The treatment of choice for uncomplicated brucellosis is extended therapy with doxycycline plus either rifampin or gentamicin. Neurobrucellosis requires several months of combined ceftriaxone, doxycycline, and rifampin.

KEY POINT

- The treatment of choice for uncomplicated brucellosis is doxycycline plus either rifampin or gentamicin; neurobrucellosis requires several months of combined ceftriaxone, doxycycline, and rifampin.

Japanese Encephalitis

Japanese encephalitis virus is a flavivirus transmitted by mosquitos. It is the most prevalent cause of vaccine-preventable infectious encephalitis throughout most of Asia and parts of the western Pacific. The risk of infection for most travelers is low, and most infected persons remain asymptomatic. A few persons (<1%) who develop clinical disease present with encephalitis. The mortality rate is 20% to 30%.

Diagnosis is confirmed by the detection of virus-specific IgM antibodies in the cerebrospinal fluid. Viral RNA detection is definitive but insensitive. Treatment is supportive. In the United States, a two-dose inactivated vaccine is available and recommended for travelers to endemic areas based on risk stratification.

Tick-Borne Encephalitis

Tick-borne encephalitis is caused by three related subtypes of flaviviruses classified by their endemic geographic areas (European, Siberian, and Far Eastern). Most infections occur between early spring and late fall. Those older than 50 years have the greatest incidence of clinical infection. A biphasic illness occurs in about one third of infected persons after an incubation period (1-2 weeks), beginning with a nonspecific phase (fever, headache, malaise, and arthralgia). A second neuroinvasive phase may develop in the few patients who do not fully recover, manifested by meningitis, encephalitis, altered mental status, seizures, cranial nerve palsies, and flaccid paralysis. Disease severity, case fatality, and permanent neurologic deficits increase with age and vary by geographic location (Far Eastern is most severe, followed by Siberian and European).

Diagnosis is confirmed by detection of IgM antibodies from cerebrospinal fluid or serum.

Inactivated vaccines based on European and Far Eastern strains of virus (two each) are available in Europe and Russia but not licensed in the United Sates. Treatment is supportive.

Yellow Fever

The yellow fever flavivirus belongs to the viral hemorrhagic fever group. Infection is transmitted by mosquitoes in endemic areas of sub-Saharan Africa and tropical regions of South America. Clinical manifestations range from mild to severe life-threatening disease with a 30% to 60% mortality rate. Diagnosis is confirmed by detection of viral RNA by reverse transcriptase PCR or virus isolation performed early in the course of disease or by the presence of IgM antibodies. Treatment is supportive. Vaccination with the approved, live-attenuated yellow fever vaccine is recommended for travelers to endemic areas of Africa and South America. A certificate of proof of vaccination is required for entry into several endemic countries, and travelers who have recently visited yellow fever zones are prohibited entrance to some nonendemic countries without similar documentation (www.cdc.gov/travel). The yellow fever vaccine in the United States is currently unavailable. Authorization from the FDA to use an alternate European vaccine can be obtained.

Infectious Gastrointestinal Syndromes

Overview

Diarrhea is defined as three or more unformed stools daily. Diarrhea lasting less than 14 days is considered acute, 14 to 30 days is persistent, and longer than 30 days is chronic. Acute infectious diarrheal presentations include acute gastroenteritis, with associated fever, nausea, vomiting, flatulence, tenesmus, and crampy abdominal pain. Chronic infectious diarrhea is most likely caused by parasites. Not all diarrheal presentations are infectious, such as inflammatory bowel disease, endocrine disorders, celiac disease, irritable bowel syndrome (IBS), and medication-induced diarrhea.

Generally, patients with mucoid or bloody diarrhea (i.e., dysentery), fever, significant abdominal cramping, or suspected sepsis and those who are immunocompromised or require hospitalization should have diagnostic assessment of their stool to guide antimicrobial use. Additional areas of concern include persistent symptoms (>1 week) or outbreak settings where day-care participants, institutional residents, health care providers, or food handlers are involved. Increasingly available, rapid multiplex molecular gastrointestinal assays that identify common bacterial, parasitic, and viral pathogens from a stool sample are generally more sensitive than stool culture and microscopy with special stains (**Table 46**). Isolates from culture, however, can provide antibiotic susceptibilities and strain-typing information in outbreak situations that are unavailable from culture-independent diagnostic assays.

Most healthy patients with watery diarrhea of less than 3 days' duration can be treated with supportive care without diagnostic assessment. When acute diarrhea is debilitating and associated with travel, antibiotic therapy with a fluoroquinolone, azithromycin, or rifaximin is recommended; if not travel associated and fever of 38.3 °C (101 °F) or greater persists for 3 or more days, then microbiologic assessment should be

TABLE 46. Causative Agents, Clinical Presentation, and Management of Infectious Diarrhea

Agent	Clinical Findings	Diagnosis[a]	Antimicrobial Treatment[b]
Bacterial Agent			
Campylobacter	Fever, chills, diarrhea (watery or bloody), crampy abdominal pain; postinfection Guillain-Barré syndrome, IBS, intestinal perforation, glomerulonephritis, erythema nodosum, hemolytic anemia, or reactive arthritis	Routine stool culture or NAAT; blood culture	Azithromycin; fluoroquinolone such as ciprofloxacin (alternative)
Shigella	Dysentery (fever, abdominal cramps, tenesmus, bloody/mucus-filled stools; possibly vomiting); postinfection HUS, reactive arthritis, erythema nodosum, glomerulonephritis, or IBS	Routine stool culture or NAAT; blood cultures (with severe disease)	Fluoroquinolone such as ciprofloxacin, or azithromycin or ceftriaxone
Salmonella	Fever, chills, diarrhea (watery or bloody), cramps, myalgia; bacteremia in 10%-25% of patients; postinfection reactive arthritis, erythema nodosum, or IBS	Routine stool culture or NAAT; blood cultures (moderate to severe disease); bone marrow and duodenal fluid cultures may also be helpful when enteric fever suspected	Mild: none Underlying disease or severe illness: fluoroquinolone such as ciprofloxacin and/or parenteral third-generation cephalosporin such as ceftriaxone
EHEC/STEC, most commonly *Escherichia coli* O157:H7	Bloody stools in >80% of patients; fever often absent or low grade; may be associated with HUS	Stool culture with specialized media and immunoassay for Shiga toxin or NAAT for gene(s) encoding Shiga toxin	None
ETEC (travelers' diarrhea)	Nonbloody, watery stools; constitutional symptoms rare	None–usually a clinical diagnosis	Fluoroquinolone (such as ciprofloxacin), azithromycin, or rifaximin
Yersinia	Fever, diarrhea, right lower quadrant pain (may mimic appendicitis); pharyngitis; intestinal perforation; postinfection reactive arthritis, hemolytic anemia, or erythema nodosum	Stool culture with specialized media (or culture of other involved sites); NAAT	Fluoroquinolone such as ciprofloxacin Third-generation cephalosporin such as ceftriaxone plus gentamicin for severe disease
Vibrio parahaemolyticus	Bloody stools (>25% of patients), fever, vomiting (>50% of patients)	Stool culture with specialized media (blood culture with suspected invasive disease); NAAT	Usually no treatment unless invasive Doxycycline, fluoroquinolone (such as ciprofloxacin), or azithromycin if treating severe noninvasive gastrointestinal illness Doxycycline plus ceftriaxone for invasive infection
Clostridioides difficile	Diarrhea (gross blood in stool uncommon), fever, abdominal pain/cramping, colonic distention (with possible sepsis, hypotension, ileus, toxic megacolon in fulminant disease), leukocytosis, acute kidney injury	Stool NAAT alone or stool EIA toxin test as part of stepwise approach, including NAAT plus toxin, or GDH plus toxin, or GDH plus toxin followed by NAAT when results are discordant	Nonsevere: oral vancomycin or oral fidaxomicin; if neither is available, oral metronidazole Severe: oral vancomycin or fidaxomicin Fulminant: oral vancomycin, IV metronidazole, and (possibly) vancomycin enema
Viral			
Norovirus	Watery, noninflammatory diarrhea and fever; vomiting in >50% of patients; short incubation period and high attack rate	NAAT, particularly for outbreak investigations	None

(Continued on the next page)

TABLE 46. Causative Agents, Clinical Presentation, and Management of Infectious Diarrhea (Continued)

Agent	Clinical Findings	Diagnosis[a]	Antimicrobial Treatment[b]
Parasitic			
Giardia	Watery, "greasy", floating, foul-smelling diarrhea, abdominal cramping, nausea, steatorrhea, flatulence, weight loss; fever uncommon; postinfection lactose intolerance or IBS	EIA or NAAT preferred; stool microscopy for ova and parasites	Tinidazole, nitazoxanide, or metronidazole
Cryptosporidium	Watery diarrhea; abdominal cramping; malaise; weight loss	Modified acid-fast stain; direct fluorescent antibody immunoassay; EIA; NAAT	Nitazoxanide Effective antiretroviral therapy in patients with HIV infection
Amebiasis	Most asymptomatic; dysentery, abdominal pain, fever, weight loss; intestinal perforation	Stool microscopy for ova and parasites; stool antigen immunoassay; NAAT; serologic antibodies	Tinidazole or metronidazole followed by paromomycin or diloxanide
Cyclospora	Watery diarrhea, bloating, flatulence, weight loss, nausea, anorexia, crampy abdominal pain; sometimes fever	Modified acid-fast stain; fluorescence microscopy; NAAT	Trimethoprim-sulfamethoxazole

EHEC = enterohemorrhagic *E. coli*; EIA = enzyme immunoassay; ETEC = enterotoxigenic *E. coli*; GDH = glutamate dehydrogenase; HUS = hemolytic uremic syndrome; IBS = irritable bowel syndrome; IV = intravenous; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction; STEC = Shiga toxin-producing *E. coli*.

[a]Multiplex molecular (i.e., PCR/NAAT) assays are becoming increasingly available for identification of bacterial, parasitic, and viral gastrointestinal pathogens in stool.

[b]Empiric treatment, with the final choice of the antimicrobial agent to use guided by in vitro susceptibility testing.

considered followed by empiric azithromycin treatment. Microbiologic assessment should guide treatment of chronic diarrhea.

Patients with dysentery and a temperature of 37.8 °C (100 °F) or less should have microbiologic assessment to guide therapy. When severe debilitating dysentery is present with temperatures of 38.3 °C (101 °F) or greater, microbiologic assessment should be considered, followed by empiric azithromycin treatment; if travel associated, empiric azithromycin treatment is recommended. Antimotility agents, such as loperamide, are discouraged in patients with inflammatory diarrhea (fever, abdominal pain, bloody stools) or *Clostridioides difficile*-associated infection.

KEY POINTS

- Patients with mucoid or bloody diarrhea (dysentery), fever, significant abdominal cramping, or suspected sepsis and those who are immunocompromised or require hospitalization should have diagnostic assessment of their stool to guide antimicrobial use.

HVC

- Most healthy patients with watery diarrhea of less than 3 days' duration can be treated with supportive care and no diagnostic assessment; when the illness is debilitating and associated with travel, antibiotic therapy with a fluoroquinolone, azithromycin, or rifaximin is recommended.

Campylobacter Infection

Campylobacter-associated gastroenteritis is usually foodborne, often secondary to undercooked poultry. The incubation period is about 3 days; see Table 46 for clinical findings and postinfection complications. Stools are visibly bloody in approximately 15% of patients. Stool culture and molecular testing can be used for diagnosis; blood cultures can identify extraintestinal disease. Diarrhea usually resolves spontaneously. Patients who have severe disease (bloody stools, bacteremia, high fever, or prolonged [>1 week] symptoms) or are immunocompromised should receive antibiotic therapy. When indicated, macrolide therapy is preferred empirically because of increasing fluoroquinolone resistance.

KEY POINT

- *Campylobacter*-associated diarrhea usually resolves spontaneously; azithromycin is generally the preferred empiric treatment for those who have severe disease or are immunocompromised.

Shigella Infection

Shigella infection is most commonly spread from person to person and by consumption of contaminated food or water. Fewer than 100 bacteria can cause infection, and the incubation period is approximately 3 days. Patients typically present with dysentery: crampy abdominal pain, tenesmus, small-volume bloody and/or mucoid diarrhea and high fever. More serious complications include bacteremia, seizures, and intestinal obstruction and perforation; postinfectious sequelae may also occur (see Table 46). Routine stool culture and molecular testing can assist with diagnosis. Blood cultures can confirm invasive disease in patients with severe infection. Treatment

with antibiotics is recommended for those with severe illness (those requiring hospitalization, with invasive disease, or with complications) and those who are immunocompromised. Treatment may also be recommended when outbreaks occur. Ciprofloxacin, azithromycin, and ceftriaxone have been used for treatment, but ideally antibiotic susceptibilities should be obtained because of increasing resistance rates. National Antimicrobial Resistance Monitoring System (http://www.cdc.gov/narms) data can help guide empiric decisions.

KEY POINT

- In patients with *Shigella* infection, treatment with antibiotic agents is recommended for those with severe illness and those who are immunocompromised.

Salmonella Infection

Salmonella infections can be typhoidal or nontyphoidal. The typhoidal types cause enteric fever, a syndrome consisting of fever, abdominal pain, rash (see Travel Medicine), hepatosplenomegaly, and relative bradycardia. This type of infection is uncommon in the United States, with most affected persons traveling to endemic areas and ingesting contaminated water or food. In contrast, nontyphoidal serotypes are the most common bacterial cause of foodborne illness in the United States.

Nontyphoidal *Salmonella* infection usually results from ingesting fecally contaminated water or food of animal origin, including poultry, beef, eggs, and milk. Contact with infected animals (including pet reptiles, amphibians, and poultry) is a less common mode of transmission. The incubation period is usually less than 3 days, and symptoms typically include crampy abdominal pain, fever, diarrhea (not usually visibly bloody), headache, nausea, and vomiting. Stool culture or molecular testing can be diagnostic. Illness is usually self-limited, although bacteremia with extraintestinal infection (involving vascular endothelium, joints, or meninges) may occur. *Salmonella* osteomyelitis is classically associated with sickle cell disease. Severe invasive disease is more likely in infants, older adults, patients with cell-mediated immunodeficiency, and patients with hypochlorhydria. Postinfection complications may also occur (see Table 46).

Most uncomplicated *Salmonella* infections in adults younger than 50 years resolve within 1 week and require only supportive care. Antibiotics are typically reserved for patients with more serious illness (including severe diarrhea requiring hospitalization, bacteremia, high fever, or sepsis) and those at high risk for severe complicated invasive disease (including infants, patients ≥50 years, or those with prosthetic materials, significant atherosclerotic disease, or immunocompromising conditions). Fluoroquinolones (such as ciprofloxacin) are most likely to be effective, but azithromycin and trimethoprim-sulfamethoxazole are potentially active empiric agents. A fluoroquinolone or third-generation cephalosporin (such as ceftriaxone) are often initiated as empiric therapy for patients with severe disease requiring hospitalization. Local antibiotic susceptibilities of *Salmonella* should dictate empiric therapy.

KEY POINTS

- Nontyphoidal *Salmonella* serotypes are the most common bacterial cause of foodborne illness in the United States; diagnosis is made by stool culture or molecular testing, and the illness is usually self-limited, although bacteremia with extraintestinal infection may occur.
- Most uncomplicated *Salmonella* infections in adults younger than 50 years resolve within 1 week and require only supportive care; when empiric treatment is indicated for those with more severe or invasive disease, fluoroquinolones (such as ciprofloxacin) are most likely to be effective.

HVC

Escherichia coli Infection

Although *Escherichia coli* are normal inhabitants of the intestinal microbiome, some strains can become enteropathogenic (**Table 47**).

Enterotoxigenic *E. coli* infection (ETEC) is the most common cause of travelers' diarrhea. ETEC results from ingestion of water or food contaminated with stool and has an incubation period of 1 to 3 days. Enterotoxins cause watery diarrhea with abdominal cramping, nausea, and low-grade or no fever. Usually self-limiting, the illness resolves after approximately

TABLE 47. Diarrheagenic Strains of *Escherichia coli*

Strain	Epidemiology	Clinical Findings
Enteroaggregative *E. coli* (EAEC)	Diarrhea in travelers, young children, and patients with HIV infection	Watery diarrhea, fever typically absent
Enteroinvasive *E. coli* (EIEC)	All ages, primarily in developing countries	Inflammatory diarrhea (dysentery) with fever, abdominal pain
Enteropathogenic *E. coli* (EPEC)	Sporadic, occasionally persistent diarrhea in young children	Nausea, vomiting, malnutrition (when chronic)
Enterotoxigenic *E. coli* (ETEC)	Diarrhea in travelers, foodborne outbreaks	Watery diarrhea, fever typically absent or low grade
Shiga toxin–producing *E. coli* (STEC)/ Enterohemorrhagic *E. coli* (EHEC)	Foodborne outbreaks (associated with beef and other contaminated food), person-to-person, and zoonotic transmission	Bloody stools, progression to hemolytic uremic syndrome, fever typically absent

4 days. Hydration and empiric antibiotic therapy with fluoroquinolones, azithromycin, or rifaximin are recommended in travelers with ETEC when symptoms restrict activities.

Enterohemorrhagic *E. coli* (EHEC) strains, most commonly -O157:H7, produce a Shiga toxin (i.e., Shiga-toxin producing *E. coli*, or STEC) that can cause hemorrhagic colitis. These bacteria are found in cow intestines and are transmitted by ingesting undercooked hamburgers or fecally contaminated food and water; fecal-oral transmission through exposure to infected animals is also possible. The incubation period is 3 to 4 days, and patients typically have visibly bloody diarrhea, crampy abdominal pain, and no fever, the latter a distinguishing feature from other causes of bloody diarrhea. Alerting the laboratory is recommended so that appropriate media, antigen testing, and Shiga toxin assays can be performed. Hemolytic uremic syndrome develops in less than 10% of patients infected with EHEC and manifests as microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury. Treatment is primarily supportive; antibiotics and antimotility agents may increase the risk of developing hemolytic uremic syndrome and do not appear to shorten infection duration.

KEY POINTS

HVC
- Enterotoxigenic *Escherichia coli* infection is usually a self-limiting illness that resolves without treatment after approximately 4 days; hydration and empiric antibiotic therapy with fluoroquinolones, azithromycin, or rifaximin are recommended in travelers when symptoms restrict activities.

HVC
- Enterohemorrhagic *Escherichia coli* strains produce a Shiga toxin that can cause hemorrhagic colitis; treatment is primarily supportive because antibiotics and antimotility agents may increase the risk of developing hemolytic uremic syndrome and do not appear to shorten infection duration.

Yersinia Infection

Most *Yersinia* species diarrheal illness is caused by *Yersinia enterocolitica*, usually after ingestion of contaminated food, particularly undercooked pork. Patients with iron overload states, including hemochromatosis, are at increased risk for infection (including bacteremia) owing to the siderophilic characteristics of *Yersinia* species. The incubation period is approximately 5 days, and patients typically have fever, abdominal pain, diarrhea (possibly bloody), and (sometimes) nausea and emesis. The organism is drawn to lymphoid tissue (including tonsillar tissue and mesenteric lymph nodes), which results in pharyngitis or right lower-quadrant pain mimicking appendicitis. Postinfection complications may occur (see Table 46). The diagnosis is confirmed by stool molecular testing or culture of stool, blood, a throat swab, or infected tissue; the testing laboratory should be alerted when *Yersinia* infection is suspected so that optimal media and enrichment conditions are applied. Uncomplicated gastrointestinal illness in healthy, immunocompetent adults does not require treatment. When treatment is indicated, a fluoroquinolone (such as ciprofloxacin) is recommended. If disease is severe, empiric intravenous ceftriaxone with an aminoglycoside like gentamicin is used.

KEY POINTS

- Most *Yersinia* species diarrheal illness is caused by *Yersinia enterocolitica*, usually after ingestion of contaminated food, particularly undercooked pork; the diagnosis is confirmed by molecular testing of stool or by culture of stool, blood, a throat swab, or infected tissue.
- When treatment is indicated, a fluoroquinolone (such as ciprofloxacin) is recommended; if disease is severe, empiric intravenous ceftriaxone with an aminoglycoside like gentamicin is used.

Vibrio Infection

In the United States, *Vibrio parahaemolyticus* is the most common *Vibrio* species to cause gastrointestinal illness, usually after consumption of undercooked oysters and other shellfish. The incubation period is about 2 days; typically reported presenting symptoms are diarrhea (can be bloody), fever, nausea or emesis, and crampy abdominal pain. Septicemia can develop in patients who have liver disease and may lead to secondary necrotizing skin infections. Severe noninvasive gastrointestinal illness can be treated with doxycycline, although fluoroquinolones and macrolides are alternatives. Patients with septicemia require more aggressive combination therapy, typically with doxycycline plus ceftriaxone.

KEY POINTS

- *Vibrio parahaemolyticus* can cause septicemia and necrotizing skin infections in patients who have liver disease.
- Severe noninvasive *Vibrio parahaemolyticus* gastrointestinal illness is treated with doxycycline, although fluoroquinolones and macrolides are alternatives.

Clostridioides difficile Infection

Clostridioides difficile is the leading cause of hospital-acquired infectious diarrhea and results from fecal-oral transmission. The number of these infections reported in the United States increased significantly beginning in 2000, owing in large part to the emergence of a hypervirulent strain associated with fluoroquinolone use, but recent estimates suggest declining disease burden. Risk factors for infection include exposure to antibiotic and chemotherapeutic agents, older age, severe underlying comorbidities, presence of inflammatory bowel disease, solid organ transplantation, gastrointestinal surgery,

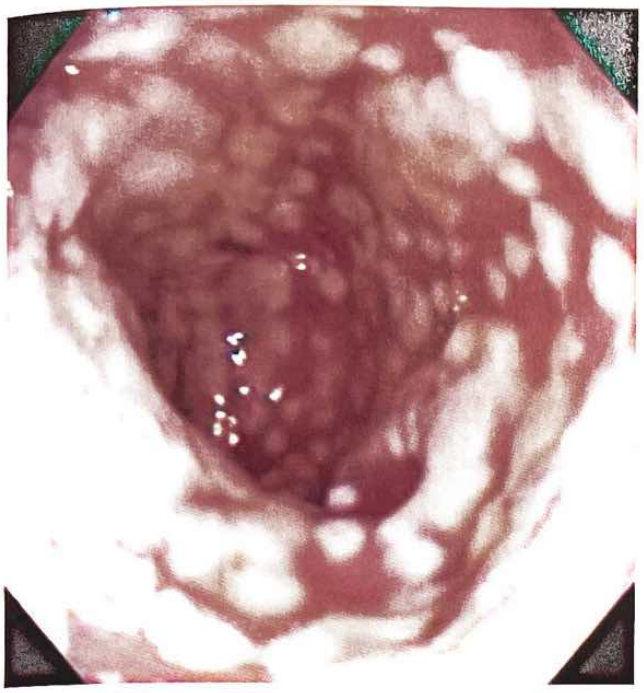

FIGURE 32. *Clostridioides difficile* colitis showing exudative pseudomembranes.

TABLE 48. Treatment of *Clostridioides difficile* Infection[a]

Severity of Disease	Treatment
Nonsevere	Vancomycin, 125 mg four times daily PO × 10 d *or* Fidaxomicin, 200 mg twice daily PO × 10 d If neither oral vancomycin or fidaxomicin is available (or both are contraindicated), metronidazole, 500 mg three times daily PO × 10 d
Severe	Vancomycin, 125 mg four times daily PO × 10 d *or* Fidaxomicin, 200 mg twice daily PO × 10 d
Fulminant	Vancomycin, 500 mg four times daily PO or by NGT, plus metronidazole, 500 mg every 8 h IV When ileus is present, consideration of vancomycin PR at a dose of 500 mg in approximately 100 mL normal saline every 6 h

IV = intravenously; NGT = nasogastric tube; PO = by mouth; PR = per rectum.

[a]Initial presentation.

and (possibly) gastric acid suppression with proton pump inhibitors. Antibiotic stewardship is paramount in reducing incidence of infection, and hand washing with soap and water is the gold standard for infection control; alcohol-based gels do not eliminate spores.

Asymptomatic colonization can occur; for those with pathologic infection, the incubation period can be as long as 3 months after perturbation of the intestinal flora with antibiotic agents. Community-acquired infections without previous exposure to health care settings, antibiotic agents, or both have been increasingly reported.

C. difficile produces an enterotoxin (toxin A) and a cytotoxin (toxin B) that are pathogenic. Symptomatic patients typically have watery diarrhea (rarely bloody), crampy abdominal pain, malaise, and sometimes nausea and fever. Abnormal laboratory study findings are nonspecific but can include marked leukocytosis, an elevated serum creatinine level, and hypoalbuminemia. Radiographic imaging, also nonspecific, may demonstrate colonic wall thickening, mucosal edema, fat stranding, and megacolon. Colonoscopy, although not a routine diagnostic modality, may show pseudomembranes (**Figure 32**).

Diagnosis is usually established by testing unformed stools from persons not taking laxatives who have unexplained new-onset diarrhea occurring three or more times daily. Although highly specific and rapid, enzyme immunoassay (EIA) testing for presence of toxin A or B lacks sensitivity. EIA testing for glutamate dehydrogenase (GDH), an antigenic protein present in all *C. difficile* isolates, is sensitive but lacks specificity. Nucleic acid amplification testing (NAAT) for *C. difficile* toxin genes is sensitive and specific if appropriate institutional stool submission criteria are strictly met (no laxative use; more than three new-onset, unformed, and unexplained stools in 24 hours). In this setting, NAAT alone is sufficient. Combined EIA tests for GDH plus toxin (discordant results require NAAT testing) or NAAT plus toxin should be performed in those institutional settings not adherent to the specified criteria for stool submission.

In infected patients, the antibiotic agent associated with the infection should be stopped if possible. Treatment is dictated by severity of disease (**Table 48**). Severe disease is defined clinically by a leukocyte count of 15,000/μL (15×10^9/L) or greater or a serum creatinine level of 1.5 mg/dL (133 μmol/L) or greater. Oral vancomycin or fidaxomicin for 10 days is recommended for severe and nonsevere disease. Oral metronidazole can be used for nonsevere disease if neither of these agents is available. Fulminant disease includes associated shock, hypotension, toxic megacolon, or ileus. Higher-dose oral or nasogastric vancomycin, intravenous metronidazole, and (possibly) vancomycin enema (when ileus is present) are recommended. Patients with fulminant disease warrant surgical evaluation.

Recurrent infection is reported in as many as 25% of patients, and treatment recommendations are provided in **Table 49**. Studies have shown that fecal microbiota transplantation is effective in the management of patients with multiple recurrences. Retesting stool for *C. difficile* after treatment for evidence of cure in patients who have no symptoms is not recommended.

KEY POINTS

- *Clostridioides difficile* is the leading cause of hospital-acquired infectious diarrhea; antibiotic stewardship is paramount in reducing incidence of infection, and hand washing with soap and water is important to eliminate spores. HVC

(Continued)

TABLE 49. Treatment of Recurrent *Clostridioides difficile* Infection

First recurrence/ second episode	Vancomycin, 125 mg four times daily PO × 10 d, if metronidazole used for initial episode *or*
	Prolonged tapered and pulsed vancomycin if standard regimen was used for initial episode (that is, vancomycin, 125 mg four times daily PO × 10 d, then 125 mg twice daily PO × 7 d, then 125 mg every 2 or 3 d PO for 2-8 wk) *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d, if vancomycin PO was used for the initial episode
Second and subsequent recurrence(s)/ third and subsequent episodes	Prolonged tapered and pulsed vancomycin PO (see above) *or*
	Vancomycin, 125 mg four times daily PO × 10 d, followed by rifaximin, 400 mg three times daily PO × 20 d *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d *or*
	Fecal microbiota transplantation (after two recurrences treated with appropriate antibiotics)

PO = by mouth

KEY POINTS *(continued)*

- Nucleic acid amplification testing for *Clostridioides difficile* toxin genes is rapid, highly sensitive, and specific; enzyme immunoassay testing for presence of toxin A or B is highly specific and rapid but lacks sensitivity, and enzyme immunoassay testing for presence of glutamate dehydrogenase is quite sensitive but lacks specificity.
- Treatment of an initial *Clostridioides difficile* infection is dictated by disease severity, with nonsevere disease treated with oral vancomycin or fidaxomicin, severe disease treated with oral vancomycin or fidaxomicin, and fulminant disease treated with higher-dose oral vancomycin, intravenous metronidazole, and (when ileus is present) vancomycin enema.

Viral Gastroenteritis

Viruses are responsible for acute gastroenteritis in most patients. Rotavirus infects young children, and noroviruses, which are the most common cause of gastroenteritis in the United States, affect all ages. Norovirus outbreaks on cruise ships and in schools and other institutionalized settings are well documented. Transmission from person to person is primarily fecal-oral. Infection can develop after ingestion of fewer than 100 viral particles. The incubation period is typically less than 2 days, and infected patients usually have self-limited watery diarrhea, nausea, vomiting, and fever. Treatment is supportive. Diagnostic molecular testing is available. Viral shedding persists for as long as 2 weeks after symptom resolution, which contributes to its high infectivity.

KEY POINT

- Noroviruses are the most common cause of gastroenteritis in the United States; viral shedding persists as long as 2 weeks after symptom resolution, which contributes to high infectivity.

Parasitic Infection

Parasitic infection should be considered in patients with chronic diarrhea. Immunosuppressed persons are at increased risk for more chronic and severe infection.

Giardia lamblia Infection

Giardia lamblia is the most common parasitic pathogen in the United States. Cysts from infected animals are excreted in stool into reservoirs of fresh water, and subsequent ingestion of contaminated water (or food) can lead to human infection. Secondary person-to-person transmission is also possible. Persons at risk for infection include outdoor travelers, children in day-care centers, immunocompromised hosts (particularly those with humoral immunodeficiency), and persons engaged in sexual activity that includes oral-anal contact. The incubation period ranges from 1 to 3 weeks. More than half of infected patients are asymptomatic; however, if present, symptoms, can last for several weeks until spontaneously resolving (see Table 46). Chronic infection may develop, particularly in persons with hypogammaglobulinemia. Immunoassays for antigen detection and molecular testing of stool are more sensitive than stool microscopy for confirming the diagnosis. Treatment is recommended for symptomatic patients; metronidazole, tinidazole, or nitazoxanide can be used. Postinfection lactose intolerance or IBS may be mistaken for recurrent or resistant *Giardia* infection.

KEY POINTS

- Parasitic infection should be considered in patients with chronic diarrhea.
- More than half of patients infected with *Giardia lamblia* are asymptomatic; in symptomatic patients, treatment with metronidazole, tinidazole, or nitazoxanide can be used.
- Postinfection lactose intolerance or irritable bowel syndrome may be mistaken for recurrent or resistant *Giardia* infection.

Cryptosporidium Infection

Cryptosporidium species can infect humans and other mammals. Infection occurs after consumption of fecally contaminated water or food or through close person-to-person or animal-to-person transmission. Municipal water supplies and swimming pools can be a source of infection because the thick-walled oocysts are chlorine resistant and can evade filtration. It is highly infectious, and ingestion of fewer than 50 oocysts may result in infection. The incubation period is 7 days. Clinical findings are described in Table 46. Symptoms

usually last less than 2 weeks before spontaneously resolving in immunocompetent hosts. Immunocompromised patients, in particular patients with AIDS, can develop serious and prolonged infection. Diagnosis from stool can be pursued microscopically by visualization of oocysts with modified acid-fast staining, EIA or direct immunofluorescent antibody testing, or molecular testing. Treatment for immunocompetent patients usually consists of supportive care. When antimicrobial agents are considered for severe or prolonged infection, nitazoxanide is recommended. In HIV-infected patients, antiretroviral therapy is most effective in resolving infection.

KEY POINTS

- Municipal water supplies and swimming pools can be a source of *Cryptosporidium* infection.
- Microscopic visualization of oocysts in stool using modified acid-fast staining, enzyme immunoassay or direct immunofluorescent antibody testing, or molecular testing can provide a diagnosis of *Cryptosporidium* infection.
- Treatment of *Cryptosporidium* infection consists of supportive care for most immunocompetent hosts or nitazoxanide for severe or prolonged infection; antiretroviral therapy is most effective in resolving infection in HIV-infected patients.

Amebiasis

Entamoeba histolytica is responsible for amebiasis. In the United States, most infections are diagnosed in travelers returning from visits to unsanitary tropical or developing countries, immigrants from these areas, persons in institutionalized settings, or those who practice oral-anal sex. Amebiasis is highly infectious, with ingestion of only a small number of infective cysts needed for infection. The incubation period is 2 to 4 weeks. Clinical findings are described in Table 46. Colonic perforation, peritonitis, and death may complicate more fulminant infections. Risk factors for severe infection in adults include immunodeficiency. Microscopic visualization of cysts or trophozoites, stool antigen immunoassay testing, stool molecular testing, and serologic antibody testing can provide a diagnosis, although the latter does not distinguish current from remote infection. Treatment is recommended for all infected patients. In symptomatic patients, treatment with metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide, such as paromomycin or diloxanide, for cyst clearance. In asymptomatic infections, an intraluminal agent for eradication of cysts is recommended.

KEY POINT

- Treatment is recommended for all patients with amebiasis; for symptomatic patients, metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide for cyst clearance, and for asymptomatic patients, an intraluminal agent for eradication of cysts is recommended.

Cyclospora Infection

Cyclospora infections are typically acquired after consumption of food or water that is fecally contaminated with *Cyclospora* oocysts. In the United States, many of these infections have been traced to imported fresh produce from tropical and subtropical areas or have occurred in travelers to endemic areas. The incubation period is approximately 1 week. Symptoms can last for several weeks and may be more pronounced in HIV-infected patients (Table 46).

KEY POINT

- *Cyclospora* infection is typically diagnosed microscopically by visualization of oocysts with modified acid-fast staining, microscopy with ultraviolet fluorescence, or molecular testing; trimethoprim-sulfamethoxazole is recommended for treatment of symptomatic infection.

Infections in Transplant Recipients

Introduction

The occurrence of solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) procedures continues to increase, as do long-term survival rates owing to improved management of rejection and decreased complications. With more patients living longer after transplantation, awareness of principles involved in the recognition and prevention of infection in transplant recipients remains important for physicians who are not transplant specialists.

Despite improvements in immunosuppression and antimicrobial therapy, infection remains a significant cause of morbidity and mortality after SOT and HSCT. Infection is the most common cause of death in the first year after SOT. Additionally, the interaction of the immune system and infection is bidirectional; although immune suppression to prevent rejection increases risk of infection, infection also raises the risk of rejection.

Antirejection Drugs in Transplant Recipients

Success after transplantation depends on modulating the immune system to prevent organ rejection in SOT and to minimize graft-versus-host disease (GVHD) in allogeneic HSCT. Antirejection regimens involve multiple agents (**Table 50**) with different mechanisms of action, which are chosen to minimize overlapping toxicities. After SOT, an induction and maintenance strategy is applied; immunosuppression is most intensive in the first month after transplantation and often includes lymphocyte depletion therapy. Immunosuppression may require intensification during episodes of rejection, with associated increased risk of infection.