personnel stationed abroad, and immunocompromised patients.

ETIOLOGY

1 The etiology of GI infections and enterotoxigenic poisonings includes a wide variety of viruses, bacteria, and parasites, although the specific incidence of each is difficult to quantify. Etiologic agents are rarely identified due to the infrequent collection of stool samples, or inability of many laboratories to detect the full range of pathogenic organisms. In this chapter, discussions of pathogens responsible for enterotoxigenic diarrhea focus on viral pathogens (rotavirus and norovirus), enterotoxigenic *Escherichia coli* (ETEC), and cholera. Common pathogens associated with dysenteric diarrhea discussed will be *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., enterohemorrhagic *E. coli* (EHEC), *Yersinia enterocolitica*, and *C. difficile*. Characteristics of watery and dysenteric diarrhea and common pathogens responsible for them are outlined in Table 136-1.

TABLE 136-1

Acute Infectious Diarrhea Clinical Syndromes: Watery Versus Dysentery

	Watery	Dysentery
Percentage of patients	90-95	5-10
Stools		
Appearance	Watery	Bloody
Volume	Increased: ++/+++	Increased: +/++
Number per day	<10	>10
Reducing substances	0 to +++	0
pH	5-7.5	6-7.5
Occult blood	Negative	Positive
Fecal polymorphonuclear cells	Absent or few	Many
Mechanisms	• Toxins • Reduced absorption	• Toxins • Mucosal invasion
Complications • Dehydration • Others	• Could be severe • Acidosis, shock, electrolyte imbalance	• Mild • Tenesmus, rectal prolapse, seizures
Etiology	*Vibrio cholerae*	*Shigella* spp.
	Enterotoxigenic *Escherichia coli* (ETEC)	*Salmonella* spp.
	Rotaviruses	*Campylobacter* spp.
	Noroviruses	*Yersinia* spp.
		Enterohemorrhagic *E. coli* (EHEC)
		Clostridioides difficile

Viruses are now the leading global cause of infectious diarrhea. Noroviruses, previously known as Norwalk-like viruses, account for greater than 90% of viral gastroenteritis among all age groups, and 50% of outbreaks worldwide. In the United States, noroviruses have been responsible for about 21% of all acute gastroenteritis cases in young children with outpatient visits, emergency department visits, and annual hospitalizations numbering 627,000, 281,000, and 14,000, respectively.[8] Outbreaks occur throughout the year and have been documented in families, healthcare systems, cruise ships, and college dormitories.

In infants and children, rotavirus, a double-stranded, wheel-shaped, RNA virus, is the most common cause of infectious diarrhea globally, and 1 million

people die annually from the infection.[9] In the United States, approximately 3.5 million cases of diarrhea, 500,000 physician visits, 50,000 hospitalizations, and 20 deaths occur each year in children younger than 5 years. Rotavirus is a ubiquitous contagion, infecting the vast majority of children younger than 5 years. After the initial infection, 40% of children are protected against subsequent rotavirus infection, 75% are protected against subsequent gastroenteritis, and up to 88% are protected against severe gastroenteritis. After more extensive vaccination coverage for rotavirus in recent years, hospitalizations from this infection have significantly decreased.[9] Other viral etiologies include astrovirus, enteric adenovirus, pestivirus, coronavirus, and enterovirus. These viruses are increasingly identified as causative etiologies of diarrhea. Characteristics of viral pathogens causing gastroenteritis are outlined in Table 136-2.

TABLE 136-2

Characteristics of Agents Responsible for Acute Viral Gastroenteritis

Virus	Peak Age of Onset	Time of Year	Duration	Mode of Transmission	Common Symptoms
Rotavirus	6 months to 2 years	October to April	3-7 days	Fecal–oral, water, food	Nausea, vomiting, diarrhea, fever, abdominal pain, lactose intolerance
Norovirus	All age groups	Peak in winter	2-3 days	Fecal–oral, food, water, environment	Nausea, vomiting, diarrhea, abdominal cramps, myalgia
Astrovirus	<7 years	Winter	1-4 days	Fecal–oral, water, shellfish	Diarrhea, headache, malaise, nausea
Enteric adenovirus	<2 years	Year-round	7-9 days	Fecal–oral	Diarrhea, respiratory symptoms, vomiting, fever
Pestivirus	<2 years	NR	3 days	NR	Mild
Coronavirus-like particles	<2 years	Fall and early winter	7 days	NR	Respiratory disease
Enterovirus	NR	NR	NR	NR	Mild diarrhea, secondary organ damage

NR, not reported.

2 Bacterial causes of acute gastroenteritis in the United States account for more than 5 million cases of diarrhea annually; however, these are vastly underreported and a causative pathogen is identified in less than 3% of cases.[4] FoodNet in 2019 identified 25,866 laboratory confirmed infections, resulting in 6,164 hospitalizations and 122 deaths from these infections.[4,10] Common pathogens responsible for watery diarrhea in the United States are norovirus and ETEC, while those most commonly associated with dysentery diarrhea are *Campylobacter* spp., EHEC, *Salmonella* spp., and *Shigella* spp. Other organisms that are responsible for dysentery include *Aeromonas* spp., noncholera *Vibrio*, and *Y. enterocolitica*. Characteristics of acute bacterial pathogens causing gastroenteritis are summarized in Table 136-3.

TABLE 136-3

Characteristics of Acute Bacterial Gastroenteritis

Bacteria	Incubation Period	Duration	Mode of Transmission	Common Symptoms
Watery Diarrhea				
Vibrio cholerae	2-3 days	1-3 days	Contaminated food or water with human feces usually in areas of inadequate treatment of sewage and drinking water	Profuse watery diarrhea, vomiting, and leg cramps Death can occur within hours without treatment
Enteroaggregative *E. coli*	NR	NR	Contaminated food or water with animal or human feces	Chronic, watery, mucoid, secretory diarrhea with low-grade fever in immunocompromised persons (HIV infections)
Enteroinvasive *E. coli*	10-18 hours	NR	Contaminated food or water with animal or human feces	Watery diarrhea in young children in the developing world
Enteropathogenic *E. coli*	9-12 hours	NR	Contaminated food or water with animal or human feces	Acute onset of profuse watery diarrhea, vomiting, and low-grade fever in young children (<2 years of age) in the developing world
Enterotoxigenic *E. coli*	1-3 days	3-4 days	Contaminated food or water with animal or human feces	Watery diarrhea and abdominal cramping
Dysentery Diarrhea				
Campylobacter jejuni	2-5 days	5-7 days	Contaminated food (particularly poultry), water, or contact with infected animals	Diarrhea (often bloody), cramping, abdominal pain, and fever
Enterohemorrhagic *E. coli*	3-4 days	5-7 days	Contaminated food (particularly cattle) or water with animal or human feces	Severe stomach cramps, diarrhea (often bloody), and vomiting
				Approximately 5%-10% develop hemolytic uremic syndrome
Nontyphoid *Salmonella*	12-36 hours	1-5 days	Contaminated food, water, or contact with infected animals	Diarrhea (sometimes bloody), fever, and abdominal cramps
Shigella	1-3 days	1-7 days	Fecal–oral Contaminated food or water with infected human feces	Watery or bloody diarrhea (8-10 stools/day), severe abdominal pain, fever, and malaise
Yersinia	4-7 days	1-3 weeks	Contaminated food or water	Fever, abdominal pain, and diarrhea (often bloody)

NR, not reported.

Cholera has been rare in the United States because of advanced water and sanitation systems, although slight increases in its incidence have occurred

in recent years without clear causes. It is endemic on the Indian subcontinent and sub-Saharan Africa with five countries, Democratic Republic of the Congo, Haiti, Somalia, the United Republic of Tanzania, and Yemen, causing 80% of all cases.[11-13] *Vibrio cholerae* is a gram-negative bacillus sharing similar characteristics with the family Enterobacterales. Cholera is caused by toxigenic *V. cholerae* serogroups O1 or O139. Infections due to *V. cholerae* result in severe and voluminous diarrhea that can quickly result in dehydration. Approximately half of those persons infected with *V. cholerae* O1 are symptomatic, whereas only 1% to 5% of those infected with *V. cholerae* O139 manifest symptoms.[12,13] Vaccination is available to affected areas and to people traveling to those areas that might help in reducing prevalence and severity of disease.[13]

E. coli is a gram-negative bacillus commonly found in the human GI tract, and *E. coli*–associated diarrhea may be differentiated into several distinct categories based on pathogenic features of diarrheal disease: enteroaggregative *E. coli* (EAEC), EHEC, enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), and ETEC. ETEC occurs most commonly, and accounts for about half of all cases of *E. coli* diarrhea. There are an estimated 79,000 cases of ETEC in the United States each year.[4] ETEC is also the most common cause of traveler's diarrhea and a common cause of food- and water-associated outbreaks. Infections with EIEC and EPEC are primarily a disease of children in developing countries.[14] EAEC strains are implicated in persistent diarrhea (≥14 days) in human immunodeficiency virus (HIV)-infected patients.[15] EHEC, also known as Shiga toxin–producing *E. coli* (STEC), causes watery diarrhea that becomes bloody in 1 to 5 days in 80% of patients.[14]

EHEC is believed to be the major etiologic factor responsible for the development of hemorrhagic colitis and hemolytic uremic syndrome (HUS). The annual disease burden of STEC in the United States is more than 20,000 infections and as many as 250 deaths; however, the failure of many clinical laboratories to screen for this organism greatly complicates any estimates.[16] In the United States, STEC causes 50% to 60% of all EHEC infections, but in the southern hemisphere, including Argentina, Australia, Chile, and South Africa, non-STEC serotypes are often more prevalent. Non-STEC strains generally produce a lower frequency of dysentery than STEC-positive strains (62% vs 85%).

The *Campylobacter* spp. are flagellated, curved, gram-negative rods. Although there are 14 different species, *Campylobacter jejuni* is the species responsible for more than 99% of *Campylobacter*-associated gastroenteritis. Approximately 2.4 million persons are affected each year in the United States, involving almost 1% of the entire population.[4]

Salmonella enterica is a gram-negative bacilli belonging to the family Enterobacterales. The most prevalent *S. enterica* serotypes are Typhi and Paratyphi, which cause enteric fever. Gastroenteritis is caused by *S. enterica* serotypes Typhimurium or Enteritidis. In the United States, the largest burden of *Salmonella* infection is due to nontyphoidal serotypes, causing approximately 1.4 million cases of salmonellosis, 16,000 hospitalizations, and 600 deaths, occurring annually.[17]

Approximately 165 million cases of shigellosis occur worldwide with 450,000 cases from the United States annually.[18,19] *Shigella* spp. are gram-negative bacilli belonging to the family Enterobacterales. Four species most often associated with disease are *Shigella dysenteriae* type 1, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*.[18,19] *Shigella sonnei* and *S. flexneri* are the most common causes of gastroenteritis in the United States. The other two *Shigella* spp. are more commonly acquired during travel to developing countries. Poor sanitation or personal hygiene, inadequate water supply, malnutrition, and increased population density are associated with an increased risk of *Shigella* gastroenteritis epidemics.

Yersinia spp. are non–lactose-fermenting gram-negative coccobacilli that are widely distributed in nature. The genus *Yersinia* includes six species known to cause disease in humans. *Yersinia enterocolitica* and, to a lesser extent, *Y. pseudotuberculosis* are most likely associated with intestinal infection, but overall both are a relatively infrequent cause of diarrhea and abdominal pain. More than 50 serotypes of *Y. enterocolitica* exist; of these, serotypes 0:3, 0:8, and 0:9 are associated most frequently with enterocolitis.[20] Children are most likely to experience illness with *Y. enterocolitica* infection.

PATHOPHYSIOLOGY

Acute gastroenteritis and its resulting diarrhea are caused by altered movement of ions and water resulting in increased colonic secretion. Under normal conditions, the GI tract has tremendous capacity to absorb fluid and electrolytes, allowing only 100 to 200 mL of fluid to be excreted in the stool daily.[21] The classic enteric pathogen that causes secretary diarrhea is *V. cholerae*, but ETEC and rotavirus also cause watery diarrhea and are much more predominant etiologies in the United States.

V. cholerae is an enteric pathogen that causes classical secretory diarrhea due to changes in ion secretion and absorption. Among the toxins produced by *V. cholerae*, the most important is cholera toxin.[11] Cholera toxin consists of two subunits, A and B. The B subunits are responsible for delivery of the A subunit into the cell. The A subunit stimulates adenylate cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP) and results in protein kinase A–mediated activation of cystic fibrosis transmembrane conductance regulator. This leads to increased chloride secretion and decreased sodium absorption producing the severe watery diarrhea characteristic of the disease.[21] The toxin likely acts along the entire intestinal tract, but most fluid loss occurs in the duodenum. The net effect of the cholera toxin is isotonic fluid secretion early in the intestinal tract that exceeds the absorptive capacity of the latter intestinal tract.

ETEC also causes watery diarrhea characterized by severe intestinal water secretion by producing plasmid-mediated enterotoxins: heat-labile toxin and heat-stable toxin. The heat-labile toxin has two subunits (A and B) that have similar antigenic properties and action on the gut mucosa as cholera toxin. Heat-labile toxins increase chloride secretion via activation of cAMP. The net effect is luminal accumulation of electrolytes that draws water into the intestine, and production of a cholera-like secretory diarrhea.[22] Heat-stable toxin is thought to be nonantigenic and produces watery diarrhea by acting on the small intestine.

Rotavirus induces changes in transepithelial fluid balance, and causes malabsorption as a consequence of destruction of the epithelial lining of intestine, and vascular damage and ischemia in villi. Once rotavirus infects small intestinal villus cells, viroplasms are formed and its toxin, nonstructural protein 4, is released. The viral enterotoxin increases intracellular calcium, and the increase in calcium disrupts microvillus cytoskeleton, as well as barrier function. Changes to the villi include shortening of villus height, crypt hyperplasia, and mononuclear cell infiltration of the lamina propria.[23]

Inflammatory diarrhea is caused by two groups of organisms—enterotoxin-producing, noninvasive bacteria (eg, EAEC, EHEC) or invasive organisms (eg, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp.). The enterotoxin-producing organisms adhere to the mucosa, activate cytokines, and stimulate the intestinal mucosa to release inflammatory mediators. Invasive organisms, which can also produce enterotoxin, invade the intestinal mucosa to induce an acute inflammatory reaction, involving the activation of local and systemic cytokines and inflammatory mediators.

Ingestion of as few as 10 to 200 viable organisms of the *Shigella* spp. causes disease in healthy adults.[18,19] *Shigella* multiply and spread within the submucosa of the small bowel, but they rarely extend beyond the mucosa. Inflammatory diarrhea is caused by the pathogens invading the epithelial barrier through M cells where they encounter and eliminate macrophages. The destruction of macrophages after emergence from M cells causes an initial release of interleukin (IL)-1β. This initial inflammatory process is exacerbated by free bacteria binding to toll-like receptor that causes the production of IL-6 and IL-8. Both IL-1β and IL-8 attract polymorphonucleocytes.[24] Release of polymorphonucleocytes activates chloride secretion and subsequent diarrhea. Degranulation and release of toxic substances by neutrophils cause ulceration of the epithelium, distortion of the crypts, death to intestinal epithelium, sloughing of mucosal cells, bloody mucoid exudate into the gut lumen, and submucosal accumulation of inflammatory cells with microabscess formation.[25] Microabscesses eventually may coalesce, forming larger abscesses. *Shigella* will frequently affect the entire colon. In addition to the virulence characteristics of invasiveness, *S. dysenteriae* type 1 and, to a lesser degree, *S. flexneri* and *S. sonnei* produce a cytotoxin or Shiga toxin, which can lead to HUS.[14]

The pathogenicity of EHEC is related to the production of Shiga-like toxins, so named because of their resemblance to the Shiga toxin of *S. dysenteriae*.[21] The cytotoxic effect of Shiga-like toxins disrupts the mucosal integrity of the large intestine, causing diarrhea. In addition, the toxin is able to pass through the intestinal epithelium to reach the endothelial cells lining small blood vessels that supply the gut, kidney, and other viscera, causing the myriad metabolic events that could eventually lead to HUS.

CLINICAL PRESENTATION

Gastroenteritis is an illness characterized by diarrhea, which may be accompanied by nausea, vomiting, fever, and abdominal pain. For effective diagnosis and management, it is important to distinguish noninflammatory diarrhea that produces watery diarrhea from inflammatory diarrhea or dysentery. Most enteric pathogens produce acute diarrhea and pathogens associated with dysentery will often result in grossly bloody stools and mucus. Systemic symptoms of gastroenteritis, such as fever, are often associated with dysentery of infectious origin. Symptoms of enteric pathogens that cause watery and dysentery diarrhea are listed in Table 136-1.

A physical examination and careful history that includes information about symptoms and symptom duration, the number of individuals affected, and

recent history of travel, diet, and medications are important factors in making a diagnosis. Infections with norovirus or ETEC will often result in mild, self-limiting disease, whereas cholera will commonly produce severe dehydrating diarrhea. Infections with enteric pathogens such as *Campylobacter* spp., EHEC, *Salmonella* spp., *Shigella* spp., and *Y. enterocolitica* can result in severe symptomatology due to dysentery. The utilization of serum C-reactive protein (CRP) in young adult patients with infectious diarrhea may be able to help differentiate between noninflammatory and inflammatory causes.[26] Assessing CRP could assist with diagnosis, prognosis, and treatment selection. The clinical presentation of acute viral and bacterial gastroenteritis is summarized in Tables 136-2 and 136-3, respectively.

Stool culture is an important tool in making an organism-specific diagnosis and determining susceptibility to antimicrobial agents. Due to the low yield, stool cultures are not recommended in most mild-to-moderate watery diarrhea. Instead, indications for stool cultures include dysenteric diarrhea, persistent diarrhea in immunocompromised patients (ie, persons aged 65 years and older with comorbid diseases, neutropenia, or HIV infection), and diarrhea where an outbreak is suggested.[1] An appropriately obtained stool culture identifies the presence of *Campylobacter*, *Salmonella*, and *Shigella* spp. The yield of stool cultures for other pathogens is increased if the test is ordered specifically based on history and physical examination. For dysenteric diarrhea, the laboratory should be instructed to evaluate for EHEC including STEC (*E. coli* O157:H7). In hospitalized patients who develop diarrhea 3 days after hospitalization or in those with recent exposure to antimicrobials or chemotherapy, stool specimen should be sent for *C. difficile* toxins A and B. In addition to stool cultures, microscopic examination for fecal polymorphonuclear cells, or a simple immunoassay for the neutrophil marker lactoferrin, can further provide evidence of an inflammatory process and increase the yield of cultures in patients presenting with dysenteric diarrhea.[1]

Complications

Complications associated with acute diarrhea most likely result from dehydration so treatment focuses primarily on rehydration therapy, regardless of the etiology. Dysenteric diarrhea is more likely to have severe complications, especially in children younger than 5 years and in elderly. Bacteremia is the most common complication of gastroenteritis and can be seen after infections with nontyphoid *Salmonella*, *C. jejuni* or *C. fetus*, and *Y. enterocolitica*.[16] Nontyphoid *Salmonella* is most common in children younger than 5 years, elderly, and patients with hemoglobinopathy, malaria, or immunosuppression. Bacteremia due to *Campylobacter* spp. has been reported in patients with HIV infection, malignancy, transplantation, and hypogammaglobulinemia. *Y. enterocolitica* bacteremia has been rarely reported, but has an increased prevalence in patients with diabetes mellitus, severe anemia, hemochromatosis, iron overload (frequent transfusion), cirrhosis, malignancy, and in the elderly.[27] Persistent bacteremia with these pathogens will commonly result in prolonged intermittent fever with chills. Potentially complicating the diagnosis, stool cultures frequently are negative and leukocyte counts are often within the normal range. Vascular complications such as seeding of atherosclerotic plaques or aneurysms in arterial vessels occur in 10% to 25% of adults with bacteremia. Localized infections involving bone, cysts, heart, kidney, liver, lungs, pericardium, and spleen develop in 5% to 10% of patients with bacteremia.

A severe complication in patients infected with EHEC is HUS. HUS is defined by the triad of acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia and is more commonly observed in children younger than 5 years and in the elderly.[28] Approximately 2% to 7% of cases infected with STEC strains are complicated by development of HUS, which increases mortality associated with this infection. *S. dysenteriae* type 1 can also cause HUS, although more rarely than observed with EHEC.[18]

Shigella infection may also lead to complications such as generalized seizures, sepsis, toxic megacolon, perforated colon, arthritis, and protein-losing enteropathy. Mortality is rare, but it may be more likely with *S. dysenteriae* type I. Less than 3% of persons who are infected with *S. flexneri* will later develop Reiter syndrome, characterized by pains in the joints, irritation of the eyes, and painful urination. This can lead to chronic arthritis.[29]

Infection with *C. jejuni* has been associated with Guillain-Barré syndrome (GBS), but the relationship is not well understood.[30] The risk of developing GBS after *C. jejuni* infection appears to be low (approximately 1 case of GBS per 1,000 *C. jejuni* infections). The weakness associated with GBS usually starts in the legs, with difficulty in walking, and may progress to a complete paralysis of all extremities that lasts several weeks and usually requires intensive care.

Approximately 10% to 30% of adult patients develop a reactive arthritis 1 to 2 weeks after recovery from gastroenteritis secondary to *S. flexneri*, *Salmonella* spp., *C. jejuni*, and *Y. enterocolitica*. This arthritis, involving the knees, ankles, toes, fingers, and wrists, usually resolves in 1 to 4 months but may persist in approximately 10% of patients.[30] This complication is more common in persons with the HLA-B27 antigen.

A general complication that could occur long after an infectious gastroenteritis, especially with dysentery and toxin-mediated dysentery, is postinfectious irritable bowel syndrome (IBS). This is classified as IBS symptoms for at least 3 months following an episode of gastroenteritis or traveler's diarrhea showing recurrent abdominal pain or discomfort.[31] Albeit rare, some long-term complications associated with these infections strengthen the need for appropriate diagnosis and treatment.

TREATMENT

Mortality associated with infectious diarrhea has declined substantially in the past two decades, especially among children younger than 1 year. Preventative measures including improved sanitation, breast-feeding and weaning practices, and increased use of oral rehydration therapy (ORT) for affected individuals are responsible for the decrease in case-fatality rates.

General Approach to Treatment

The cornerstone of management for all GI infections and enterotoxigenic poisonings is to prevent dehydration by correcting fluid and electrolyte imbalances. In mild, self-limiting acute gastroenteritis, a diet of oral fluids and easily digestible foods is recommended. In patients with severe dehydrating watery diarrhea and dysenteric diarrhea, IV rehydration therapy, antibiotics, and/or antimotility treatments are needed.

Rehydration Therapy

Initial assessment of fluid loss is essential for successful rehydration therapy and should include acute weight loss, as it is the most reliable means of determining the extent of water loss. However, if accurate baseline weight is not available, clinical signs are helpful in determining approximate deficits (Table 136-4). Physical assessment generally is more reliable in young children and infants than in adults.

TABLE 136-4

Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss[a]

Variable	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild-to-Moderate (3%-9% Loss of Body Weight)	Severe (≥10% Loss of Body Weight)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Weak, thready, or not palpable
Heart rate	Normal	Normal to increased	Increased (bradycardia in severe cases)
Breathing	Normal	Normal to fast	Deep
Mental status	Normal	Normal to listless	Apathetic, lethargic, or comatose
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/absent tears
Mouth and tongue	Moist	Dry	Parched
Thirst	Normal	Eager to drink	Drinks poorly; too lethargic to drink
Skin fold	Normal	Recoil in <2 seconds	Recoil in >2 seconds
Extremities	Warm, normal capillary refill	Cool, prolonged capillary refill	Cold, mottled, cyanotic, prolonged capillary refill
Urine output	Normal to decreased	Decreased	Minimal
Hydration therapy	None	ORS 50-100 mL/kg over 3-4 hours	• Lactated Ringer's solution or normal saline 20 mL/kg over 15-30 minutes IV until mental status or perfusion improves • Followed by 5% dextrose/0.45% sodium chloride IV at higher maintenance rates or ORS 100 mL/kg over 4 hours
Replacement of ongoing losses	• For each diarrheal stool or emesis • <10 kg body weight: 60-120 mL ORS • >10 kg body weight: 120-240 mL ORS	Same as minimal dehydration	If unable to tolerate ORS, administer through nasogastric tube or administer 5% dextrose/0.45% sodium chloride with 20 mEq/L (mmol/L) potassium chloride IV

ORS, oral rehydration solution.

[a]Percentages vary among patients for each dehydration category; hemodynamic and perfusion status is most important; when unsure of category, therapy for more severe category is recommended.

Fluid replacement is the cornerstone of therapy for dehydration due to diarrhea regardless of etiology. For the treatment of mild-to-moderate dehydration, ORT is superior to administration of IV fluids. Oral replacement therapy reverses dehydration in nearly all patients with mild-to-moderate diarrhea with 94% to 97% efficacy.[1] It offers advantages of being inexpensive, noninvasive, and not requiring inpatient administration. Moreover, thirst drives use of ORT and provides a safeguard against overhydration. Replacement of ongoing losses as well as continuation of normal feeding should also be addressed.

The necessary components of oral rehydration solutions (ORS) include carbohydrates (typically glucose), sodium, potassium, chloride, and water. Using both salt and glucose in the ORS takes advantage of glucose-coupled sodium transport in the small bowel and enhances sodium and subsequently water transport across intestinal walls. The World Health Organization/United Nations Children's Fund (WHO/UNICEF) endorsed a reduced osmolarity solution (osmolarity ≤250 mOsm/L) as the use of these solutions reduced stool volume, shortened duration of diarrhea, and decreased need for unscheduled IV therapy when compared with previously used ORS more than or equal to 310 mOsm/L.[32] The newer formulation of ORS less than or equal to 250 mOsm/L was, however, more likely to cause hyponatremia (blood sodium levels <130 mEq/L [mmol/L]).[33] If commercial ORS are unavailable, one can be roughly duplicated by mixing ½ teaspoon of salt with 6 teaspoons of sugar in 1 L of water.[34]

In restoring fluid and electrolyte balance in cholera infections, polymer-based ORS may be more efficacious than glucose-based ORS. Polymer-based ORS contains rice, wheat, sorghum, or maize. This polymer-based ORS releases glucose more slowly after digestion and, when absorbed in the small bowel, enhances the reabsorption of water and electrolyte secreted into the bowel lumen during diarrhea. Polymer-based ORS reduces the duration of diarrhea in adults with cholera when compared with glucose-based ORS more than or equal to 310 and less than or equal to 270 mOsm/L.[35]

Guidelines for rehydration therapy based on the degree of dehydration and replacement of ongoing losses are outlined in Table 136-4. ORS should be given in small and frequent volumes (5 mL every 2 to 3 minutes in a teaspoon or oral syringe). Nasogastric administration of ORS is an alternative method of administration in a child with persistent vomiting. For breast-fed infants, nursing should be continued. The composition of commercial ORS and commonly consumed beverages is listed in Table 136-5. Clear fluids, such as soft drinks, sweetened fruit drinks, chicken broth, and sports drinks, should be avoided in the treatment of dehydration. These hyperosmolar solutions may cause an osmotic diarrhea.

TABLE 136-5

Comparison of Common Solutions Used in Oral Rehydration and Maintenance

Product	Na (mEq/L)[b]	K (mEq/L)[b]	Base (mEq/L)	Carbohydrate (mmol/L)	Osmolarity (mOsm/L)
WHO/UNICEF (2002)	75	20	30	75	245
Pedialyte	45	20	30	140	250
Infalyte	50	25	30	70	200
Oralyte	60	20	0	90	260
Rehydralyte	75	20	30	140	250
Cola[a]	2	0	13	700	750
Apple juice[a]	5	32	0	690	730
Chicken broth[a]	250	8	0	0	500
Sports beverage[a]	20	3	3	255	330

[a]These solutions should be avoided in dehydration.

[b]Concentration of monovalent ions expressed in mEq/L is numerically equivalent to mmol/L concentration.

In the treatment of severe dehydration, the primary goal of therapy is rapid restoration of fluid losses, correction of metabolic acidosis, and replacement of potassium deficiency. Severely dehydrated patients should be resuscitated initially with IV lactated Ringer solution or normal saline to restore hemodynamic stability. Lactated Ringer solution is preferred initially over normal saline because normal saline does not assist in correcting a metabolic acidosis. As GI and renal perfusion should be addressed aggressively, rapid IV administration is preferred over prolonged administration regimens for restoring extracellular fluids and electrolytes.[36] After rehydration, maintenance fluid is given based on accurate recording of intake and output volumes. ORT should be instituted as soon as it can be tolerated.

Early refeeding with age-appropriate unrestricted diet is recommended in children. Early refeeding during or immediately following the start of rehydration did not increase the risk of complications such as unscheduled IV fluids, vomiting, or development of persistent diarrhea compared with late refeeding that ranged from 20 to 48 hours after start of rehydration.[36] Initially, easily digested foods such as bananas, applesauce, and cereal should be introduced and foods high in fiber, sodium, and sugar should be avoided. One caveat would be that lactase deficiency may be exacerbated among known lactase-deficient patients and may persist up to 10 days.

Antimicrobial Therapy

4 The indiscriminate use of antimicrobial therapy produces increases in antimicrobial resistance, side effects of antimicrobial agents, and the threat of superinfections owing to eradication of normal flora. Increasing fluoroquinolone resistance in *Campylobacter* and multidrug resistance in *Salmonella* spp. worldwide reinforces the importance of judicious use of antibiotics and prudent infection control measures.[37,38] Antibiotic therapy is recommended in severe cases of diarrhea, moderate-to-severe cases of traveler's diarrhea, most cases of febrile dysenteric diarrhea, and culture-proven bacterial diarrhea. Antimicrobial therapy is not recommended in EHEC diarrhea as it may increase HUS risk.

Antibiotic therapy is recommended in severe cases of cholera and ETEC diarrhea. In cases of cholera, antibiotics shorten the duration of diarrhea,

decrease fluid loss, and shorten the duration of the carrier state.[1,12] It is important to consider local susceptibility patterns in the selection of the antimicrobial regimen. In areas of high fluoroquinolone resistance, azithromycin has been effective in patients with cholera. In patients with ETEC diarrhea, empiric antibiotics reduce severity and duration of diarrhea. A short course of therapy with fluoroquinolones is the most commonly recommended therapy due to increased resistance among other drug classes.[39] Rifaximin has been effective for ETEC for travel in Mexico.[40] Further discussions of antibiotic prophylaxis and treatment can be found in the section on traveler's diarrhea. Table 136-6 summarizes antibiotic recommendations. Further details regarding treatment of *C. difficile*–associated diarrhea, traveler's diarrhea, and foodborne illnesses are discussed in respective sections.

TABLE 136-6

Recommendations for Antibiotic Therapy

Pathogen	Children	Adults
Watery Diarrhea		
Enterotoxigenic *Escherichia coli*	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Ciprofloxacin 750 mg orally once daily × 1-3 days. Alternatives: rifaximin 200 mg orally three times daily × 3 days; azithromycin 1,000 mg orally × 1 day *or* 500 mg orally daily × 3 days
Vibrio cholerae O1	Erythromycin 30 mg/kg/day divided every 8 hours orally × 3 days; azithromycin 10 mg/kg/day given orally once daily × 3 days	Doxycycline 300 mg orally × 1 day Alternatives: azithromycin 500 mg orally once daily × 3 days; ciprofloxacin 750 mg orally once daily × 3 days; ceftriaxone IV
Dysenteric Diarrhea		
Campylobacter species[a]	Azithromycin 10 mg/kg/day given orally once daily × 3-5 days; erythromycin 30 mg/kg/day divided into two to four doses orally × 3-5 days	Azithromycin 500 mg orally once daily × 3 days Alternatives: ciprofloxacin 750 mg orally once daily × 7 days
Salmonella Nontyphoidal[a]	Ceftriaxone 100 mg/kg/day divided IV every 12 hours × 7-10 days; azithromycin 20 mg/kg/day orally once daily × 7 days	Ceftriaxone 2 g IV/IM once; ciprofloxacin 750 mg orally once daily × 7-10 days; Alternatives: ampicillin 250-500 mg orally every 6 hours × 7 days; azithromycin 500 mg orally once daily × 7 days; Trimethoprim-sulfamethoxazole 160/800 mg twice daily × 7 days For immunocompromised patients, duration should be increased to 14 days for both fluoroquinolones and azithromycin
Shigella species[a]	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Azithromycin 500 mg orally once daily × 3 days; ceftriaxone 2 g IV/IM once; ciprofloxacin 750 mg orally once daily × 3 days; Alternatives: ampicillin 250-500 mg orally every 6 hours × 7 days; Trimethoprim-sulfamethoxazole 160/800 mg twice daily × 7 days
Yersinia species[a]	Treat as children with shigellosis	Trimethoprim-sulfamethoxazole 160/800 mg twice daily × 7 days Alternatives: cefotaxime IV or ciprofloxacin 750 mg orally once daily × 7 days
Traveler's Diarrhea		
Prophylaxis[a]		None recommended
Treatment		Azithromycin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days, Ciprofloxacin 750 mg orally × 1 day or 500 mg orally twice daily × 3 days; levofloxacin 500 mg orally daily × 3 days, ofloxacin 400 mg twice daily × 1-3 days, rifamycin SV 388 mg twice daily × 3 days, rifaximin 200 mg three times daily × 3 days

[a]For high-risk patients only. See the preceding text for the high-risk patients in each infection.

Antibiotic therapy is indicated in at-risk and febrile patients with dysenteric diarrhea. In shigellosis, antibiotics shorten the period of fecal shedding and attenuate the clinical illness. Antibiotic therapy is reserved for the elderly, those who are immunocompromised, children in daycare centers, malnourished children, and healthcare workers. In the United States, *Shigella* spp. remain susceptible to fluoroquinolones. Fluoroquinolone resistance among *Shigella* spp. is of increasing concern in developing countries, and azithromycin may be a better choice in patients with a recent history of travel to a developing region.[1,18] Similar antibiotic regimens can be used for high-risk patients who develop *Yersinia* bacteremia (ie, infants younger than 3 months and patients with cirrhosis or iron overload) or in patients with bone and joint infections.[41] With Campylobacteriosis, antibiotics are not useful unless started within 4 days of the start of the illness because they do not shorten the duration or severity of diarrhea and only shorten the duration of bacterial excretion. Antibiotics are warranted in patients with high fevers, severe bloody diarrhea, prolonged illnesses (more than 1 week), pregnancy, and immunocompromised states, including HIV infection. Fluoroquinolone resistance among *Campylobacter* spp. has increased, and is now 10% to 13% in the United States and 41% to 88% in Europe and Asia. Resistance may be the result of the use of fluoroquinolone antibiotics in poultry and other animal feed, and the frequent use of these agents internationally in treating enteric infections. Macrolides like azithromycin are recommended especially in patients with a recent history of travel to Asia.[39]

Nontyphoid *Salmonella* infection leads to bacteremia in approximately 8% of otherwise healthy adults. However, patients with increased risk of bacteremia should be treated with antibiotics if appropriate diagnosis is made. High-risk patients include neonates or infants younger than 1 year, persons older than 50 years, and patients with primary or secondary immunodeficiency such as acquired immunodeficiency syndrome (AIDS) or chemotherapy-induced inflammatory bowel disease, sickle cell disease, vascular abnormalities (prostatic heart valve or abdominal aneurysm), or prosthetic joints.[18] If cultures are positive for Salmonellosis and antibacterial therapy is warranted, susceptibility testing should be done for appropriate targeted therapy due to concern of resistance. *Salmonella enterica* serotype Typhi can cause enterocolitis and is a risk for typhoid fever. Although this pathogen is less prevalent, recent data have shown extensive drug resistance (susceptible to carbapenem or macrolide only), especially when travel to certain areas of the world (eg, Pakistan) were involved.[42] When treatment is required, it is important to take a full patient history to see if a patient may have a drug-resistant pathogen as the causative agent.

Outcomes of some bacterial diarrheal illnesses may be worsened by the use of antibacterials, therefore precluding their use. In patients infected with EHEC, use of a fluoroquinolone or trimethoprim-sulfamethoxazole may increase the risk of HUS by increasing the production of Shiga-like toxin.[1,41] Empiric antimicrobial therapy should be withheld when clinical suspicion is high due to the high local prevalence EHEC, patient clinical presentation suggestive of EHEC infection, or a known foodborne outbreak of dysentery with an incubation period of longer than 2 days. Antibiotics should not be given to infants or children due to a higher incidence of HUS in this population. Treatment of EHEC infection is primarily limited to supportive care, which may include fluid replacement therapy, hemodialysis, hemofiltration, transfusion red blood cells and/or platelets, and other interventions as indicated clinically. Severe disease may lead to chronic kidney failure and potential need of renal transplantation.

Antimotility Agents

5 Antimotility drugs such as diphenoxylate/atropine and loperamide offer symptomatic relief in patients with watery diarrhea by reducing the number of stools. However, in both enterotoxigenic and dysenteric diarrhea, slowing of fecal transit time with these agents is thought to result in extended toxin-associated damage, worsening symptomatology and leads to complications. Therefore, antimotility drugs should be avoided if possible and are not recommended in patients with toxin-mediated dysenteric diarrhea (ie, EHEC, pseudomembranous colitis, shigellosis). However, some evidence suggests that in adults with dysenteric diarrhea these agents do not appear to be harmful if given concomitantly with antibacterial therapy.[41]

Probiotics

Probiotics are preparations of microorganisms and most commercial products have been derived from food sources, particularly cultured milk products (ie, lactobacilli and bifidobacteria). When used in the treatment or prophylaxis of infectious diarrhea and antibiotic-associated diarrhea, efficacy is variable. Most individual studies have not shown significant benefit from the use of probiotics and meta-analyses have shown conflicting results, with one demonstrating efficacy when trials were assessed in aggregate[43] and another demonstrating no benefit.[44] Significantly decreased rates of CDI followed lactobacillus use in patients receiving 2 or more days of systemic antibacterials.[45] No serious adverse effects have been reported in otherwise healthy persons; however, there are data suggesting a rare but increased incidence of fungemia or bacterial sepsis with probiotic use. With confounding data both supporting and refuting the use of probiotics for prevention, the decision should be based upon patient-specific criteria.

Oral Zinc Supplementation

Zinc deficiency is largely due to inadequate dietary intake and is common in many developing countries where morbidity and mortality associated with acute diarrhea in children remains high. In children older than 6 months who demonstrate moderate signs of malnutrition, zinc supplementation may shorten the duration of diarrhea by approximately 27 hours (95% CI −14.62 to −39.34).[46] Therefore, oral zinc supplementation of 20 mg/day for 1 to 2 weeks may have an additional benefit over ORS alone in reducing childhood mortality in developing countries. Common side effects include metallic taste and vomiting. At high doses, zinc supplementation may cause epigastric pain, lethargy, and fatigue.

PREVENTION OF GASTROINTESTINAL INFECTIONS

6 Public health measures of improved water supply and sanitation facilities and the quality control of commercial products are important for the control of the majority of GI infections. In addition, following simple rules of personal hygiene and safe food preparation can prevent many diarrheal diseases. Hand washing with soap and running water is instrumental in preventing the spread of illness and should be emphasized for caregivers and persons with diarrheal illnesses. Safe food handling and preparation practices can significantly decrease the incidence of certain enteric infections.

Reporting suspected outbreaks and cases of notifiable illness to local health authorities is vital to investigation of threats of enteric infection arising from increasingly global and industrialized food supplies. The reporting of specific infectious diseases to the appropriate public health authorities is the cornerstone of public health surveillance, outbreak detection, and prevention and control efforts.

Vaccines are used to boost specific immune processes directed against the bacteria themselves or against adherence appendages, cytotoxins, or enterotoxins. Unfortunately, there are only a few vaccines available for prevention of gastroenteritis. Vaccines for typhoid fever are the parenteral Vi capsular polysaccharide vaccine (ViCPS) and the oral live-attenuated Ty21a vaccine.[47] Efficacy rates for both vaccines range from 50% to 80%. The ViCPS is indicated for children who are 2 years of age or older, and a booster dose is administered 2 years after the first. The Ty21a vaccine is indicated for children 6 years or older; one capsule should be swallowed whole every other day for a total of four doses at least 1 week before the potential exposure. A booster should be taken every 5 years if continued protection is needed.

In the United States, routine rotavirus vaccination is recommended for all infants beginning at age 2 months. There are two vaccines, RotaTeq (RV5) and Rotarix (RV1), available for reducing rotaviral gastroenteritis.[48] The RV5 vaccine is a live, oral vaccine that offers 74% efficacy against gastroenteritis of any severity and 98% efficacy against severe disease. This vaccine also decreased office visits by 86%, emergency department visits by 94%, and hospitalizations by 96%. The RV1 vaccine is a live-attenuated human rotavirus vaccine. This vaccine has clinical efficacy of 79% against gastroenteritis of any severity and 96% efficacy against severe rotavirus disease. Rotarix reduced hospitalizations by 100% and medically attended visits by 92% in the first rotavirus season, and reduced hospitalizations by 96% through two seasons.[48] The RV5 vaccine is administered orally in a three-dose series at ages 2, 4, and 6 months while the RV1 vaccine is administered orally in a two-dose series at ages 2 and 4 months. The first dose may be given between 6 weeks and 14 weeks and 6 days of age and all doses should be given before 8 months of age. The vaccines are contraindicated in infants with severe allergic reactions to vaccine components, diagnosed with severe combined immunodeficiency, and with history of intussusception.[49]

Although not available in the United States, two oral vaccines against diarrheal pathogens are available in other countries. Dukoral consists of killed *V. cholerae* O1 organisms and the cholera B subunit, and is licensed in over 60 countries. Shanchol consists of killed whole cells from a mix of pathogenic strains of *V. cholerae* (O1 and O139) and is licensed in India.[11,13] Both vaccines are given in two doses (three doses of Dukoral are required for children aged 2-5 years) and administered about 7 to 14 days apart (up to 42 days apart for Dukoral). Dukoral must be administered with a buffer that requires 75 to 150 mL of clean water while Shanchol does not require the buffer. Both vaccines demonstrated protective efficacy of 47% to 87% after two doses but almost none after a single dose. Protection is achieved in approximately 1 week following the last dose and persists for approximately 2 years. The common side effects of the vaccines were considered mild and included abdominal pain, headache, fever, and nausea. The WHO does not require vaccination for international travel to or from endemic areas because vaccines require two doses and provide incomplete protection for a relatively short period of time.[13]

There are vaccines in development for common enteric pathogens including ETEC and *Shigella* spp. with the potential for combining them in a single vaccine. These are still in preliminary and animal-based studies, but could significantly affect global public health if they come to fruition for human administration, especially in the infants and children.[50]

EVALUATION OF THERAPEUTIC OUTCOMES

Appropriate follow-up care of patients with acute diarrhea is based on successful restoration of fluid losses. The clinical signs and symptoms that lead to the diagnosis also can assess adequate rehydration, and should be monitored frequently. With ORT preferred, routine laboratory testing often is unnecessary. Electrolytes should be measured in those receiving IV fluids, when oral replacement fails, or when signs of hypernatremia or hypokalemia are present. Follow-up stool samples to ensure complete evacuation of the infecting pathogen may be necessary only in patients who are at high risk to initiate or contribute to a community outbreak. All patients should be monitored for complications associated with the infecting pathogen, resolution of the diarrhea, and adverse reactions to the pharmacologic agents used. Prompt discharge of hospitalized patients is recommended when rehydration is achieved, IV fluids have not been required, oral intake equals or exceeds losses, or adequate education and medical follow-up are ensured. For most patients, discharge can occur in 16 to 24 hours.

CLOSTRIDIOIDES DIFFICILE

Epidemiology

C. difficile is the most commonly recognized cause of infectious diarrhea in healthcare settings with high rates of disease in the elderly and those exposed to antibiotic agents. While almost all antibiotics have been implicated in *C. difficile* infection (CDI), those most commonly associated include fluoroquinolones, clindamycin, carbapenems, and third-/fourth-generation cephalosporins. CDI often occurs during or shortly after completion of antimicrobial therapy; however, disease onset can be delayed for 3 or more months.[51] Other risk factors for acquisition of *C. difficile* include recent healthcare exposure, chemotherapy, patients undergoing gastrointestinal surgery or receiving tube feeding, and potentially those receiving acid suppressive medications. While some studies show an association between *CDI* and acid suppressing medications, such as proton pump inhibitors (PPIs) and histamine-2 blockers, there is variability in the literature and a need for prospective randomized trials to confirm this link.[51,52]

Incidence of CDI was steadily rising in the early 2000s, appearing to peak around 2010 at approximately 500,000 cases annually in the United States and Europe. Growing concern for CDI, especially in the healthcare facilities, led to the creation of the Centers for Disease Control and Prevention (CDC) Emerging Infection Program (EIP) CDI tracking program. This program has been conducting population-based surveillance of *C. difficile* in 10 US cities since 2011 in order to estimate the national burden of CDI. While the epidemiology of CDI has remained relatively steady, trends indicate a decline in healthcare associated infecitons.[51,53] One confounding factor in the estimation of CDI incidence is the introduction of more sensitive tests, such as nucleic acid amplification tests (NAATs), which may lead to overdiagnosis.[53] Recurrent CDI is a major problem, with escalating risk of infection and increased mortality with subsequent infections.[51,52]

Etiology and Pathophysiology

C. difficile is a gram-positive spore-forming obligate anaerobic bacterium that may colonize the large intestine of healthy individuals, as well as those experiencing a symptomatic CDI. *C. difficile* is transmitted most commonly by the fecal-oral route through ingestion of *C. difficile* spores. Pathogenic CDI occurs when there is disruption of the bowel flora and/or an inadequate immune response. Two major toxins (toxin A [TcdA] and toxin B [TcdB]) are released and lead to a loss of integrity of colonic epithelial cells.[54] This mediates an inflammatory cascade that causes tissue damage and results in diarrhea. Initially, raised white and yellowish plaques form in the colon and the surrounding mucosa may become inflamed. With progression of disease, pseudomembranous plaques become enlarged and scattered over the colorectal mucosa resulting in pseudomembranous colitis.[51] The production of binary toxin, mutations causing hyperproduction of toxins, antibiotic resistance, increased sporulation, and mutations that increase adherence to the intestinal epithelium may contribute to the virulence and disease severity in the host. Some strains, such as BI/NAP1/027, express multiple mutations that make it hypervirulent and are a cause of significant clinical concern.[54]

CLINICAL PRESENTATION

Symptoms of CDI range from mild diarrhea to fulminant disease and toxic megacolon. The diarrhea is typically watery and nonbloody, and is often associated with abdominal discomfort, fever, and leukocytosis. Patients with new and unexplained diarrhea (>3 unformed stools in 24 hours) should be evaluated for CDI.

Diagnosis of CDI is confirmed by identification of *C. difficile* organisms/toxin in stool or by colonoscopic or histopathologic findings revealing pseudomembranous colitis.[51]

The optimal test for laboratory diagnosis remains controversial. Nucleic acid amplification tests (NAAT), such as PCR-based toxin testing, are very popular in the United States and have high sensitivity and specificity; however, they should only be used in patients with acute diarrhea due to the possibility of detecting the toxins in asymptomatic patients.[51,52] Alternatively, a stepwise approach uses screening for glutamate dehydrogenase (GDH) as the initial step. GDH assays detect a common antigen present in all isolates of *C. difficile*, including nontoxigenic strains, thus requiring combination with another test (typically a toxin test with or without NAAT). The stepwise approach may be preferred in institutions where there is no criteria for stool submission in order to minimize the false positive results that may result with NAAT alone. Utility of toxigenic culture or cell culture neutralization assays are limited due to delayed results and high cost. Use of toxin enzyme immunoassay (EIA) alone has a low sensitivity and has largely been replaced by NAAT testing or incorporated into multistep algorithms along with GDH assays.[51,55]

PATIENT CARE PROCESS

Patient Care Process for *Clostridioides difficile* Infections (CDI)

Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family), including any previous episodes of CDI
- Social history (eg, tobacco/ethanol use) and dietary habits
- Current medications including OTC, herbal products, dietary supplements, acid suppressive medication, and previous antibiotic use (within the past 3 months)
- Characteristics of diarrhea including onset, number of episodes per day, and presence of blood
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including white blood cell count (WBC) and serum creatinine (SCr)
  - Stool sample to be tested for *C. difficile* toxins
  - Radiographic abdominal imaging if concern for ileus or megacolon

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg, HR >110 bpm, O_2-sat <90% [0.90], RR)
- Radiographic studies for the presence of ileus, megacolon, or perforation
- Presence of CDI risk factors (age, antibiotic use, recent healthcare exposure, chemotherapy, GI surgery, tube feeding, acid suppressive medications)
- Ability to stop offending antibiotic agent if applicable
- Ability/willingness to pay for first-line treatment options
- Ability/willingness to try investigational therapies such as fecal microbiota transplant (if applicable for recurrent disease)
- Ability/willingness to pay for adjunctive therapy with bezlotoxumab

Plan*

- Drug therapy regimen including specific antibiotic dose, route, frequency, and duration (see Table 136-7)
- Discontinuation of offending antibiotic agent if applicable
- Monitoring parameters, such as resolution of diarrhea; frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, and prevention of disease transmission)
- Self-monitoring for resolution of diarrhea and when to seek emergency medical att ention
- Referrals to other providers when appropriate (eg, infectious diseases, gasteroenterology)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of diarrhea
- Presence of adverse effects (eg, CNS effects, metallic taste if metronidazole used; nausea, abdominal pain)
- Patient adherence to treatment plan using multiple sources of information
- Educate on limiting risk factors, such as antibiotic agents and acid suppressive medications

**Collaborate with patient, caregivers, and other healthcare professionals.*

TABLE 136-7

***Clostridioides difficile* Infection Severity and Treatment**

Severity	Markers of Disease Severity	Recommended Treatment
Nonsevere	WBC ≤15,000 cells/mm^3 (15 × 10^9/L) SCr <1.5 mg/dL (133 μmol/L)	Vancomycin 125 mg orally four times daily for 10 days, OR Fidaxomicin[a] 200 mg orally twice daily for 10 days, OR Metronidazole[b] 500 mg orally every 8 hours for 10 days.
Severe	WBC >15,000 cells/mm^3 (15 × 10^9/L) SCr >1.5 mg/dL (133 μmol/L)	Vancomycin 125 mg orally four times daily for 10 days, OR Fidaxomicin 200 mg orally twice daily for 10 days
Fulminant	Hypotension or shock Ileus and/or megacolon	Metronidazole 500 mg IV every 8 hours *PLUS* vancomycin 500 mg every 6 hours via NG or orally (if ileus present use rectally)

[a]Fidaxomicin is preferred over vancomycin for patients with an initial CDI per IDSA/SHEA 2021 Focused Update.

[b]Metronidazole is an alternative therapy if other agents are unavailable or too costly.

Data from References 51 and 56.

NG, nasogastric; SCr, serum creatinine; WBC, white blood cell.

Treatment

Supportive care of CDI includes fluid and electrolyte replacement therapy, in addition to discontinuation of the offending antimicrobial if possible. Antimotility agents (such as diphenoxylate/atropine and loperamide) and exchange resins (such as cholestyramine and colestipol) have been used in CDI; however, in general their use is discouraged. Empiric therapy for CDI may be considered if the patient has a strong pre-test suspicion for CDI and is severely ill, or if there is an expected substantial delay in laboratory confirmation. Antibiotic therapy is based on disease severity and may vary for first episode or recurrent infection.[51] Table 136-7 outlines CDI disease severity and treatment regimens for initial episodes according to the IDSA/SHEA 2017 clinical practice guidelines. Differences exist among the available guidelines with regard to the definitions of nonsevere, severe, and fulminant or complicated CDI and slight treatment differences. There is a need for prospectively validated severity scores for patients with CDI.

7 In the United States, vancomycin and fidaxomicin are FDA approved for CDI. These treatments are well tolerated because they have minimal systemic absorption when administered orally; the main adverse effects are nausea and abdominal pain. The recommended treatment course is 10 days and repeat stool testing is not recommended as a test of cure.[51] For nearly three decades oral metronidazole was the drug of choice for mild-to-moderate CDI; however, it has fallen out of favor based on evidence showing it is significantly less effective than vancomycin or fidaxomicin. The IDSA/SHEA 2017 clinical practice guidelines recommended therapies for both nonsevere and severe CDI include oral vancomycin or fidaxomicin. However, based on emerging data demonstrating the sustained response and safety profile of fidaxomicin, it is now the preferred therapy for initial CDI episodes. Vancomycin represents an acceptable alternative if fidaxomicin is not available, which may be reasonable based on the cost and variable medical insurance coverage of fidaxomicin.[56] When used for CDI, vancomycin must be administered orally because IV vancomycin does not achieve adequate gut lumen concentrations for effective bacterial elimination. Vancomycin is available as a capsule and there are several reconstituted oral solution or suspensions commercially available. The IV formulation has also been compounded and administered orally as a cost-effective option.

In patients with severe/complicated or fulminant CDI the preferred regimen is combination therapy with IV metronidazole and vancomycin.[57] The route of vancomycin administration is patient-dependent; oral is preferred, but if ileus is present, rectal administration via retention enema is recommended at a dose of 500 mg in 100 mL of saline administered four times daily. Fidaxomicin has not been studied in complicated or fulminant disease, therefore is not recommended.[51] Some patients with fulminant disease may require surgical intervention with procedures such as diverting loop ileostomy or total colectomy.

Recurrent CDI (rCDI) is typically defined as an episode of CDI within 8 weeks from the previous episode. Approximately 15% to 35% of patients will have a recurrence and the rate nearly doubles after two or more recurrences.[58] Risk factors for recurrent CDI include increasing age, use of additional antimicrobials, gastric acid suppression, hypervirulent strains, and low antibody response to *C. difficile* toxins.[51,58] The preferred regimen for the first episode of rCDI is fidaxomicin standard dose or an extended-pulsed regimen (200 mg twice daily for 5 days, then once every other day for 20 days). Pulsed and tapered oral vancomycin is an alternative approach for the first recurrence. If metronidazole was used initially, then a standard vancomycin course can be utilized for the first recurrence. For patients with multiple recurrences fidaxomicin remains the preferred agent; however, pulsed/tapered vancomycin, vancomycin followed by rifaximin, or fecal microbiota transplantation (FMT) are acceptable alternatives.[56]

The importance of the gut microbiome and its relationship to primary and recurrent CDI has led to research on several emerging therapies for CDI. Multiple randomized controlled trials have shown efficacy of FMT with resolution rates up to 90%. The American College of Gastroenterology recommends FMT by colonoscopy or capsule formulation oral ingestion with rCDI.[58,59] Protocols that have been studied include stool suspension administered to the lower bowel (through colonoscopy, rectal tube, or enema) or the upper GI tract (through nasogastric or duodenal tube or gastroscope). Several microbiota products available in a capsule formulation are undergoing clinical trials and may be available for use in the near future.[6,60]

A monoclonal antibody, bezlotoxumab, that binds to and neutralizes toxin B is FDA approved as an adjunctive therapy to reduce the recurrence of CDI. The approved dose is 10 mg/kg IV as a single dose during antibacterial treatment for CDI. Bezlotoxumab is not an antibiotic and should not be used as monotherapy. For patients with rCDI within 6 months, IDSA/SHEA suggest bezlotoxumab use during the administration of standard of care antibiotics. There may be feasibility concerns, such as cost and logistics, with this approach. The benefit of adding bezlotoxumab to fidaxomicin is unknown at this time due to limited data with concurrent use of these agents.[56] While generally well tolerated, adverse effects were greater in patients with heart failure who were treated with bezlotoxumab; use in these patients should be considered carefully.[61]

Growing concern for CDI has led to an influx of new antibiotics targeting *C. difficile*. A common characteristic of many of the emerging therapies for CDI is a narrow spectrum of activity with the aim to minimize gut dysbiosis. As many of these agents complete phase III trials, it may change the treatment landscape for CDI in the future.[62]

Prevention of CDI involves both preventing the acquisition of the infection and stopping transmission of *C. difficile* spores to other patients. CDI has become the focus of antimicrobial stewardship efforts aimed at eliminating unnecessary antibiotics and reducing durations of therapy, which may be responsible for the plateau of CDI rates in recent years. The use of probiotics to prevent CDI remains controversial.[60,63]Some studies and meta-analyses have shown no benefit, while other evidence supports probiotic safety and efficacy in preventing CDI. Currently, there is insufficient evidence to recommend probiotics and they are not recommended by the American College of Gastroenterology.[1,51] Hand washing and contact precautions are imperative measures in preventing the spread of the organism. Alcohol is less effective at eliminating *C. difficile* spores compared to use of soap and water; however, there is no association between alcohol-based hand hygiene and increased CDI incidence. Nonetheless, the use of soap and water to prevent disease transmission is the preferred strategy. Proper environmental disinfecting measures in healthcare settings include use of sporicidal cleaning agents.[51,60,61,63]

TRAVELER'S DIARRHEA

Traveler's diarrhea describes the clinical syndrome manifested by malaise, anorexia, and abdominal cramps followed by the sudden onset of diarrhea that incapacitates many travelers. It interferes with planned activities or work in 30% of those affected. In particular, an increased risk lies with North Americans and Northern Europeans traveling to Latin America, southern Europe, Africa, and Asia. The highest risk is observed with patients with immunocompromised conditions, achlorhydria, inflammatory bowel disease, and people with chronic debilitating medical conditions. Overall, 30% to

70% of people traveling to high-risk areas will develop the illness.[39]

8 The onset of symptoms usually occurs during the first week of travel but can occur anytime during the visit or after returning home. Traveler's diarrhea is caused by contaminated food or water. The most common pathogens are bacterial and include ETEC, *Campylobacter* spp., *Shigella* spp., and *Salmonella* spp.[10] Viral causes occur in less than 10% of cases with 80% to 90% of cases resulting from bacterial etiologies.[39] Enterotoxigenic *E. coli* is predominantly pathogenic in Latin America, Africa, and South Asia. The invasive enteric pathogens (*Campylobacter* spp., *Salmonella* spp., and *Shigella* spp.) are more important causes of traveler's diarrhea in Asia.

The severity of the syndrome is determined by the number of stools per day and the presence of cramping, nausea, and vomiting. Mild diarrhea is defined as one to three loose stools per day that are associated with abdominal cramps lasting less than 14 days. Moderate diarrhea indicates more than four loose stools daily associated with dehydration, and severe diarrhea is defined as the presence of blood in stools or a fever. Traveler's diarrhea is rarely life-threatening and in most cases, symptoms resolve in several days without treatment. Travelers to high-risk areas should pack a kit that includes a thermometer, loperamide, antibiotics (3-day course) (see "Treatment" section below), ORS salts, and a water purification method.[39]

Prevention

9 Patient education in avoiding high-risk food and beverages should be the best method for minimizing the risk. High-risk foods and beverages include raw or undercooked meat and seafood, moist foods served at room temperature, fruits that cannot be peeled, vegetables, milk from a questionable source, hot sauces on the table, tap water, unsealed bottled water, iced drinks, and food from street vendors. Although education is readily available, the incidence of diarrhea was similar in travelers who followed advice and those who engaged in riskier eating habits.[64] Rationales for this include that cooking foods does not always kill pathogens and food should not be considered safe unless it is cooked until steaming hot. Nonetheless, advisement of avoidance measures regarding safe foods, beverages, and eating establishments is recommended to heighten awareness.

Bismuth subsalicylate 524 mg (two chewable tablets or 2 ounces) orally four times daily for up to 3 weeks is a commonly recommended prophylactic regimen.[39] Bismuth subsalicylate may inhibit enterotoxin activity and prevent diarrhea. Persons taking this regimen should be informed of adverse events, including temporary black discoloration of tongue and stools, and, rarely, tinnitus.

Although the efficacy of prophylactic antibiotics has been documented, their use is not recommended for most travelers due to the potential side effects of antibiotics (eg, photosensitivity), predisposition to other infections such as CDI or vaginal candidiasis, the increased risk of selection of drug-resistant organisms, cost, lack of data on the safety and efficacy of antibiotics given for more than 2 or 3 weeks, and availability of rapidly effective antibiotics for treatment. Prophylactic antibiotics are recommended only in high-risk individuals or in situations in which short-term illness could ruin the purpose of the trip, such as a military mission. A fluoroquinolone is the drug of choice when traveling to most areas of the world.[39] Due to fluoroquinolone resistance among *Campylobacter* spp., azithromycin can be considered when traveling to South and Southeast Asia.

Rrifaximin is a nonabsorbed oral rifamycin that has activity against enteric pathogens and may have a role in the prevention of traveler's diarrhea in select populations. Rrifaximin 200 mg once, twice, or three times daily with meals for 2 weeks resulted in equal protection of 72% for each of the three dosing regimens compared with placebo.[40] Since rifaximin is effective against traveler's diarrhea due to noninvasive strains of *E. coli*, this agent should be reserved for travel regions where *E. coli* predominates, such as Latin America and Africa. Rifaximin has a tolerability and safety profile comparable to that of placebo. The concern with the rifamycin class is the emergence of resistance when used as monotherapy.

Treatment

The goals of treatment are to avoid dehydration, reduce the severity and duration of symptoms, and prevent interruption of planned activities. Fluid and electrolyte replacement should be initiated at the onset of diarrhea. ORT is generally not required in otherwise healthy individuals; flavored mineral water offers a good source of sodium and glucose. In infants and young children, elderly, and those with chronic debilitating medical conditions, ORT is recommended. For symptom relief, loperamide is preferred because of its quicker onset and longer duration of relief relative to bismuth. Standard dosing of loperamide is 4 mg orally initially and then 2 mg with each subsequent loose stool to a maximum of 16 mg/day in patients without bloody diarrhea and fever. Loperamide should be discontinued if symptoms persist for more than 48 hours. Other symptomatic therapy in mild diarrhea includes bismuth subsalicylate 524 mg every 30 minutes for up to eight doses.[39] As previously discussed, there is insufficient evidence to warrant the recommendation of probiotics.

Since behavioral modification has limited efficacy and chemoprophylaxis is not recommended in most travelers, the current recommendation relies on self-treatment. A single dose of antibiotic and up to 3 days of treatment will improve the condition within 24 to 36 hours, shortening the duration of diarrhea by 1 to 2 days.[39] A single dose of fluoroquinolone is recommended initially and if diarrhea is improved within 12 to 24 hours, antibiotics should be discontinued. Otherwise, it can be continued for up to 3 days. A fluoroquinolone is recommended when traveling to most areas of the world. Where fluoroquinolone-resistant *Campylobacter* is common, such as in South and Southeast Asia, azithromycin should be used.[39] Azithromycin can also be used in pregnant women and children younger than age 16 years. Empiric treatment of young children should be instituted with caution.

Rifaximin was as effective as a 3-day course of ciprofloxacin in shortening the duration of diarrhea in noninvasive traveler's diarrhea. However, rifaximin was not as effective in patients with fever and bloody diarrhea and in those with invasive pathogens. Therefore, a 3-day course of rifaximin has been approved for the treatment of traveler's diarrhea caused by noninvasive strains of *E. coli* in people 12 years or older and can be considered when traveling to areas where *E. coli*–associated traveler's diarrhea is common, such as Mexico and Jamaica.[39]

For rapid improvement in symptoms, antibiotic therapy with adjunctive treatment with loperamide has shown benefit.[65] All clinical trials concluded that the combination therapy was safe, and the worsening of the disease with the use of antimotility treatment has not been encountered.

FOOD POISONING

10 Foodborne illnesses result from the ingestion of food containing pathogenic microorganisms that cause GI infections or preformed toxins that were produced by microorganisms that cause enterotoxigenic poisonings. In the United States, foodborne diseases cause approximately 76 million illnesses, 325,000 hospitalizations, and 5,200 deaths each year.[4] Foodborne transmission may account for up to 80% of acute gastroenteritis. However, the incidence and outbreaks of foodborne illness have declined in recent years.[66] Common enteric pathogens responsible for foodborne diseases have been discussed in the previous sections (*Campylobacter* spp., *E. coli*, norovirus, nontyphoidal *Salmonella*, *Shigella*). Common foodborne pathogens that cause enterotoxigenic poisonings include *Bacillus cereus*, *Clostridioides botulinum, Clostridioides perfringens*, and *Staphylococcus aureus*. Characteristics of pathogens responsible for foodborne illnesses are summarized in Table 136-8.

TABLE 136-8

Food Poisonings

Organism	Principal Foods	Peak Incidence (United States)	Time to Symptoms	Duration	Common Symptoms
Enterotoxigenic Poisonings					
Bacillus cereus	Fried rice, dairy products, spices, bean sprouts, vegetables	None	1-6 hours 6-24 hours	1 day 1 day	Nausea, vomiting Diarrhea
Clostridioides botulinum	Home-canned fruits, vegetables, meats, honey	None	18-36 hours		Double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness
Clostridioides perfringens (type A)	Meats, poultry, gravies, dried or precooked foods	Fall, winter, spring	8-12 hours	1 day	Abdominal cramps, diarrhea
Staphylococcus aureus	Salad, pastries, ham, sandwiches, puddings, unpasteurized milk, cheese products	Summer	1-6 hours	1 day	Nausea, vomiting, abdominal cramps, diarrhea
GI Infections					
Campylobacter spp.	Poultry, dairy products, clams, water	Spring, summer	2-5 days	7 days	Diarrhea (may be bloody), cramping, abdominal pain, fever
Enteropathogenic *E. coli*	Water	None	1-3 days	5-7 days	Severe diarrhea, vomiting, dehydration
Enterotoxigenic *E. coli*	Water, ice, food	None	1-3 days	3-4 days	Profuse watery diarrhea, abdominal cramping
Salmonella spp.	Beef, poultry, water, eggs, dairy products	Summer	12-72 hours	4-7 days	Diarrhea (sometimes bloody), fever, abdominal cramps
Shigella spp.	Salad, water	Summer	1-2 days	5-7 days	Diarrhea (often bloody), fever, abdominal cramps
Vibrio cholerae	Water	None	2 hours to 5 days	2-3 days	Profuse watery diarrhea, vomiting, leg cramps
Vibrio parahemolyticus	Shellfish (oysters)	Spring, summer, fall	24 hours	3 days	Watery diarrhea, abdominal cramping, nausea, vomiting, fever, chills
Yersinia enterocolitica	Dairy products, raw or undercooked pork products	None	4-7 days	1-3 weeks	Fever, abdominal pain, diarrhea (often bloody)

Because foodborne disease can appear as sporadic cases or outbreaks, the diagnosis should be suspected whenever two or more people present with acute GI or neurologic manifestations after sharing a meal within the previous 72 hours. Important clues about etiologic agents can be gathered from demographic information (age, gender, etc.), the clinical syndrome, incubation period, and medical history, type of foods consumed, seasonality, and geographic location of the outbreak.

Enterotoxigenic poisonings result from ingestion of food contaminated by preformed toxins. Therefore, symptoms are rapid in onset, but most cases of food poisoning are of short duration with recovery occurring within 1 to 2 days. *B. cereus* causes two different types of clinical syndromes. The first one is characterized by a short incubation period and vomiting. The second syndrome has a longer incubation period and is characterized by diarrhea. Foodborne *C. perfringens* infection may present as two distinct syndromes. Type A organisms are seen in Western Hemisphere nations and result in a 24-hour illness characterized by watery diarrhea and epigastric pain. Type C organisms can be found in undercooked pork and occur in underdeveloped tropical regions. They can produce a toxin-related syndrome called *enteritis necroticans*, which is a coagulative transmural necrosis of the intestinal wall.[67] This syndrome can result in intestinal perforation leading to sepsis and mortality in approximately 40% of victims.

Foodborne botulism results from the ingestion of food contaminated with preformed toxins or toxin-producing spores from *C. botulinum*. Poisoning from *C. botulinum* is rare; only 110 cases are reported per year in the United States. Botulism is almost always associated with improper preparation or storage of food. Seven distinct toxins (A to G) have been described. The toxins prevent the release of acetylcholine at the peripheral cholinergic nerve terminal. Toxin activity has prompted the use of minute locally injected doses to treat select spastic disorders, such as blepharospasm, hemifacial spasm, and certain dystonias. Foodborne botulism is suspected when patients present with acute GI symptoms concurrently or just prior to the onset of a symmetric descending paralysis without sensory or central nervous system involvement. Diagnosis is made by culturing *C. botulinum* from the stool. The clinical presentation may resemble GBS associated with *C. jejuni* infection. The difference lies in the onset of neurologic symptoms, which typically occur 1 to 3 weeks after the onset of *C. jejuni* infection, and the condition usually is manifested by an ascending paralysis in *C. jejuni*–associated GBS.

Treatment consists primarily of respiratory support and use of botulinum antitoxin. If evaluation is performed within several hours of ingestion, gastric lavage or induction of vomiting is suggested. Cathartics and enemas also can be used to remove residual toxin from the bowel, but they are contraindicated in cases of ileus. Botulinum antitoxin is a concentrated preparation of equine globulins obtained from horses immunized with toxins A, B, and E. Because trivalent antitoxin is equine in origin, patients should be tested for hypersensitivity before receiving the product intravenously. Newer and more effective methods of treatment and prevention are under development, including a botulinum toxin vaccine consisting of nontoxic botulinum fragments. Prevention always should be stressed. Botulinum toxins are heat labile and readily destroyed by 10 minutes of boiling. All home-canned foods should be processed according to directions and boiled, not just warmed, prior to consumption.

In foodborne illnesses, the cornerstone of therapy remains supportive care. ORT is preferred in replenishing and maintaining fluid and electrolyte balance, and IV fluid therapy should be reserved for those who are severely ill and cannot tolerate oral therapy. Antiemetics and antimotility agents offer symptomatic relief, but the latter should not be given in patients who present with high fever, bloody diarrhea, or fecal leukocytes. Antimicrobial therapy is not effective in the management of *S. aureus*, *C. perfringens*, or *B. cereus* food poisonings. In developed countries, many of the foodborne illnesses can be prevented with proper food selection, preparation, and storage. However, in developing countries, sanitation and clean water supply are larger concerns.

ABBREVIATIONS

AIDS	acquired immunodeficiency syndrome
cAMP	cyclic adenosine monophosphate
CDI	*Clostridioides difficile* infection
CRP	C-reactive protein
EAEC	enteroaggregative *Escherichia coli*

EHEC	enterohemorrhagic *Escherichia coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *Escherichia coli*
EPEC	enteropathogenic *Escherichia coli*
ETEC	enterotoxigenic *Escherichia coli*
FDA	Food and Drug Administration
FMT	fecal microbiota transplant
GBS	Guillain-Barré syndrome
GDH	glutamate dehydrogenase
HIV	human immunodeficiency virus
HUS	hemolytic uremic syndrome
IDSA	Infectious Diseases Society of America
IBS	irritable bowel syndrome
IL	Interleukin
IVIG	intravenous immune globulin
NAAT	nucleic acid amplification tests
NAP-1	North American pulsed-field type 1
ORS	oral rehydration solution
ORT	oral rehydration therapy
PKA	protein kinase A
PPI	proton pump inhibitor
SHEA	Society for Healthcare Epidemiology of America
STEC	Shiga toxin–producing *Escherichia coli*
UNICEF	United Nations Children's Fund
ViCPS	Vi capsular polysaccharide vaccine
WHO	World Health Organization

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SELF-ASSESSMENT QUESTIONS

1. The most common cause of infectious diarrhea in American children is which of the following pathogens?

   A. *Vibrio cholerae*

   B. *Campylobacter jejuni*

C. *Yersinia enterocolitica*

D. *Escherichia coli*

E. Rotavirus

2. Which of the following pathogens is most commonly associated with dysentery (bloody) diarrhea?

A. *Vibrio cholerae*

B. *Escherichia coli*

C. *Clostridioides difficile*

D. *Yersinia enterocolitica*

3. Which of the following statements regarding the treatment of *E. coli*–related infectious diarrhea is FALSE?

A. Initial treatment should include appropriate hydration with low-osmolar or isotonic fluid replacement.

B. The use of antimotility agents, like loperamide, could potentially increase diarrheal symptoms due to prolonged exposure to bacterial toxin.

C. Using fluoroquinolone agents for treatment of this infection is appropriate when bloody stools are present and serotype is undetermined.

D. None of the above are FALSE.

4. Which of the following causes of dysentery diarrhea currently has an available vaccine in the United States that may prevent some species of the disease?

A. Shigellosis

B. Campylobacteriosis

C. Salmonellosis

D. Yersiniosis

E. None of the above have available vaccine

5. Which of the following statements regarding rehydration therapy in a patient with gastroenteritis is FALSE?

A. Intravenous fluid replacement is indicated in all pediatric patients with infectious diarrhea.

B. Glucose and other simple sugars in high concentrations can worsen diarrhea in a patient acutely ill with gastroenteritis.

C. If a patient presents with gastroenteritis and an ileus, intravenous fluid replacement is indicated.

D. None of the above are FALSE.

6. Which of the following statements regarding diagnosis of *Clostridium difficile* infection (CDI) is/are TRUE?

A. Diagnosis of CDI requires presence of bacterial-released toxin and a host response to that toxin.

B. Testing for toxin production in CDI with solid, formed stools is appropriate to ensure eradication of the organism.

C. CDI diagnosis requires anaerobic cultures for confirmation.

D. All of the above are true.

7. According to current guidelines, what class of antimicrobials would be indicated for treatment in a 62-year-old patient with confirmed enterocolitis due to a *Salmonella* species?

   A. Cephalosporin

   B. Aminoglycoside

   C. Macrolide

   D. Carbapenem

8. Treatment for an adult with campylobacteriosis that started having bloody diarrhea 2 days ago should be initiated on which of the following medication?

   A. Ciprofloxacin

   B. Doxycycline

   C. Metronidazole

   D. Azithromycin

   E. No antimicrobial therapy is warranted

9. Which of the following viral causes of infectious gastroenteritis could be seen during the winter months and would be common in adults?

   A. Rotavirus

   B. Norovirus

   C. Astrovirus

   D. Coronavirus

10. A patient is diagnosed with CDI and has a WBC of 17,500 cells/mm^3 (17.5×10^9/L). Which of the following regimens would be an appropriate selection for treatment, according to the most recent guidelines for the treatment of CDI?

    A. Metronidazole 500 mg orally every 8 hours

    B. Vancomycin 125 mg orally every 6 hours

    C. Fidaxomicin 200 mg orally twice daily

    D. All of the above are appropriate

    E. Only TWO of the above are appropriate

11. According to current guidelines, a patient diagnosed with first-episode CDI that is determined to be critically ill (has systemic symptoms including hypotension) should be treated with which of the following for *C. difficile* treatment?

    A. Metronidazole orally

    B. Vancomycin orally

    C. Vancomycin intravenously

    D. Fidaxomicin orally

E. Metronidazole intravenously + vancomycin orally

12. Which of the following statements is/are TRUE regarding CDI prevention?

A. Hand washing with soap and water can help prevent person-to-person transmission of CDI.

B. Room disinfection after a CDI patient is discharged must be performed with alcohol-based cleaners.

C. *C. difficile* spores survive only hours outside the host, so time is another method of preventing CDI transmission.

D. Respiratory precautions (masks and face shields) should be utilized when entering and taking care of a CDI patient.

E. None of the above are true.

13. Which of the following would NOT be considered a common pathogen in causing traveler's diarrhea?

A. Enterotoxigenic *Escherichia coli*

B. Rotavirus

C. *Shigella dysenteriae*

D. *Vibrio cholerae*

E. All of the above are common pathogens in traveler's diarrhea

14. Recommended prophylaxis for traveler's diarrhea should include which of the following?

A. Education on proper food and personal hygiene

B. Famotidine 20 mg orally twice daily while traveling

C. Ciprofloxacin 750 mg orally once daily while traveling

D. All of the above should be recommended

15. A patient is having some diarrhea and is diagnosed with food poisoning following eating potato salad and tapioca pudding at his family reunion. In all likelihood, the causative pathogen is *Staphylococcus aureus*. Which of the following antibacterials should be recommended for his treatment in combination with ORT?

A. Ciprofloxacin

B. Azithromycin

C. Trimethoprim-sulfamethoxazole

D. Linezolid

E. No antibiotic therapy is warranted

SELF-ASSESSMENT QUESTION-ANSWERS

1. **E.** Diarrhea is a common malady in children, although more problematic in the developing world. In the United States, the most common pathogen is still viral pathogens so rotavirus is the most likely cause.

2. **D.** Dysentery diarrhea needs to be distinguished from enterotoxigenic (watery) diarrhea based on symptoms and pathogens. Although some pathogens may produce similar symptoms after prolonged illness, *Yersinia* spp. causes dysentery type diarrhea more commonly whereas the other

options are most commonly causes of enterotoxigenic diarrhea.

3. **C.** If only the pathogen is known and the serotype is not, we could precipitate hemolytic uremic syndrome if the serotype is E. coli O157:H7. Preference would be to avoid antimicrobials, if possible, or obtain serotype testing prior to initiating antimicrobial therapy with fluoroquinolones or any potential agent.

4. **C.** The only bacterial pathogen causing gastrointestinal infections that would have an available vaccine is *Salmonella* spp.

5. **C.** Fluid replacement therapy should be instituted for all patients with infectious diarrhea. However, intravenous therapy is not required in pediatric or adult patients unless certain severity criteria are met. The other statements are true.

6. **A.** Diagnosis of *C. difficile* infections require symptoms and a positive toxin test. Cultures are not recommended and solid stools should never be tested for *C. difficile*.

7. **A.** Treatment strategies for salmonellosis include ceftriaxone, ciprofloxacin, or ofloxacin. Of these options, ceftriaxone is a cephalosporin and the fluoroquinolones are not listed as an option. Recall there could be utility of other agents based on resistance profiles, but generally using ceftriaxone should be sufficient.

8. **A.** Because the patient is showing signs of dysentery diarrhea, antimicrobial therapy is often recommended for campylobacteriosis. Here the preferred agent is a macrolide and azithromycin would be the preferred option.

9. **D.** Although common causes of gastroenteritis in the pediatric population, viral causes are less common in adults. Of the choices, norovirus would be predominant in the adult population during winter months, if not bacterial. The other viruses are uncommon in adults.

10. **B.** Treatment for CDI is based upon symptoms and with this patient showing severe etiology, based upon the treatment guidelines, metronidazole should be avoided here and in general for treatment of *C. difficile*. Oral vancomycin or fidaxomicin is the recommended treatment option at this point.

11. **E.** Treatment of first-episode CDI should include oral vancomycin or fidaxomicin. Metronidazole should be avoided, if at all possible, for the treatment of CDI in all settings. IV vancomycin does not readily achieve appropriate concentrations in the GI tract and thus would be ineffective. While fidaxomicin is an appropriate choice, it is significantly more expensive than oral vancomycin for CDI treatment and thus oral vancomycin should be used initially in this patient.

12. **A.** CDI is problematic and can contaminate and spread readily if appropriate precautions are not taken. Hand sanitizer is not appropriate in the prevention of CDI, so hand washing with soap and water is recommended. Rooms must be fully cleaned with chlorine-based disinfectants. *C. difficile* spores can remain on surfaces for long periods of time so caution needs to be taken with any possible infectious patient. And finally, respiratory precautions are not necessary for *C. difficile* patients, only stringent contact precautions.

13. **E.** Traveler's diarrhea can be from a number of different pathogens, either enterotoxigenic or dysentery. However, *Vibrio* spp. is an uncommon cause of traveler's diarrhea.

14. **D.** Although there are recommendations for certain people to have antimicrobial therapy with them while traveling, it is not recommended for most people. Acid-suppression could increase the risk of infection acquisition. Food and personal hygiene are of utmost importance in preventing traveler's diarrhea.

15. **A.** Food poisonings can occur with a large variety of pathogens. However, no antimicrobial therapy is recommended in patients with acute food poisoning. If the duration of the symptoms last longer than 24 hours, a patient should be seen by a physician and potential options delineated. Fluid replacement is appropriate in these patients as well.