

2

Infectious Gastroenteritis and Colitis

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CONTENTS

INTRODUCTION
ETIOLOGY
CLINICAL PRESENTATION
SPECIFIC INFECTIONS
CLINICAL EVALUATION
DIAGNOSTIC EVALUATION
TREATMENT
CONCLUSION
REFERENCES

Summary

In this chapter, we discuss the epidemiology, etiology, presentation, diagnosis, and treatment of infectious diarrhea in immunocompetent persons. The features of small intestinal and ileocolonic disease as related to possible causative agents are presented. Additionally, there is an emphasis on specific pathogens, with a comprehensive review of viral, bacterial, and parasitic causes of diarrhea. We then discuss the intricacies of the clinical and diagnostic evaluation, as well as treatment. Specifically, we evaluate the severity of illness, historical clues to etiology, the appropriateness of diagnostic testing in various clinical situations, and which diagnostic tests are clinically relevant. Rehydration therapy is discussed along with nutrition and electrolyte

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support. The appropriate use of antidiarrheal and antimicrobial medications is reviewed, along with a brief discussion of empiric therapy and the individual and public health consequences associated with infection and treatment.

Key Words: Acute diarrhea, Infectious diarrhea, Enteritis, Colitis, Enterocolitis, Microorganisms, Virus, Bacteria, Parasites

INTRODUCTION

Infectious diarrhea is a major cause of morbidity and mortality worldwide. Children in developing countries are disproportionately affected by acute diarrhea, averaging 1–3 episodes per year. In these settings, infectious diarrhea accounts for approximately 20–25% of the mortality in children less than 5 years of age [1]. In addition, morbidity of repeated infections is manifest as malnutrition with cognitive and physical developmental delays. Around the world, there is a substantial difference in incidence of disease among children from different socioeconomic strata [1]. This difference is likely related to variability in sanitation, living quarters, and access to treated food and water. Over the last several decades, mortality from infectious diarrhea has significantly decreased, yet morbidity remains largely unchanged. The decline in mortality is believed to be the result of the widespread implementation of oral rehydration therapy as recommended by the World Health Organization (WHO) [2]. The lack of improvement in morbidity and incidence of disease is likely related to limited improvement in living conditions.

In developed nations, the mortality rate is lower, seen predominantly at the extremes of age. Morbidity still remains a major problem, with children experiencing 2–3 episodes and all persons experiencing 1–2 episodes of acute diarrhea per year [3]. In the United States alone, there are an estimated 200–300 million episodes of diarrheal illness each year, resulting in 73 million physician consultations, 1.8 million hospitalizations, and an estimated 6 billion dollars spent each year on medical costs and loss of productivity [3]. With globalization of food processing and distribution, the number of foodborne diarrheal illnesses has risen [3].

With the morbidity, mortality, and cost of infectious diarrhea, it is important to promptly determine the appropriate diagnostic evaluation and treatment.

ETIOLOGY

The major pathogens causing acute infectious diarrhea are viruses, bacteria, and parasites. Most cases are self-limited, resolve within 24–48 h,

and in developed nations, are likely to be viral. A pilot study in the USA identified a pathogen in approximately 70% of cases, three-quarters of which were norovirus [4]. In healthy adults, the most likely pathogens causing severe diarrheas are bacteria [5]. In developing nations and in returning travelers, enterotoxigenic *Escherichia coli* (ETEC) is the most likely pathogen. Parasites are identified less frequently as the cause of acute infectious diarrhea.

CLINICAL PRESENTATION

Diarrhea is classified as acute (duration less than 2 weeks), persistent (2–4 weeks), and chronic (greater than 4 weeks). Most infectious diarrhea are brief and self-limited, and managed by patients alone. Of those patients who do present to clinicians, their illness can generally be divided into small intestinal or ileocolonic disease (see Table 2.1).

Pathogens affecting the small intestine are usually noninvasive organisms. These patients present with high-volume watery stools and in some cases malabsorption, frequently leading to dehydration. Patients often have periumbilical pain and cramping. The most common pathogens in this category are viruses, such as norovirus and rotavirus, but also include bacteria: enterotoxigenic *E. coli*, *Vibrio cholerae*, toxin-producing *Staphylococcus aureus*, and the parasites *Giardia lamblia*, *Isospora belli*, and cryptosporidia (see Table 2.2). These enteropathogens typically cause disease via enterotoxin production, ingestion of preformed toxin, and/or bacterial adherence to epithelial cells [6].

Colonic and distal small intestinal pathogens are more likely to be invasive. They result in a syndrome of lower abdominal pain; small-volume, frequent stools which can be bloody and tenesmus (when the rectum is involved) (see Table 2.1). The most common pathogens causing this presentation are bacteria including *Campylobacter*, *Shigella*, *Salmonella* and *Shiga* toxin-producing *E. coli*, and *Clostridium difficile*.

Table 2.1
Features of small intestinal and ileocolonic disease

<i>Features of small intestinal disease</i>	<i>Features of ileocolonic disease</i>
Diffuse periumbilical pain	Lower abdominal pain
Large volume stools	Small-volume stools
Watery stools	Stools may be bloody
Dehydration	Tenesmus
Possible malabsorption	Dehydration

Table 2.2
Small intestinal and ileocolonic pathogens

<i>Small intestinal pathogens</i>	<i>Ileocolonic pathogens</i>
Viruses	Viruses
Caliciviruses (norovirus)	CMV
Rotavirus	Adenovirus
Enteric adenovirus	Bacteria
Bacteria	<i>Salmonella</i>
<i>E. coli</i>	<i>Shigella</i>
ETEC	<i>Campylobacter</i>
EPEC	STEC or EHEC
EAEC	EIEC
DAEC	<i>C. difficile</i>
<i>V. cholera</i>	<i>Yersinia</i>
<i>L. monocytogenes</i>	Non-cholera vibrios
<i>C. perfringens</i>	<i>P. shigelloides</i>
<i>S. aureus</i>	<i>A. hydrophila</i>
Parasites	Tuberculosis
<i>G. lamblia</i>	<i>K. oxytoca</i>
<i>Cryptosporidium</i>	<i>C. perfringens</i>
<i>Microsporidium</i>	Parasites
<i>Cyclospora</i>	<i>E. histolytica</i>
<i>Isospora</i>	<i>T. trichiura</i>
	<i>B. coli</i>
	<i>B. hominis</i>

The parasite *Entameba histolytica* has a predilection for the ileocolonic area. Fungi are rare in the immunocompetent host (see Table 2.2). The major mechanisms by which the pathogens cause ileocolonic illness are cytotoxin production and mucosal invasion leading to inflammation and ulceration [6].

Although there is some overlap between these two categories, this distinction is useful to help delineate the likely enteropathogen.

SPECIFIC INFECTIONS

Small Intestinal Pathogens

VIRUSES

Viral gastroenteritis. Viral gastroenteritis is the most common cause of self-limited, acute diarrhea worldwide, in both children and adults [7]. Viruses cause illness by diverse mechanisms. In general they infect

mature villous enterocytes, resulting in loss of the brush border and impaired absorption [6–8]. New evidence suggests that rotaviruses may also cause villous ischemia, produce a viral enterotoxin, and even affect the enteric nervous system [7–9]. Patients typically present with dehydrating diarrhea and vomiting, and may have associated fever. The diarrhea typically resolves within a few days, although adenovirus may cause persistent, severe disease in immunosuppressed patients [8]. Rotaviruses and noroviruses are the most common causes of diarrhea in the pediatric population [7], and noroviruses are the most common in adults. Both viruses are highly contagious as demonstrated by high rates of transmission in day cares, hospitals (rotavirus) [7], cruise ships, and banquets (noroviruses). Noroviruses can be acquired by ingestion of raw oysters from fresh water estuaries. Since viral gastroenteritis is generally self-limiting, diagnostic tests are usually unnecessary. Treatment is supportive with oral rehydration. Hand washing with soap is imperative for containment, as alcohol hand gels may not adequately kill these viruses. The American Academy of Pediatrics recommends routine immunization of infants with either of the two available rotavirus vaccines [10]. Norovirus vaccines are under development.

BACTERIA

Escherichia coli. Several groups of *E. coli* cause diarrhea. Those *E. coli* that affect the small intestine include enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), and diffusely adherent (DAEC) *E. coli*. These bacteria all cause illness by enterotoxin production or adherence to the brush border causing effacement of cells; DAEC also has cytotoxic effects [11]. Symptoms include self-limited watery diarrhea, occurring within 2 days of ingestion and resolving within 3 days of onset. Diarrhea may occasionally be associated with nausea, vomiting, or fever. Both ETEC and EAEC are major causes of traveler's diarrhea [11, 12], and EAEC is an important cause of bacterial diarrhea in children in both the USA and developing countries [11, 13]. EAEC can also cause chronic diarrhea in persons with HIV [11]. ETEC is increasingly a cause of foodborne illness [13]. DAEC is a cause of diarrhea in children less than 2 years old [14]. EPEC is uncommon but can cause both sporadic and epidemic diarrhea, primarily in young children in developing countries. EPEC may cause severe dehydration or malnutrition, especially when infection is chronic. Historically, there have not been good diagnostic tests for these infections. However, newer techniques are allowing for identification of the different *E. coli* species when suggested by clinical history [13]. Treatment is directed at rehydration therapy. Fluoroquinolones

(FQ), trimethoprim–sulfamethoxazole (TMP–SMX), azithromycin, or rifaximin can be used in conjunction with antidiarrheals to decrease symptoms of traveler’s diarrhea, when appropriate [3, 13].

Vibrio cholera. *Vibrio cholerae* causes epidemics of dehydrating diarrhea affecting all ages and may lead to high mortality rates if the public health interventions are inadequate [1]. *Vibrio cholerae* serogroups O1 (biotypes classical and El Tor) and O139 are responsible for these epidemics. Non-O1 non-O139 vibrios are pathogenic but do not cause epidemics or pandemics [15]. Studies now suggest that the majority of individuals are asymptomatic or have only mild diarrheal disease [16]. In developing countries, cholera transmission is via contaminated food and water; in the USA, it is usually associated with ingestion of undercooked seafood from the Gulf of Mexico [15]. Risk factors for infection include blood group O, HIV [17], and low gastric acid. Cholera is rare in travelers. *Vibrio cholerae* colonizes the upper small intestine and causes diarrhea by stimulating cAMP-mediated chloride secretion, inhibiting sodium absorption, and producing platelet-activating factor with possible resultant alteration in prostaglandin synthesis. Diarrhea is abrupt in onset, resembles rice water, and is associated with vomiting. Without proper treatment, the case–fatality rate approaches 50% [15]. Treatment is initially aimed at rehydration. Antibiotics are given to shorten the duration of diarrhea. For severe cases, intravenous fluids are necessary and should be isotonic. For mild cases, oral rehydration therapy (ORT) is preferred. Recent evidence suggests that rice, wheat, or amylase-resistant starch solutions may be better than standard glucose-based solutions [18–20]. Patients should eat as soon as they can tolerate oral intake, and infants should continue to breastfeed [15, 21, 22]. Without antibiotics, patients generally recover in 4–5 days, so mild diarrhea does not require treatment. Oral vaccines are in development; the older parenteral vaccine is not recommended.

Listeria monocytogenes. *Listeria* was not thought to cause gastrointestinal illness until the 1990s when an outbreak of contaminated chocolate milk caused acute febrile gastroenteritis. Since then, multiple epidemics have been reported, linked to chocolate milk [23], lunch meats, and unpasteurized cheeses. Immunocompromised persons and pregnant women are at increased risk of infection and invasive disease. Watery diarrhea and fever are often accompanied by myalgias, arthralgias, headache, and fatigue or sleepiness [23–25]. Invasive infections can be fatal. The diagnosis should be considered in patients with febrile gastroenteritis when routine cultures do not identify a pathogen. Stool

culture on selective media is diagnostic; blood or cerebrospinal fluid cultures may be useful in invasive disease. Since *Listeria* gastroenteritis is generally self-limited and noninvasive, treatment is not currently recommended [24]. Ampicillin or penicillin G is used for treatment of invasive disease.

Staphylococcus aureus. Enterotoxin-producing *S. aureus* has long been an important cause of food poisoning, leading to vomiting 2–7 h after ingestion of the toxin [13]. More recently, however, it has been studied as a cause of antibiotic-associated diarrhea (AAD). Studies have shown that many AAD *S. aureus* isolates can produce enterotoxins, leukotoxins, or toxic shock syndrome toxin 1 [26, 27]. *Staphylococcus aureus* can be part of normal gut flora, and colonization rises with duration of hospitalization and placement of nasogastric tubes. Among hospitalized patients with AAD, the majority of *S. aureus* isolates were methicillin-resistant *S. aureus* (MRSA). In these patients, MRSA was found in the blood, suggesting colitis as the cause of bacteremia [27]. MRSA is shed in stools. Therefore, testing for MRSA-associated AAD in *C. difficile*-negative patients should be considered to avoid dissemination of MRSA throughout the hospital. Testing may also be considered in community-acquired cases of severe *C. difficile*-negative AAD.

PARASITES

***Giardia intestinalis* (also called *Giardia lamblia*).** *Giardia* is the most commonly isolated intestinal parasite in developed countries [28]. It is prevalent throughout the world and is transmitted person-to-person or via contaminated water. Ingested cysts, which are resistant to chlorine and gastric acid, become trophozoites in the small intestine and attach to the mucosa. Genotype appears a predictor of disease severity [29, 30]. Symptoms range from asymptomatic carriage to severe cramps, bloating and gas, nausea, vomiting, and malabsorption resulting in explosive fatty diarrhea. Chronic infection can occur in immunocompetent patients as well as in those with hypogammaglobulinemia, especially IgA deficiency. Diagnosis is based on the detection of cysts in stool. Since cyst excretion is intermittent, three stools over 6 days are necessary; one stool has a yield of 50–70% and three stools have a yield of 90%. The *Giardia* stool antigen EIA is excellent, with a sensitivity of 95% and a specificity of 100%. Duodenal aspiration of trophozoites is also possible. In the USA, the principal treatment is metronidazole. Alternatives include nitazoxanide and

tinidazole. Approximately 10–20% of patients will relapse and require retreatment [31].

Cryptosporidiosis. *Cryptosporidium* was recognized as a pathogen in humans in 1976 when case reports documented it to cause severe diarrhea in immunosuppressed patients. Although the organism primarily infects immunocompromised hosts, it can also infect normal hosts. Transmission is caused by fecal contamination of water and subsequent ingestion of the chlorine-resistant oocysts. Symptoms range from mild-to-severe watery diarrhea and can be chronic in patients with immunodeficiency. Patients may also have dyspepsia, weight loss, and anorexia. Diagnosis is by stool examination with acid-fast stains. In normal hosts, disease is self-limited to 2–4 weeks. While previously there was no effective antimicrobial therapy and treatment was supportive [32], recent controlled trials showed efficacy of nitazoxanide [33]. It is now FDA approved for children and immunocompetent patients.

Cyclospora cayetanensis. *Cyclospora* causes prolonged watery diarrhea, often lasting 4–6 weeks. The organism resembles *Cryptosporidium*, but is larger, and has blue autofluorescence when examined by UV epifluorescence microscopy, hence the older names “cyanobacter” and “blue-green algae.” It is transmitted by contaminated food or water. After ingestion and excystation, trophozoites invade epithelial cells in the small intestine. Since 1990, there have been at least 11 foodborne outbreaks in the USA and Canada [34]. If untreated the diarrhea may last 10–12 weeks and follow a relapsing course. Associated symptoms include anorexia, weight loss, nausea, vomiting, abdominal pain, and myalgias. Diagnosis is made by light microscopy detecting oocysts in stool; excretion can be intermittent, so multiple stools should be examined. Treatment with TMP–SMX shortens the course of illness.

Isospora belli. *Isospora belli* predominantly causes disease in immunocompromised hosts; however, the organism can also cause traveler’s diarrhea and outbreaks in immunocompetent individuals. Similar to cryptosporidia, *Isospora* causes self-limited watery diarrhea in normal hosts and chronic diarrhea in immunosuppressed patients. Eosinophilia may be present. Diagnosis is made by identifying oocysts in stool with a modified acid-fast stain or by small bowel biopsy. Treatment is with TMP–SMX. Metronidazole and pyrimethamine are alternatives for patients with sulfa allergies [34].

Microsporidiosis. Microsporidia are increasingly recognized as opportunistic infections. Fourteen species infect humans, two of

which cause gastrointestinal illness: *Enterocytozoon bienersi* and *Encephalitozoon intestinalis*. These pathogens cause chronic watery diarrhea and weight loss; *E. bienersi* can also cause acalculous cholecystitis and *E. intestinalis* can disseminate to the eye, urinary, and respiratory tracts. Diagnosis is by light microscopy, which cannot distinguish species, or electron microscopy, which is expensive and time-consuming. Treatment for *E. bienersi* is oral fumagillin [34]. *Encephalitozoon intestinalis* and disseminated microsporidiosis are treated with albendazole [34].

Ileocolonic Pathogens

BACTERIA

Campylobacter. *Campylobacter* species are common causes of diarrheal illness worldwide. *Campylobacter jejuni* causes the overwhelming majority of illness in the USA, with *Campylobacter coli* a distant second [35]. Campylobacteriosis is primarily a foodborne illness with poultry being the leading source of infection. *Campylobacter* can also be transmitted by the fecal–oral route or by contaminated milk, eggs, or water. *Campylobacter* is an invasive organism that induces an inflammatory response which can lead to edema, mucosal bleeding, formation of microabscesses, and ulcerations [6]. Symptoms include cramping, nausea, anorexia, and watery or bloody diarrhea. Infection is self-limited and usually resolves within a week. Colitis is common and can occasionally mimic appendicitis. Complications of infection include post-infectious irritable bowel syndrome, reactive arthritis (formerly Reiter’s syndrome), and is the most common cause of Guillain–Barré syndrome [13]. Diagnosis is made by stool culture. Treatment is not indicated for mild-to-moderate illness and in fact may lead to increasing antimicrobial resistance. Treatment is appropriate in patients with severe disease or symptoms lasting longer than 1 week. Macrolides are the treatment of choice [3, 13, 35]. Fluoroquinolones can still be used, but there are increasing numbers of ciprofloxacin-resistant strains [36]. Resistance to macrolides is now being reported but tends to occur more often with *C. coli* than *C. jejuni* [35].

Salmonella. *Salmonella enterica* subspecies *enterica* has multiple serotypes. The most common serotypes infecting humans are *Salmonella enteritidis*, *Salmonella heidelberg*, *Salmonella newport*, *Salmonella typhimurium*, and *Salmonella typhi*. These organisms cause two distinct clinical syndromes: enterocolitis (nontyphoidal serotypes) and typhoid fever (*S. typhi*).

Enterocolitis (gastroenteritis). Nontyphoidal *Salmonella* gastroenteritis is a major cause of bacterial diarrhea in the USA with over 1 million cases estimated yearly [37]. In North America, *S. typhimurium* and *S. enteritidis* account for over half of cases; *S. newport* and *S. heidelberg* account for approximately 20% of cases [38]. *Salmonella* enterocolitis is commonly caused by contaminated foods such as poultry, egg yolks, fresh produce, ground beef, and milk. It has also been linked to exposure to animals. It is manifest most commonly as an acute self-limited illness of the small intestine, but the colon can also be affected. Dysentery (multiple small, bloody, mucoid stools with tenesmus) is uncommon. Severe complications such as bacteremia, meningitis, and endovascular lesions may occur in 5–10% of healthy individuals [37]. Risk factors for invasive infection include corticosteroid use, extremes of age, inflammatory bowel disease, immunosuppression, and hemoglobinopathies [13]. Most nontyphoidal *Salmonella* infections are limited to uncomplicated gastroenteritis and do not require treatment. Antibiotics do not decrease duration of symptoms. Instead, they contribute to adverse public health consequences such as prolonged shedding, increased likelihood of a carrier state and emergence of resistant strains [37]. Antibiotic therapy is indicated for severe symptoms, systemic disease, and patients with severe comorbid conditions or risk factors for invasive infection [13]. Multi-drug-resistant strains have emerged and are increasing in prevalence. Several studies have shown that compared to pansusceptible strains, resistance is associated with increased risks of hospitalization, bacteremia, invasive illness, and death [37, 39–41]. Treatment of severe disease has generally been with fluoroquinolones or ceftriaxone; azithromycin may be used [13]. Ciprofloxacin-resistant strains are increasing, and ceftriaxone-resistant strains are being reported [42, 43].

Typhoid fever. Typhoid fever is caused by *S. typhi* and is common in developing countries but rare in the USA. Symptoms occur in four distinct stages each lasting about 1 week: (1) nonspecific symptoms (including fevers and chills), (2) right lower quadrant pain with diarrhea and rose spots, (3) complications of infection, and (4) resolution of illness. Diagnosis is made by blood culture early in the course of illness or stool culture late in the course. Treatment is fluoroquinolones. However, as noted above, multi-drug-resistant strains are emerging.

Shigella. *Shigella* colitis is very common worldwide and is caused by four species: *Shigella dysenteriae* (which has 13 serotypes), *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*. *Shigella dysenteriae* serotype 1 is a major cause of dysentery worldwide, accounting for approximately 75% of all diarrhea deaths [44]. In the USA, *S. sonnei*

and *S. flexneri* are the most common and cause less severe illness. Transmission is fecal–oral; *S. sonnei* is transmitted by uncooked food or contaminated water. Humans are the only natural host. *Shigella* is highly contagious, requiring less than 100 organisms to cause infection. The pathogenesis of *Shigella* is via invasion of colonic epithelium and production of enterotoxins [6, 44]. Symptoms usually include a 2-day prodrome of constitutional symptoms and secretory diarrhea, followed by dysentery, fever, abdominal cramps, and tenesmus. Colitis predominantly involves the left colon and rectum, and patients may have more than 20 dysenteric stools per day [44]. Shigellosis may be complicated by intestinal perforation, toxic megacolon, dehydration, metabolic derangements, sepsis, and multiple extraintestinal manifestations including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). *Shigella* should be suspected clinically in patients who present with watery diarrhea followed by dysentery. Diagnosis is made with stool culture; susceptibility tests should be performed on all confirmed isolates. Initial treatment is with ORT. Antibiotics are always recommended for public health reasons, although most infections would resolve within 5–7 days without treatment. Antibiotics reduce the duration of diarrhea and the period of *Shigella* excretion. TMP–SMX is the treatment for shigellosis acquired in the USA, and fluoroquinolone is recommended for disease acquired outside the USA. However, as with *Salmonella*, there are increasing numbers of fluoroquinolone-resistant isolates. Other effective antibiotics include azithromycin [3, 13, 45], second- and third-generation cephalosporins (for invasive disease), and rifaximin [46].

Escherichia coli. Two types of *E. coli* affect the colon: enteroinvasive *E. coli* (EIEC) and Shiga toxin-producing *E. coli* (STEC). STEC strains that cause hemorrhagic colitis are also called enterohemorrhagic *E. coli* (EHEC).

EIEC causes a disease similar to *S. sonnei* infection clinically and also shares some biochemical and serologic properties with the organism [44]. EIEC invades the epithelium and produces a self-limited watery diarrhea or dysentery. The symptoms are generally mild and can be treated with a fluoroquinolone or azithromycin [3, 13].

While over 470 STEC serotypes may cause human disease, only 10 serotypes are responsible for the majority of cases [47], including *E. coli* O157:H7. Both O157 and non-O157 strains cause epidemics that peak in the summer. It is estimated that non-O157 strains cause 20–40% of all STEC infections [13, 48]. Ruminants, including cattle, are a major reservoir for STEC and contribute to the contamination of beef, water, and produce, such as basil pesto and alfalfa sprouts. STEC

is not invasive but produces two distinct toxins: Shiga toxin 1 (Stx1) which is identical to that of *S. dysenteriae* serotype 1 and Shiga toxin 2 (Stx2), which is responsible for the vascular endothelial injury that leads to dysentery and TTP/HUS [47]. STEC has some capacity for invasion, but the majority of systemic effects are caused by absorption of toxin from the intestine [47].

The typical presentation is nausea, vomiting, and low-grade or absent fever, followed within 2–3 days by severe abdominal pain and diarrhea, which may become bloody. The stool may lack fecal leukocytes. Symptoms generally resolve within a week unless there are complications. *Escherichia coli* O157 strains often localize to the right colon and the illness may be mistaken for ischemic colitis in the elderly and intussusception or inflammatory bowel disease in the pediatric population. The most dreaded complication is TTP/HUS, which occurs in approximately 5–10% of patients, several days after the diarrhea begins [47]. Young children and the elderly are at greatest risk. TTP/HUS may lead to permanent renal failure, seizure, and death. Thrombocytopenia is usually the first abnormality seen, followed by hemolysis and renal failure [49]. Diagnosis of STEC infection is made by stool culture, with specialized testing of lipopolysaccharides for O157 organisms, and enzyme immunoassay (EIA) for Shiga toxin. When Shiga toxin is positive and O157:H7 is negative, testing should be performed for non-O157 serotypes [13].

Treatment of both STEC and resultant TTP/HUS is supportive with hydration; there is no role for plasmapheresis since ADAMTS-13 deficiencies are not the cause of disease [50]. Antibiotics and antimotility agents should be avoided, as there is no clear reduction of symptoms, and these agents likely increase the risk of developing TTP/HUS by increasing the release of toxin by bacteriolysis and phage induction [49–52]. Recent studies show that rifaximin, azithromycin, and fosfomycin do not induce Shiga toxin production or release [13, 53] and may be future antimicrobial treatment options.

Clostridium difficile. *Clostridium difficile* infection (CDI) is an important cause of both nosocomial and community-acquired diarrhea. Epidemics have been documented in hospitals and nursing homes, and more recently, community-acquired CDI has become a serious problem. *Clostridium difficile* causes infection by production of two toxins, enterotoxin A and cytotoxin B, which cause colonic mucosal inflammation. A new strain called NAPI/B1 is responsible for recent epidemics. This strain produces a binary toxin, carries a partial gene deletion allowing increased production of toxins A and B, and has quinolone resistance [54]. These properties likely make the strain *in*

vitro more virulent and allow for selection of the strain in patients taking fluoroquinolones.

Patients with CDI may present with watery or rarely bloody diarrhea, lower abdominal cramping, fever, and leukocytosis. Signs of severe disease include severe pain, abdominal distension, hypovolemia, lactic acidosis, and marked leukocytosis ($>15,000$). Predictors of mortality are severe leukocytosis or leukopenia ($\geq 35,000/\mu\text{L}$ or $<4,000/\mu\text{L}$), bandemia (neutrophil bands $\geq 10\%$), age ≥ 70 , immunosuppression, and cardiorespiratory failure (intubation or vasopressors) [55, 56]. The host immune response may play an important role in pathophysiology. For example, patients that develop IgG against toxin A are more likely to remain asymptomatic carriers [57].

CDI should be suspected in anyone who develops diarrhea during or several weeks following antibiotic therapy. Patients who develop diarrhea while hospitalized should be tested for *C. difficile*. Because of the recent epidemics, even patients with community-acquired diarrhea may need to be tested for *C. difficile*. Diagnosis may be made by detection of the toxin in the stool. Many laboratories screen stools for *C. difficile* with a glutamate dehydrogenase antigen; if negative, no further testing is done. If positive, a confirmatory test for toxin A and/or B is done, either by EIA or PCR. However, stool tests vary in sensitivity and specificity; thus if clinical suspicion is high, empiric therapy should be given.

Treatment of CDI depends on severity of disease; however, in all cases, the offending antibiotic should be discontinued if possible, and antidiarrheals should be avoided [58]. For mild-to-moderate disease, treatment with either metronidazole 250 mg QID or 500 mg TID, or vancomycin 125 mg QID for 10–14 days is recommended. The lower dose of vancomycin (compared to 250 mg QID) is sufficient for mild-to-moderate disease and is less costly [59]. Since vancomycin is more expensive and poses the public health risk of increasing vancomycin-resistant *enterococcus*, metronidazole is the recommended first-line agent [58]. If there is no improvement after 3 days of metronidazole therapy, then vancomycin should be initiated.

However, for severe colitis, vancomycin 500 mg QID for four times a day is recommended. Some patients with severe CDI develop ileus or toxic megacolon and are unable to take oral antibiotics. In these cases, intravenous metronidazole 500 mg every 6–8 h should be used. In some cases, vancomycin may be given via nasogastric tube or rectally. Colectomy may be required for severe disease [56].

Following treatment for initial CDI, approximately 15–20% of patients will develop recurrent disease, usually within 5–8 days after completing antibiotic therapy. Risk factors for recurrence include older

age, intercurrent antibiotics, renal disease, and prior recurrences of CDI. There is no standard regimen for recurrent CDI. It is important to understand that recurrence is not due to resistant organisms, and therefore retreatment with the same or alternate antibiotic is recommended. Additionally, vancomycin pulses or tapers for an extended duration are often used [60]. Two weeks of rifaximin following 2 weeks of vancomycin has shown promise. The probiotic *Saccharomyces boulardii* was also found to be a beneficial adjunct to high-dose vancomycin therapy but should not be used in immunosuppressed patients. Bacteriotherapy is an area of active study: fecal enemas, colonoscopic delivery of fecal material, and delivery of colonic flora through nasogastric tubes have shown success in small studies [61, 62].

Yersinia. Two *Yersinia* species cause gastrointestinal illness: *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. *Yersinia* is not common in the USA but is common in Northern Europe and is transmitted by ingestion of contaminated milk products or pork (especially chitterlings – hog intestines). It has also rarely been associated with red blood cell transfusions [63]. These species commonly cause acute colitis with abdominal pain (often in the right lower quadrant), fever, and diarrhea which may be bloody. Symptoms may mimic appendicitis or Crohn's disease. Extraintestinal manifestations include reactive arthritis, erythema nodosum, myocarditis, pulmonary infection, nephritis, osteomyelitis, and sepsis [64]. The diagnosis can be made by stool culture on special cold-enrichment medium. Cultures from nodes, blood, and peritoneal fluid may also be diagnostic. Serology with elevated titers in a typical clinical setting may be useful. Treatment is not necessary in most cases. For severe disease including enteritis, mesenteric adenitis, erythema nodosum, and arthritis, it is probably wise to treat. Recommended antibiotics are fluoroquinolones, TMP-SMX, or doxycycline in combination with an aminoglycoside [3].

Non-cholera Vibrios. The non-O1 non-O139 vibrios are often referred to as non-cholera vibrios. These include *Vibrio vulnificus*, *Vibrio parahaemolyticus*, *Vibrio fluvialis*, *Vibrio alginolyticus*, as well as other less common vibrios. These pathogens do not cause epidemics or pandemics but can cause small outbreaks, usually associated with ingestion of raw or undercooked shellfish [65]. In the USA, the Gulf states have the highest prevalence of disease, and several cases occurred following Hurricane Katrina [66]. Patients with chronic liver disease are at increased risk of infection and should not eat undercooked shellfish. The non-cholera vibrios invade the colonic mucosa causing a self-limited bloody diarrhea and fever. However, several

extraintestinal manifestations have been reported, including peritonitis, sepsis, necrotizing soft-tissue infections, septic arthritis, keratitis, and endophthalmitis [67–73]. Treatment is generally not required, but tetracycline, azithromycin, or fluoroquinolone may be used for severe illness [13].

***Plesiomonas shigelloides*.** *Plesiomonas* is an uncommon organism that may cause an acute secretory, acute dysenteric, or persistent diarrhea. Consumption of raw seafood and international travel may be risk factors [13, 74]. Rarely, it has been associated with biliary tract disease [75–77]. Treatment is usually not necessary, but if needed, TMP–SMX, fluoroquinolones, and azithromycin may be used [3, 13]. Susceptibility testing should be performed if treatment is needed.

***Aeromonas hydrophila*.** This organism may affect either the small bowel or the colon. Outbreaks have been associated with water, food, and day care. *Aeromonas* primarily affects children, and the reported prevalence varies significantly in studies. Symptoms include watery diarrhea that may become bloody, abdominal cramps, nausea, vomiting, and fever. Illness generally resolves in 1–2 weeks but can become persistent or chronic, requiring antibiotics. Extraintestinal manifestations include bacteremia, cellulitis, peritonitis, meningitis, and respiratory disease [76]. Susceptibility varies greatly among strains, so susceptibility testing should be performed. Possible antimicrobial agents include azithromycin, fluoroquinolones, and TMP–SMX [3, 13].

Tuberculosis. In the USA, intestinal tuberculosis is most commonly seen in immigrants from high-risk regions and in persons with HIV. It often involves the ileocecal area. Findings are nonspecific, and patients may present with chronic abdominal pain, a palpable right lower quadrant mass, or constitutional symptoms; diarrhea is uncommon. Less than half of patients will have active pulmonary tuberculosis [78]. Skin tests may be positive. Diagnosis is made with colonoscopy and biopsy. Typical colonoscopic findings are discrete ulcers, often in the cecum [79].

***Klebsiella oxytoca*.** For decades, the role of *K. oxytoca* as a pathogen was unclear. Recent evidence suggests that certain strains produce cytotoxin and are responsible for antibiotic-associated hemorrhagic colitis (AAHC), which can be acquired in the community or nosocomially [27, 80]. AAHC typically presents with the sudden-onset bloody diarrhea 2–7 days after initiation of treatment with penicillins and some cephalosporins [27, 80]. AAHC may mimic ischemic colitis. Less commonly, the illness may be nonhemorrhagic and delayed in onset [80].

Klebsiella oxytoca leads to mucosal hemorrhage and edema, predominantly in the right colon. Diagnosis is made by stool culture or biopsy and requires selective media. Most cases studied had rapid clinical and endoscopic resolution after withdrawal of antibiotics [26].

***Clostridium perfringens* type A.** *Clostridium perfringens* is ubiquitous in the environment and has been found to be part of the residential gut flora in up to 40% of healthy persons [27]. Only about 2–5% of *C. perfringens* isolates, usually type A, produce enterotoxin and can cause food poisoning. Patients usually develop watery diarrhea without vomiting within 48 h of ingestion of contaminated poultry, vegetables, or meat [13]. New evidence suggests that these enterotoxin-producing strains may also cause *C. difficile*-negative AAC in elderly patients due to alterations in gut flora [26].

PARASITES

***Entameba histolytica*.** Several *Entameba* species colonize humans, but most are not pathogenic. *Entameba histolytica* is a well-recognized human pathogen. The protozoa are transmitted by the ingestion of cysts in contaminated food and water or by anal–oral sexual practices. Entamebae are found worldwide, with highest incidence in developing regions with poor sanitation [34]. Therefore, travelers to and immigrants from these regions are at risk. Patients may be asymptomatic or develop invasive intestinal and/or extraintestinal amebiasis. Invasive disease is caused by adherence to and lysis of colonic epithelium. Subsequent invasion of the bloodstream and extraintestinal spread may then occur [81]. Patients may present with abdominal pain, weight loss, and watery diarrhea, sometimes with blood. In the USA, dysentery is less common, and patients may present with colicky abdominal pain and diarrhea alternating with constipation, mimicking irritable bowel syndrome [82]. Rare manifestations of disease include acute necrotizing colitis, toxic megacolon, and ameboma. Invasive extraintestinal manifestations include liver abscesses, peritonitis, pleuropulmonary abscesses, and cutaneous or genital lesions [34]. Diagnosis may be made by stool microscopy. However, this method may not differentiate *E. histolytica* from non-pathogenic *Entameba dispar*. These organisms may be distinguished by serology, stool antigen detection, or PCR [83]. Treatment for asymptomatic infection is iodoquinol or paromomycin. Oral metronidazole three times a day is the treatment for invasive disease. Parental metronidazole can be used for severe cases and should be supplemented with broad-spectrum antibiotic coverage of intestinal flora to prevent secondary sepsis. A 3-day

course of nitazoxanide is a promising new regimen. Treatment of invasive disease should be followed by treatment with a luminal amebicide: iodoquinol or paromomycin [34, 83].

Trichuriasis (whipworm). Trichuriasis is a helminthic infection caused by the nematode *Trichuris trichiura*. It is common worldwide, especially in tropical regions and in the southern USA. It is associated with poor sanitation. Transmission is by fecal–oral spread. In mild infections, the cecum and the ascending colon are primarily involved, but the entire colon can be involved with severe infection. Most infections are asymptomatic. In severe cases, patients may have symptoms of loose stools often with blood or mucus, nocturnal stools, dysentery, and rectal prolapse. Other findings can include anemia, eosinophilia, pica, finger clubbing, and impaired growth and cognition in children. Diagnosis is by stool examination for eggs. Treatment of choice is mebendazole. Albendazole is an alternative choice [34].

***Blastocystis hominis*.** *Blastocystis hominis* has been reclassified numerous times, and most recently, was classified as a stramenopile (an assemblage of unicellular and multicellular protists). Its pathogenicity is debated. The organism occurs in both symptomatic and asymptomatic persons, suggesting that it is not pathogenic. However, others have described clinical responses to antimicrobial therapy. Reported symptoms include watery diarrhea, abdominal pain, perianal pruritus, and excessive flatulence. Diagnosis is based on finding cysts in stool. Treatment is controversial, but metronidazole, iodoquinol, and nitazoxanide have reportedly been effective [34, 84].

***Balantidium coli*.** This protozoan parasite is a rare cause of colitis. Most cases are asymptomatic, but it can cause persistent diarrhea, occasionally dysentery, abdominal pain, and weight loss. Diagnosis is made by detecting the protozoan in stool. Treatment is tetracycline or, alternatively, metronidazole [34].

VIRUSES

Cytomegalovirus. CMV can affect any part of the gastrointestinal tract in immunocompromised hosts, especially those with advanced HIV. Only enteritis and colitis cause diarrhea, with colonic disease predominating. Symptoms of colitis include explosive watery diarrhea, low-grade fever, weight loss, anorexia, malaise, abdominal pain, and bleeding [85, 86]. Diffuse mucosal hemorrhage and perforation are life-threatening complications. Diagnosis is made via colonoscopy and biopsy revealing mucosal ulcerations with characteristic intranuclear

and intracytoplasmic inclusions. Treatment involves IV ganciclovir or foscarnet for 3–4 weeks. Oral valganciclovir may be used if symptoms are not severe enough to cause malabsorption, or after several days of treatment with the IV medications [87]. For patients who may start antiretroviral therapy for HIV, it is important to ensure that the patient has had an ophthalmologic exam to rule out CMV retinitis.

CLINICAL EVALUATION

The assessment of a patient with acute infectious diarrhea includes an evaluation of volume status and severity of illness, a focused epidemiologic history, and a determination of whether or not diagnostic testing is indicated.

The initial evaluation focuses on the patient's volume status. In patients with diarrhea, the physical exam finding that best predicts volume depletion is dry axillae; severe postural dizziness, supine tachycardia, and a postural pulse increment of >30 bpm are suggestive. Although not predictive alone, the combination of confusion, extremity weakness, slurred speech, dry mucous membranes, dry or furrowed tongue, and sunken eyes suggests volume depletion, with more findings making the diagnosis more likely [88]. Because it is difficult to determine volume depletion accurately with physical exam alone, additional evaluation with a serum chemistry panel, urine electrolytes, and urine output is recommended. Rehydration therapy will be discussed below.

It is useful to distinguish between ileocolonic and small intestinal disease as this can help identify the pathogen and guide diagnostic testing (see Tables 2.1 and 2.2). Epidemiologic clues include travel history, recent hospitalizations, underlying medical illnesses, sexual history, and exposures to day care, unsafe foods, untreated fresh water, animals or ill persons (see Table 2.3). Severe disease is indicated by a prolonged illness, illness that is not improving after 48 h, passage of >6 stools per day, volume depletion, bloody or dysenteric stools, fever, and severe abdominal pain in patients older than 50 years. In evaluating infectious diarrhea, physical exam helps assess volume status and disease severity (i.e., abdominal pain or wasting) (see Table 2.4).

Diagnostic testing may be indicated for individuals or public health concerns. For the individual patient, diagnostic testing is indicated if the patient has severe disease as defined above, systemic symptoms, illness lasting > 1 week, or the patient is elderly or immunocompromised. For public health reasons, diagnostic testing is also indicated

Table 2.3
Epidemiologic features

<i>Pathogen</i>	<i>Epidemiologic features and risk factors</i>
<i>Salmonella</i>	Poultry, livestock, milk, raw eggs, fresh produce, pet turtles, and reptiles
<i>Shigella</i>	Family, day-care centers
<i>Campylobacter</i>	Poultry, meats, dairy products
<i>Non-cholera vibrios</i>	Raw or undercooked seafood, liver disease, alcoholism
<i>C. difficile</i>	Recent or current antibiotics, hospitalizations, chemotherapy
<i>S. aureus</i>	Custards and cream-based foods, poultry, eggs
<i>C. perfringens</i>	Meat, home canned foods, poultry, gravy
<i>Listeria</i>	Milk, lunch meats, and unpasteurized cheeses, pregnancy
<i>Yersinia</i>	Pork, chitterlings (hog intestine), hemochromatosis
STEC	Undercooked ground beef, day-care centers, petting zoos, unpasteurized apple cider, raw vegetables, leaf lettuce, basil pesto, salami
<i>Cryptosporidia</i>	Water, day-care centers
<i>Giardia</i>	Untreated fresh water, anal intercourse, day-care centers
<i>Cyclospora</i>	Day-care centers, imported raspberries, fresh basil
Microsporidia	HIV/AIDS
Norovirus	Fresh water, food borne, cruise ships, nursing homes, raw shellfish, schools, camps
Rotavirus	Day-care centers

Adapted from Ref. [94].

Table 2.4
Historical evaluation

<i>Important questions to ask</i>
<ul style="list-style-type: none"> – Disease severity <ul style="list-style-type: none"> Duration, onset (sudden vs gradual), frequency, volume depletion – Ileocolonic vs small intestinal disease features (see Table 2.1) – Associated symptoms <ul style="list-style-type: none"> Nausea, vomiting, abdominal pain, fever, headache, arthralgias – Epidemiology (see Table 2.3)

Table 2.5
Indications for diagnostic testing of stool specimens

Who should have diagnostic testing?

- Severe illness
Prolonged illness, illness not improving after 48 h, greater than six loose stools per day, volume depletion, bloody stools or dysentery, fever, and severe abdominal pain in persons age >50 years
 - Immunocompromised patients (see IDSA guidelines for immunocompromised patients)
 - Suspected outbreak
 - Persons with high risk to spread infection
Food handlers, caregivers, healthcare workers, day-care attendees or workers, institutionalized persons
-

when an outbreak is suspected or the patient is at high risk to transmit the infection to others (see Table 2.5).

DIAGNOSTIC EVALUATION

When diagnostic evaluation is indicated, it is important to decide what type of testing is appropriate. Diagnostic testing should be selective, based on the patient's individual clinical picture [3]. When the epidemiologic history suggests a specific pathogen, individual testing for the enteropathogen can be performed. Otherwise, the following studies should be considered.

Fecal Leukocytes and the Lactoferrin Assay

The utility of fecal leukocytes and stool lactoferrin is debated. Since these tests identify inflammatory markers, they are nonspecific to infectious enterocolitis; both have high false-positive rates, and cannot distinguish infectious from inflammatory diseases. A recent meta-analysis found that these tests performed better in evaluating patients in developed countries. The sensitivity and the specificity for fecal leukocytes in developed countries were 0.73 and 0.84, respectively, although bias in favor of the test was noted [89]. The lactoferrin assay appears to be useful when negative, but not when positive [89, 90]. Also, it may miss noninvasive infections such as STEC or ETEC [3]. Until new studies put the debate to rest, it is reasonable to consider the use of fecal lactoferrin or leukocytes as a screening tool to identify colonic inflammation. However, it is important to remember that some infections may be missed.

Stool Culture

In immunocompetent patients, indications for stool culture for enteric pathogens include bloody stools, severe diarrhea, fever, severe abdominal pain, or travel to high-risk areas. If symptoms persist for more than 1 week, stool cultures may be indicated. For nosocomial diarrhea, stool should be tested for *C. difficile*. When *C. difficile* testing is negative, other etiologies such as toxin-producing *S. aureus* and *C. perfringens*, *K. oxytoca*, and non-infectious causes should be considered. Patients with persistent diarrhea should be evaluated with stool ova and parasite testing.

TREATMENT

Rehydration, Nutrition, Electrolytes

The cornerstone of treatment for diarrheal illness is rehydration. Internationally, oral rehydration therapy (ORT) is the first-line treatment, but when available, intravenous fluids may be given for severe illness. WHO and UNICEF now recommend a reduced-osmolarity oral rehydration solution (ORS) for patients with acute, non-cholera diarrhea, as this solution was found to decrease both stool output and vomiting compared to standard ORS [91]. Electrolytes should be monitored and repleted. Newer ORS with resistant starches are being studied and show promise. Adequate nutrition is also important. Adults and children should consume easily digestible foods such as soups, crackers, and mashed potatoes. Infants should continue to breastfeed or drink formula [13, 91, 92]. Zinc supplementation reduces the duration and severity of illness in children [91, 92].

ANTIDIARRHEALS

Some antidiarrheal agents (including bismuth subsalicylate and loperamide) may be given safely in patients with infectious diarrhea. In the setting of appropriate antimicrobial therapy, most antimotility agents are unlikely to be harmful [13] and have shown benefit in traveler's diarrhea [93]. However, due to the risk of precipitating toxic megacolon or systemic illness by prolonged exposure of bacteria to the intestinal mucosa, antimotility agents are to be avoided in children, as well as in adults with severe bloody diarrhea, inflammatory diarrhea, severe colitis, or *C. difficile* infection.

ANTIMICROBIALS

Since there are individual and public health risks associated with antimicrobial therapy, it is generally best to await results of diagnostic

testing before treating. Some risks of antibiotics include inducing TTP/HUS with STEC infection, increasing antimicrobial resistance, and exposing patients to side effects of antibiotic therapy. However, in certain situations, the benefits of empiric therapy outweigh the risks. Empiric therapy is thus recommended for the following situations: severe illness requiring hospitalization (particularly admission to an intensive care unit), moderate-to-severe traveler's diarrhea, elderly or immunocompromised hosts, suspected *C. difficile* colitis with severe disease, suspected shigellosis, or persistent diarrhea with suspected *Giardia*. If these conditions are not present, or there is suspicion for STEC (bloody diarrhea and absence of fever) or nontyphoidal *Salmonella*, or clinical uncertainty is present, it is most appropriate to wait for culture results before treating. Once an organism is identified, then treatment should be initiated as discussed above for each pathogen. Traveler's diarrhea may be treated empirically with ciprofloxacin, azithromycin, or rifaximin. New evidence suggests that chemoprophylaxis with rifaximin or bismuth subsalicylate may decrease acquisition of traveler's diarrhea by 65–70% [13]. As new antimicrobial resistance patterns are continually emerging, it is important to check frequently updated sources for antimicrobial recommendations.

CONCLUSION

Infectious diarrhea is a major cause of morbidity and mortality worldwide and is increasing in the USA due to current food cultivation and distribution practices. Most diarrheas can be classified as small intestinal or ileocolonic, which aids in the identification of the causative agent. Viral gastroenteritis remains the most common cause of infectious diarrhea in the USA and is treated supportively. Most moderate-to-severe disease is caused by bacterial pathogens, some of which require specific treatment. Antimicrobial therapy should be avoided in suspected cases of STEC and *Salmonella*. Empiric therapy may be appropriate based on epidemiologic and historical clues, the severity of illness, or specific host factors. As resistance patterns are continuously changing, checking updated sources prior to initiating antimicrobial treatment is recommended.

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