

State-of-the-Art Review: Infectious Diarrhea

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In this review, we describe a multidisciplinary approach to the care of a patient with diarrhea, known or suspected to be the result of an infection, incorporating infectious disease, gastroenterology, microbiology, and pharmacy clinical perspectives. We highlight updates in the epidemiology and etiologies of infectious diarrhea, considering both the individual and community impact of disease burden since the publication of the 2017 Infectious Diseases Society of America endorsed guidelines addressing the management of infectious diarrhea. We consider the acute, chronic, and post-infectious intestinal and extra-intestinal manifestations of infectious diarrhea and the clinical challenges posed by each. We discuss the role of diagnostics, including molecular-based testing, often referred to as culture independent diagnostic testing, and culture-based platforms and their role in clinical care and public health surveillance. We discuss emerging antimicrobial resistance and the role of biotherapeutics as strategies to decrease the burden of infectious diarrhea.

Keywords. diarrhea; infectious; diagnostics; management; prevention.

Although hand hygiene and oral hydration remain the mainstay of the prevention and management of infectious diarrhea, we have benefitted from notable advances in the diagnosis, treatment, and prevention. Diarrhea is defined by the World Health Organization as “the passage of 3 or more loose or liquid stools per day (or more frequent passage than is normal for the individual)” [1]. The most common etiology is a known or presumptive pathogen, frequently a viral, bacterial, or parasitic organism, acquired through ingestion of a contaminated food or water source or via person-to-person transmission.

The diagnosis and management of infectious diarrhea can be challenging for both clinicians and patients, especially those with chronic and post-infectious presentations in which an etiology cannot be identified. The symptoms associated with acute and chronic infectious diarrhea create a notable burden and negatively impact quality of life. Diagnostics may be beneficial in situations when a directed therapeutic is available, but symptom-directed management frequently is successful. In considering an evaluation, an understanding of the benefits, limitations, and costs of test modalities and specimen

requirements through discussions with laboratory partners facilitates a comprehensive diagnostic approach. In these situations, joint decision making engaging the patient and their caregivers facilitates an understanding of specific situations, needs, and barriers to achieving an optimal outcome. A multidisciplinary care team consisting of infectious disease clinicians and gastroenterologists, along with microbiologists and pharmacists, ensures that the patient and their condition is optimally assessed. Understanding how a proposed therapeutic will be accessed, consumed, and integrated into management will optimize adherence. Consideration of patient age, past medical history, current medical conditions, exposures, and other lifestyle factors impact the approach to the management of people presumed to have infectious diarrhea (Table 1). Therefore, multispecialty engagement optimizes access, linkage to care, and judicious use of diagnostics and therapeutics for the management of infectious diarrhea.

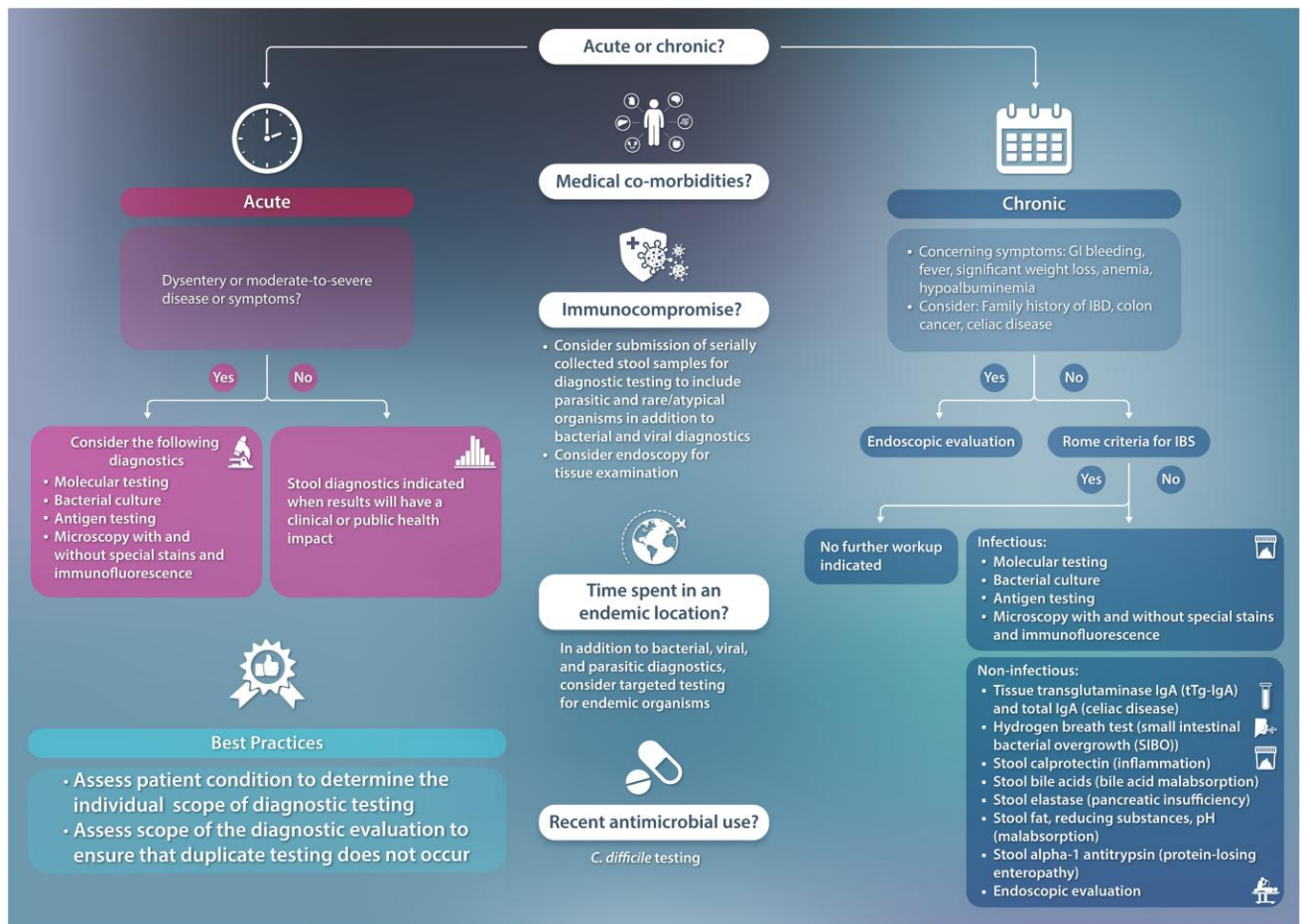
In this review, we describe a multidisciplinary approach to the care of a patient with diarrhea, known or suspected to be the result of an infection, incorporating infectious disease, gastroenterology, microbiology, and pharmacy clinical perspectives. We highlight updates in the epidemiology and etiologies of infectious diarrhea, considering both the individual and community impact of the burden of disease since the publication of the Infectious Diseases Society of America (IDSA)-endorsed guidelines addressing the management of infectious diarrhea published in 2017 [2]. We consider the acute, chronic, and post-infectious intestinal and extra-intestinal manifestations of infectious diarrhea and the clinical challenges posed by each. We discuss the role of diagnostics, including molecular based testing, often referred to as culture independent diagnostic

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DIAGNOSTICS

The aspect of management of diarrhea that has expanded notably because the publication of recent practice guidelines relates to diagnostics. With the wider availability of molecular diagnostics, clinicians have increased opportunities to identify organisms associated with clinical symptoms. One of the most challenging aspects of diagnostic testing is the interpretation of results and the association between detection and clinical relevance. The infographic outlines an approach to the diagnostic evaluation of a patient with diarrhea with an emphasis on obtaining a detailed clinical and exposure history. These factors may then be applied to the optimal selection of diagnostics.

The optimal specimen for diagnostic evaluation of infectious diarrhea is a stool specimen, collected while the patient is symptomatic and transported to the laboratory immediately.

If there is a possible delay between stool collection and laboratory receipt, specimens may be put in transport media (eg, Cary-Blair) to help maintain bacterial pathogen viability should cultures be requested. Stool for parasite microscopic or antigen testing should be placed into fixative solutions (eg, 5%–10% formalin, polyvinyl alcohol, 1-vial systems) provided by the laboratory to help preserve parasite morphology. If considering nucleic acid amplification testing (NAAT), consult with the testing laboratory for proper transport conditions and media. Testing for *Clostridioides difficile* should not be performed on formed stool specimens, except in the situation where a patient has an ileus or has developed toxic megacolon, nor for patients with recent laxative use. In addition, the results of *C. difficile* diagnostics are not clinically relevant in children <1 year of age and are rarely clinically relevant in children 1–2 years of age [3].

Numerous testing modalities are available for gastrointestinal pathogens, including stool culture (bacteria), antigen testing (bacteria, viruses, and parasites), microscopic examination (parasites) and NAAT for all 3 pathogen groups (Table 2). Clinicians should consult with their microbiology laboratory to

Table 1. Clinical Presentations of Selected Enteric Pathogens

Organism	Symptoms	Time to Symptom Onset After Exposure	Duration of Symptoms	Exposure	Extra-intestinal and Post-Infectious Manifestations
Bacterial					
<i>Aeromonas</i>	Varies; mild self-limiting watery diarrhea to a more severe dysenteric form; acute—most common; may be associated with chronic abdominal symptoms	1–2 d	Median: 7 d; range 2–18 d	Aquatic sources	Wound infections
<i>Bacillus cereus</i>	Diarrheal or emetic syndrome via toxins	Emetic: hours from ingestion to symptoms Diarrheal: longer onset from ingestion to symptoms	Symptoms from emetic and diarrheal syndromes usually resolve within 24 h	Contaminated water, food, soil; spore-forming facilitating survival in environment	Bacteremia; endocarditis, ocular infections, musculoskeletal; central nervous system infections in children emetic toxin occasionally associated with liver failure
<i>Campylobacter jejuni/coli</i>	Crampy abdominal pain; watery diarrhea with blood; colitis and abdominal pain/ pseudoperitonitis or intussusception	1–2 d	7 d; relapse or prolongation of symptoms in 20%	Foodborne; commensal in intestinal tracts of animals including poultry; waterborne and contact with animals	Febrile seizures in young children; post-infectious reactive arthritis, Guillain-Barré syndrome
<i>Clostridium botulinum</i> (foodborne botulism)	Constipation is a common gastrointestinal presentation	12–48 h (range 6 h to 10 d)	Weeks to months	Ingestion of pre-formed toxin in home-canning, inadequate refrigeration	Acute onset of bilateral cranial neuropathies with symmetrical descending weakness
<i>Clostridioides difficile</i>	Range from asymptomatic/non-severe with watery diarrhea to severe colitis	Variable: antibiotic associated 3 d to 3 m	Weeks to months; recurrence in 20%	Intestinal dysbiosis associated with antimicrobial use, gastrointestinal infection, chemotherapy, radiation	Systemic manifestations that may mimic sepsis
<i>Clostridium perfringens</i>	Sudden onset voluminous watery diarrhea with abdominal bloating; diarrheal or emetic syndrome via toxin; rarely associated with vomiting.	Average 8–12 h; range 6–24 h	Usually, less than 24 h	Spores in environment, raw meat, poultry improperly cooked or stored foods; catered events	
<i>Listeria monocytogenes</i>	Febrile gastroenteritis; fever, watery diarrhea, nausea, vomiting	Gastroenteritis—24 h	Self-limited infections 48–72 h	Foodborne: ready-to-eat meats, unpasteurized dairy products	Bacteremia, meningitis myalgia, lumbar pain; spontaneous abortion, fetal death, preterm delivery; neonatal pneumonia, granulomatosis infantisepticum, neonatal meningitis
Shiga-toxin producing <i>E. coli</i> (STEC)	Initially non-bloody diarrhea progressing to bloody diarrhea in 48–72 h; transient abdominal pain and fever in some	Average 3–4 d for STEC (range 1–10 d)	Diarrhea resolution within 7 d	Contaminated food, water, feces, or contact with infected animals	Hemolytic uremic (HUS) syndrome with microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction develops 1–2 wks after diarrhea resolution; children under 10 y old and older adults at greatest risk of severe disease resulting from Shiga toxin 2 production

Table 1. Continued

Organism	Symptoms	Time to Symptom Onset After Exposure	Duration of Symptoms	Exposure	Extra-intestinal and Post-Infectious Manifestations
Enterotoxigenic <i>E. coli</i> (ETEC)	Watery diarrhea (mild to severe) with abdominal cramps	1–3 d	1–5 d, self-limiting	Travel to areas lacking sanitation; foodborne and waterborne	Common etiology of travelers' diarrhea
Enteropathogenic <i>E. coli</i> (EPEC)	Watery with mucus; usually mild, can be persistent	½ d–6 d	Usually, self-limited	Contaminated food and water supplies	
Enteroaggregative <i>E. coli</i> (EAEC)	Watery diarrhea, occasionally with blood;	½ d–6 d	Acute or chronic—associated with prolonged symptoms >14 d	Contaminated food	Low-grade fever
<i>Plesiomonas</i>	Watery, non-bloody diarrhea; vomiting and abdominal pain	20–24 h	1–7 d; usually self-limited; antimicrobials may reduce symptom duration	Freshwater aquatic sources in tropical/subtropical areas; associated with seafood consumption	Bacteremia, sepsis, meningitis, pneumonia, osteomyelitis, and keratitis
<i>Salmonella</i>	Diarrhea, abdominal cramps	Non-typhoidal: 6–48 h with a range of up to 7 d Typhoidal: 7–14 d with a range of 3–60 d	Duration varies with manifestation: shortest duration of days for non-typhoidal gastroenteritis; duration extends to weeks for focal disease with non-typhoidal and typhoidal salmonellosis; antimicrobial therapy may prolong duration of shedding with non-typhoidal salmonellosis	Consumption of fecally contaminated food or water, improperly handled contaminated food, from other humans or farm or pet animals; travel to or contact with a returned traveler from endemic settings increases risk for typhoid salmonellosis	Enteric fever, bacteremia, endovascular infections with typhoid salmonellosis; urinary tract infection, meningitis, brain abscess, osteomyelitis associated with non-typhoid salmonellosis
<i>Shigella</i>	Watery diarrhea initially, with progression to mucoid stools; abdominal cramps; tenesmus; rare post-infectious irritable bowel syndrome	Typically, 1 to 3 d; range 1–7 d	Gastroenteritis self-limited, usually resolving within 7 d (2–3 d for <i>S. sonnei</i> /gastroenteritis); antimicrobial therapy may reduce duration of shedding	Fecal-oral route; foodborne; waterborne; recreational water; sexual contact; contaminated inanimate objects; houseflies and cockroaches may be vectors; travel to endemic settings	High fever, hypothermia, lethargy, bacteremia, seizures and leukemoid reactions in children; reactive arthritis (HLA-B27) with or without urethritis and conjunctivitis; <i>S. dysenteriae</i> type 1 associated with hemolytic uremic syndrome (HUS)
<i>Vibrio</i>	Diverse species with varying clinical manifestations; <i>V. cholerae</i> associated with voluminous watery diarrhea and dehydration with hypovolemic shock and electrolyte abnormalities in children; non-cholerae vibrios associated with gastroenteritis, wound infections and bacteremia; gastroenteritis acute onset of nonbloody diarrhea, nausea, vomiting, and abdominal cramps	Varies with species and manifestations; hours to days	Variable duration of symptoms; <i>V. cholerae</i> duration dependent on extent of rehydration required; antimicrobial therapy reduces diarrhea and shedding; gastrointestinal infection with other <i>Vibrios</i> resolves within 2–5 d	Marine and estuarine environments; active during summer months impacted by ocean warming and climate change; consumption of seafood	Wound infections, cellulitis, bacteremia; necrotizing fasciitis has been noted in immune compromised persons
<i>Yersinia</i>	<i>Y. enterocolitica</i> and <i>Y. pseudotuberculosis</i> associated with gastroenteritis; fever, abdominal pain (minimal in children), and diarrhea most common; occasional nausea and vomiting; bloody diarrhea more common in children	Average 4–6 d (range 1–14 d); onset may be subacute	12–22 d with prolonged stool shedding in some for 2 wks—3 m	Transmission largely foodborne (associated with the preparation of pork intestines) and waterborne, Person-to-person transmission rare; rarely associated with transfusion of blood products	Erythema nodosum and reactive arthritis most common; bacteremia with sepsis, pseudo-appendicitis; liver abscess, pharyngeal abscess, empyema, endocarditis, mycotic aneurysm, meningitis, osteomyelitis, septic arthritis, skin lesions, ophthalmitis

Table 1. Continued

Organism	Symptoms	Time to Symptom Onset After Exposure	Duration of Symptoms	Exposure	Extra-intestinal and Post-Infectious Manifestations
<i>Viral</i>					
Enteric Adenovirus 40/41	Watery diarrhea	Up to 10 d	Prolonged duration compared with other viral gastrointestinal pathogens;	Young children in group childcare settings; summer seasonal predisposition	May be associated with severe disease in hematopoietic stem cell transplant recipients
Astrovirus	Watery diarrhea		Usually self-limited in immunocompetent; immunocompromised may experience prolonged stool excretion	More common in winter months; more common children <4 y of age	No associated post-infectious manifestations
Cytomegalovirus (CMV)	Bloody diarrhea, fever, abdominal pain; more severe infections in immunocompromised and those with underlying medical comorbidities, manifest as inflammatory colitis and can mimic inflammatory bowel disease;		Rare and typically self-limited in immunocompetent patients; young and elderly and immunocompromised may experience prolonged stool excretion		Extraintestinal involvement may occur with systemic viremia and dissemination
Hepatitis A	Nausea, vomiting, anorexia, fever, malaise, and abdominal pain, mild to no symptoms in children <6 y of age	28 d (range 15–50 d)	Duration gastrointestinal symptoms for 7 d; jaundice peaks at 2 wks after infection	Transmitted via the fecal-oral route; person-to-person contact or consumption of contaminated food or water; sporadic infections or outbreaks	Jaundice and pruritus; rash; arthralgias; immune complex conditions; fulminant hepatic failure in >60 y old with underlying hepatobiliary disease
Norovirus	Known as “winter vomiting disease”; mild illness with vomiting, fever, and mild watery diarrhea; more severe illness with fever, vomiting, headache, and systemic symptoms; onset may be rapid	24–48 h (range 12–72 h)	Duration 48–72 h; may shed virus in stool for up to 4 wks after infection; longer duration in immunocompromised hosts	Person-to-person transmission; small inoculum needed for transmission; transmission may occur via airborne droplets of vomitus containing viral particles, consumption of contaminated food and water; stable in the environment; associated with outbreaks in congregate settings	Rarely associated with neurologic sequelae in children (seizures and encephalitis)
Rotavirus	Moderate to severe vomiting and watery diarrhea; less severe symptoms in adults	>48 h	Duration 3–7 d; viral shedding in stool up to 10 d—longer in immunocompromised	Most common in children 6–24 m in fall and winter; year-round in tropical climates; small inoculum needed for transmission; household transmission common	Rarely seizures may occur; encephalopathy or encephalitis described; post-infectious carbohydrate/lactase intolerance
Sapovirus	Acute watery diarrhea	12–48 h	Duration 1–2 d	More common in infants and toddlers; no seasonal predisposition	No associated post-infectious manifestations
<i>Parasitic</i>					
<i>Cryptosporidium</i>	Secretory diarrhea resulting in malabsorption; may be acute or chronic in onset and duration with intermittent or continuous symptoms; malaise, nausea and anorexia, crampy abdominal pain, and low-grade fever	7–10 d (range 2–28 d)	Duration 10–14 d; may persist or relapse in immunocompromised	One of the most common parasitic enteric pathogens in humans; outbreaks associated with drinking water, foodborne, animal contact, travel, recreational water facilities; associated with sporadic infections (immunocompetent) and chronic and more severe symptoms (immunocompromised); ingestion of only a few oocysts leads to infection:	Most common in those with T-cell immunodeficiencies cholecystitis, cholangitis, hepatitis, and pancreatitis, biliary tract involvement; immunocompetent may experience chronic diarrhea, weight loss; associated with post-infectious irritable bowel syndrome

Table 1. Continued

Organism	Symptoms	Time to Symptom Onset After Exposure	Duration of Symptoms	Exposure	Extra-intestinal and Post-Infectious Manifestations
<i>Cyclospora</i>	Anorexia, nausea, flatulence, fatigue, abdominal cramping, watery diarrhea, low-grade fever, and weight loss	Acute onset of watery diarrhea with mucus and blood; 7 d (range 2 to 14 d)	Single self-limited episode or waxing and waning course;	Foodborne, waterborne, and soil-transmitted; humans only host	Biliary disease; acalculous cholecystitis in persons with HIV; post-infectious gastrointestinal
<i>Cystoisospora</i>	Malaise, anorexia, and abdominal cramps followed by sudden onset of watery diarrhea	Between 4 and 14 d; earlier if higher inoculum or more intense exposure	Usually resolves in 10–14 d; may persist or relapse in immunocompromised	Implicated as an etiology of travelers' diarrhea	Post-infectious irritable bowel syndrome
<i>Entamoeba histolytica</i>	Diarrhea, bloody stools, weight loss, and abdominal pain	Onset of acute gastroenteritis over 1–3 wks	Depending on species, symptom duration weeks to months	Ingestion of amebicysts, viable for weeks to months, in food or water; sexual transmission through fecal-oral contact; outbreaks associated with using manure as agricultural fertilizer. Risk factors for severe disease include young age, pregnancy, corticosteroid treatment, malignancy, malnutrition, and alcohol use.	Liver abscess formation months to years after exposure; fever right upper quadrant pain hepatomegaly with hepatic tenderness; rarely, an amoebic liver abscess ruptures into the pleural and cardiac spaces causing pulmonary and cardiac symptoms
<i>Giardia</i>	Diarrhea, malaise, steatorrhea, flatulence, abdominal cramping, bloating, nausea, weight loss	7–14 d	1–4 wks; chronic symptoms in 50% with malabsorption may last weeks to months	Poor hygiene and limited water-treatment; waterborne, foodborne, or fecal-oral transmission; higher risk for severe manifestations in infants, young children, international adoptees, travelers, immunocompromised, and those with secretory IgA and cell-mediated immunity deficiencies	Rarely arthritis, urticaria, bile or pancreatic duct involvement
Fungi					
Microsporidia	Watery, non-bloody diarrhea and nausea with diffuse abdominal pain; protracted diarrhea in immunocompromised	Largely unknown	Largely unknown	Oral ingestion of spores through foodborne, waterborne, person-to-person, donor-derived	Pulmonary, ocular, biliary tract, cerebral, myositis, and cystitis, urethritis

Abbreviation: IgA, immunoglobulin A.

Table 2. Enteric Pathogens and Diagnostic Methodologies

Pathogens	Diagnostic Methodology	Specimen
Bacteria		
<i>Aeromonas</i> spp. <i>Edwardsiella tarda</i>	Stool culture ^a	Stool
<i>Campylobacter</i> spp. ^b <i>Plesiomonas</i> spp. <i>Salmonella</i> spp. <i>Shigella</i> spp. <i>Vibrio</i> spp. <i>Yersinia enterocolitica</i>	Stool culture ^a NAAT	Stool
Shiga-toxin-producing <i>Escherichia coli</i> (STEC)	Shiga toxin EIA Culture for <i>E. coli</i> O157:H7 ^a NAAT	Stool
<i>E. coli</i> (enteroaggregative, enteropathogenic and enterotoxigenic)	NAAT	Stool
<i>Clostridioides difficile</i> ^c	Cytotoxin cell culture GDH antigen and toxin EIA NAAT plus toxin algorithm NAAT alone	Stool
<i>Bacillus cereus</i> <i>Clostridium perfringens</i>	Specialized test at state or local public health laboratory ^d	Stool Food from outbreak
<i>Clostridium botulinum</i>	Specialized test at public health laboratory ^e	Stool Enema
Viruses		
Adenovirus 40/41 Rotavirus ^f	EIA NAAT	Stool
Astrovirus Norovirus Sapovirus	NAAT	Stool
Cytomegalovirus Herpes simplex virus	Histology PCR	Intestinal tissue biopsy
Hepatitis A virus	Serology (IgM and IgG) NAAT	Serum Plasma
Parasites		
<i>Cryptosporidium</i> spp. <i>Giardia lamblia</i>	NAAT EIA DFA Ova and parasite examination ^g	Stool
<i>Entamoeba histolytica</i>	EIA NAAT	Stool
<i>Cyclospora</i> spp.	Modified acid-fast stain NAAT Wet mount	Stool
<i>Cystoisospora</i> spp.	Modified acid-fast stain	Stool
Microsporidia	Modified trichrome stain NAAT	Stool
Other protozoa or helminths	Ova and parasite examination ^g Serology in some situations when clinical or epidemiological factors suggest utility	Stool

Abbreviations: DFA, direct fluorescent immunoassay; EIA, Enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic-acid amplification test; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction.

^aClinical laboratory stool culture workflows vary and are subject to change. Thus, the laboratory should be consulted to confirm which pathogens are routinely screened by culture. Secondary culture methods may be needed dependent on the pathogen of interest.

^b*Campylobacter* spp. antigen tests are available but have sensitivity and specificity issues and are not recommended.

^c*C. difficile* testing should only be performed on unformed stool specimens.

^d*B. cereus* and *C. perfringens* toxin testing may be performed at public health laboratories in cases of food-borne outbreaks that require approval prior to performance of testing.

^e*C. botulinum* toxin testing may be performed at public health laboratories after obtaining approval. Enema specimens should be collected using sterile non-bacteriostatic water. Suspected cases require immediate notification of public health. *C. botulinum* is considered a bioterrorism agent so special handling of specimens is required.

^fRecent rotavirus vaccination may cause positive results in testing.

^g*Cryptosporidium* spp. require modified acid-fast stain for detection while *G. lamblia* will be detected by a trichrome stain. The types of parasites stains may vary by the performing laboratory so consult the laboratory to know what stains are performed. Microscopic examination requires preservation of stool so contact the testing laboratory for appropriate stool fixatives. To maximize testing sensitivity for microscopy, up to 3 stool specimens should be collected with 2–3 d between collections.

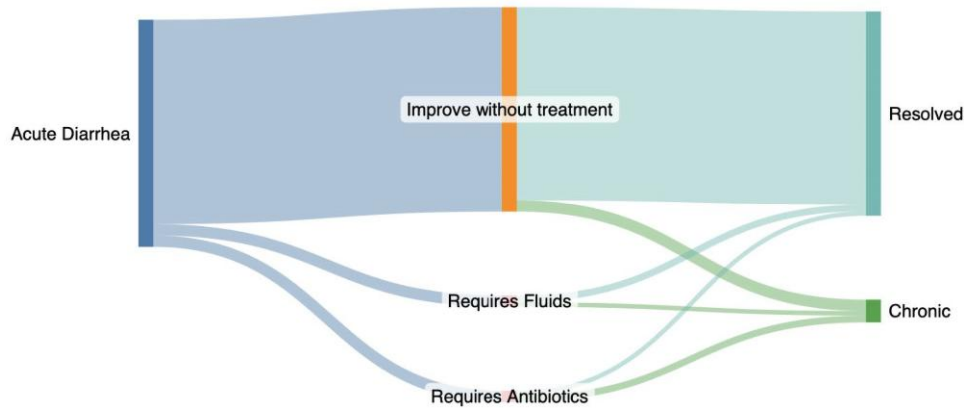


Figure 1. Expected course for adult patients following acute infectious diarrhea. Most adult patients with diarrhea will improve without the need for supplemental fluids or antibiotics. Approximately 10% of patients with infectious diarrhea may be expected to have chronic symptoms 12 months after diagnosis.

determine which organisms are detected by the available methods. For example, the bacterial organisms detected by stool culture vary by laboratory, so when interpreting a negative culture result, clinicians should be cognizant of the organisms that were assessed by the diagnostic test. Additionally, parasites assessed by microscopic testing vary by the stains performed. Finally, there are several US Food and Drug Administration (FDA)-approved/cleared multiplex NAATs available, with variability in detected targets. For proper diagnostic stewardship, clinicians should be aware of the targets reported by the laboratory performing the testing. NAATs may offer rapid results with greater sensitivity than conventional methods but may come at a higher financial cost. However, the use of NAATs could result in cost savings external to the laboratory [4] (ie, antimicrobial, and diagnostic stewardship, and infection prevention). A feature of the high sensitivity of NAAT diagnostics is that testing cannot distinguish between active infection and residual nucleic acids from a previous infection, especially in immunocompromised patients where nucleic acids can persist in stool for longer periods. For this reason, NAAT methods should not be used as a test of cure. Recent rotavirus vaccination can also result in positive rotavirus NAAT or antigen results, emphasizing the importance of clinical correlation in the interpretation of diagnostic testing results [5].

For patients hospitalized >3 days, laboratories may reject requests for stool organism testing, due to the low yield of pathogen detection, except for *C. difficile*. In these situations, communication with the microbiology laboratory, providing a rationale for diagnostic testing in a patient who has been hospitalized for >72 hours, is essential to optimize collaboration between the bedside clinician and the microbiology laboratories. Repeat testing is recommended after negative parasite microscopic examination to increase sensitivity of organism detection. Stool culture has relatively high sensitivity (87%–94%) for pathogen detection from a single specimen from

adults and increases (98%) with a second specimen [6], whereas a single specimen from pediatric patients has a higher sensitivity of organism recovery (98%) [7].

For non-infectious etiologies of diarrhea refer to the infographic for a testing algorithm. Currently, fecal biomarkers, such as lactoferrin, calprotectin, interleukin 8 and interleukin 1 β , are not recommended by the IDSA for diagnosis of *C. difficile* infection [3]. Additionally, the American Gastroenterological Association (AGA) notes that fecal biomarkers such as calprotectin can be elevated by infectious and non-infectious etiologies and recommends evaluation for enteric pathogens when considering non-infectious etiologies for patients with gastrointestinal symptoms and possible inflammatory bowel disease [8, 9]. Further studies are needed to identify biomarkers that can reliably differentiate infectious and non-infectious causes of diarrhea.

MANAGEMENT

Infectious diarrhea management is focused on supportive care guided by the severity of illness, careful observation for signs of hemodynamic shock, which suggests a bacterial pathogen that warrants early antibiotic administration, and the use of antimotility agents if concern for inflammatory diarrhea is low. There are limited recent data describing the natural history of infectious diarrhea in the United States, but most cases resolve without intervention or identification of a causal pathogen (Figure 1). Table 3 outlines management recommendations in the acute period before pathogen-specific diagnostic results may be available.

Supportive Care

The principles of supportive care in the management of people with diarrhea are volume and electrolyte monitoring and repletion. The recognition that glucose co-transporter channel activity

Table 3. Initial Clinical Management of People With Acute Diarrhea Informed by Signs, Symptoms, and Context

Sign(s)/Symptom(s)	Context	Treatment	Expected Response Based on Clinical Experience
>3 watery stools per 24-hour period ^a but volume replete without signs or symptoms of bacterial infection; absence of fever, tenesmus, abdominal pain, and bloody stools	General	<ul style="list-style-type: none"> • Oral volume repletion, avoid antibiotics, consider anti-diarrheal agent as shared decision-making with patient 	Resolution in <72 h
>3 watery stools per 24-hour period with volume depletion, without shock: <ul style="list-style-type: none"> • Dark urine • Decreased skin turgor • Orthostatic hypotension 	General	<ul style="list-style-type: none"> • Volume repletion (oral rehydration solution preferred), avoid antibiotics • Consider anti-diarrheal agent as shared decision-making with patient 	Resolution in <72 h
	Age <5 or >65 y, medical history of cardiac disease, immunocompromising conditions, or pregnancy	<ul style="list-style-type: none"> • Volume repletion (oral rehydration salts preferred) • Antibiotic therapy^b 	Resolution in 5–7 d
>3 watery stools per 24-hour period with hypovolemic shock: <ul style="list-style-type: none"> • Systolic blood pressure <90 mmHg (Adults) • Tachycardia • Elevated serum lactate • Encephalopathy 	General	<ul style="list-style-type: none"> • Volume repletion (intravenous (IV) preferred but oral rehydration salts may be effective if IV unavailable), avoid antibiotics 	Reduction in diarrhea frequency in 3–5 d
	Recent healthcare and/or antibiotic exposure, immunocompromising conditions, inflammatory bowel disease, age <5 y or >65 y	<ul style="list-style-type: none"> • Volume repletion; avoid Lactated Ringers • Consider empiric antibiotic therapy,^b directed therapy for <i>C. difficile</i>^c 	Reduction in diarrhea frequency in 3–5 d
	Age <5 y or >65 y, medical history of cardiac disease, immunocompromising conditions, recent travel, or pregnancy	<ul style="list-style-type: none"> • Volume repletion (IV rehydration preferred for patients with shock); avoid Lactated Ringers • Antibiotic therapy^b 	Reduction in diarrhea frequency in 5–7 d
>3 watery stools per day with bacterial infection manifest by one or more <ul style="list-style-type: none"> • Bloody stools • Small mucoid stools • Severe abdominal pain • Tenesmus • Fever 	General	<ul style="list-style-type: none"> • Volume repletion (oral rehydration salts preferred) • Antibiotic therapy^b 	Reduction in diarrhea frequency in 5–7 d

^aOr change from baseline number of stools for pediatric patients <5 y of age.

^bAntibiotic therapy:

Empiric regimens should be considered in context of latest antibiotic resistance surveillance data for the location.

Outpatient: rifaximin 200 mg PO TID × 3 d, or azithromycin 500 mg PO daily × 3 d; Inpatient, no shock: ceftriaxone 1–2 g IV q24h +/- azithromycin 500 mg PO/IV q24h.

Inpatient, shock: ceftriaxone 2 g IV q24h + azithromycin 500 mg IV q24h OR ertapenem 1 g IV q24h (given increasing ceftriaxone resistance among *Shigella* and *Salmonella*).

For returned travelers with persistent symptoms, consider pathogens common in their regions of travel and resistance patterns of commonly encountered pathogens <https://wwwnc.cdc.gov/travel>. With shared decision making, travelers may be provided with loperamide and an antibiotic for self-treatment. Travelers destined to southeast Asia should receive azithromycin. A fluoroquinolone, azithromycin or rifaximin can be prescribed for travel to other regions. (Note: if rifaximin is prescribed as a first-line agent, azithromycin should also be prescribed to be taken if dysentery or febrile diarrhea develops).

^c*C. difficile* antibiotic therapy: (see Infectious Diseases Society of America [IDSA] <https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update/> and American College of Gastroenterology, https://journals.lww.com/ajg/fulltext/2021/06000/acg_clinical_guidelines_prevention_diagnosis_12.aspx *C. difficile* treatment guidelines).

Fidaxomicin or vancomycin are recommended as first line for diarrhea without shock.

Vancomycin 500 mg PO q6h plus metronidazole 500 mg IV q8h are recommended for patients with *C. difficile* infection and shock.

Patients with *C. difficile* and evidence of ileus, adjunctive rectal vancomycin instillation should be considered.

is preserved in most cases of diarrhea led to the impactful development and implementation of oral rehydration solutions (ORS). Often thought to be under-utilized in healthcare settings

in higher income countries, ORS is a highly effective strategy to treat patients with volume loss [10–12]. Boluses of intravenous fluids are preferred for patients with shock or clinical findings

consistent with severe dehydration such as lethargy, sunken eyes, inability to consume oral fluids, or reduced skin turgor [13].

Antimicrobials

Empiric antimicrobial treatment of diarrhea should be limited to patients with signs of shock and inflammatory diarrhea (such as bloody stools, lymphadenopathy, fever), those who are immunocompromised, or an exposure history associated with travel to a pathogen endemic setting.

Empiric antibiotic regimens should be informed by national surveillance systems and local epidemiology data where available. The National Antimicrobial Resistance Monitoring System (NARMS) [14] monitors and reports changes in antimicrobial susceptibility of enteric bacteria (*Salmonella* spp., *Shigella*, *Escherichia coli* O157, *Campylobacter* spp., *Vibrio* spp.) from clinical isolates, meats, and food animals. According to recent NARMS data, ciprofloxacin and trimethoprim-sulfamethoxazole resistance are relatively common among this group of pathogens, which limits the utility of these antimicrobials as empiric therapy. Ceftriaxone is a reliable and attractive choice in healthcare settings where intravenous or intramuscular administration is feasible. Specifically, ceftriaxone is active for >90% of clinically significant bacterial pathogens other than *Campylobacter* spp., which is typically resistant to ceftriaxone. Azithromycin is active against most *Campylobacter* spp. isolates, but activity is variable for other bacteria, such as *Salmonella*. Of particular concern, in 2023, the US Centers for Disease Control and Prevention (CDC) issued a health alert (CDCHAN-00486) [15] warning of a sharply increased frequency of extensively drug-resistant (XDR) shigellosis that is resistant to all commonly used empiric antibiotics, including azithromycin and ceftriaxone.

The decision to empirically initiate antibiotics in a patient with infectious diarrhea should be based on illness severity and diagnostic testing availability. Collecting diagnostic specimens should be prioritized, recognizing that antibiotic administration may affect culture yield. If a bacterial pathogen is suspected in a hemodynamically stable patient with infectious diarrhea and rapid diagnostic testing is unavailable, ceftriaxone monotherapy is an adequate first line choice. For patients with septic shock, an empiric regimen of both azithromycin and ceftriaxone is an appropriate first line choice when campylobacteriosis cannot be excluded. Patients who do not respond to initial therapy or are at higher risk for XDR shigellosis (eg, people who are unhoused, people with human immunodeficiency virus [HIV], international travelers, people who are gay, bisexual, and men who have sex with men) may benefit from a carbapenem (eg, ertapenem) pending additional culture data. Of note, carbapenems have antimicrobial activity against *Campylobacter* spp., so adjunctive azithromycin is unnecessary. If a bacterial pathogen is suspected in a patient who does not have septic shock, ceftriaxone monotherapy is likely an adequate empiric choice.

Traveler's diarrhea treatment merits separate discussion due to differences in risk/benefit assessment and varying access to medical care, testing, and antibiotics.

Traveler's diarrhea treatment guidelines from the International Society of Travel Medicine (ISTM) emphasize the need to balance antimicrobial stewardship with proven effectiveness of antibiotics in reducing symptom duration and intensity. The strength of the recommendation to use antibiotics increases with illness severity, which the ISTM guidelines propose is defined by functional impact on the patient. Antibiotics are not recommended for tolerable diarrheal symptoms that do not interfere with planned activities. For moderate disease, antibiotics may be considered as an adjunct to loperamide. Antibiotics are strongly recommended for severe diarrhea that is incapacitating, including dysentery. Azithromycin is preferred for severe diarrhea given high rates of fluoroquinolone resistance among *Campylobacter* spp. and *Shigella* spp, particularly in travelers to Southeast Asia. Rifaximin is an alternative as it is not appreciably absorbed from the gastrointestinal tract, which translates to fewer adverse effects and an excellent safety profile. However, it should not be used to treat infections resulting from invasive pathogens (eg *Campylobacter*, *Salmonella*, and *Shigella* spp) and dysentery [16, 17].

Concern for Shiga toxin-producing *E. coli* (STEC) infections pose a unique management situation, as the risk of empiric antibiotic therapy may outweigh potential benefit in patients with infectious diarrhea. Specifically, epidemiologic studies and meta-analyses suggest that the risk of hemolytic uremic syndrome (HUS) is increased among patients with STEC treated with some classes of antibiotics [18–20]. When there is high clinical suspicion for STEC, for example in the context of known outbreaks or in patients with animal exposure or elevated blood urea nitrogen, empiric antibiotic treatment should be avoided if not otherwise indicated. Recognizing that causal pathogens are often unknown at time of empiric management, these data suggest careful individual assessment of the risk and benefit of empiric antibiotic treatment of most persons with diarrhea.

C. difficile Focused Therapy

Two professional societies, IDSA and the American College of Gastroenterology (ACG), recently published updated management guidelines for the management of *C. difficile* infection supported by systematic reviews [21, 22]. Although their interpretations of the data varied in some instances, the consensus supported broader use of fidaxomicin as a first line antibiotic in adults given the sustained clinical cure without relapse compared to oral vancomycin and metronidazole. Of note, there have been recent reports of *C. difficile* infection associated with isolates with reduced fidaxomicin susceptibility and reports of the development of reduced fidaxomicin susceptibility. Surveillance to monitor *C. difficile* isolate susceptibility is

indicated, especially as fidaxomicin use becomes more widespread [23]. Although the IDSA and ACG practice guidelines both recommended use of bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B as an adjunct to *C. difficile* antibiotics for patients with recurrent infection, bezlotoxumab has been discontinued by the current manufacturer. Patients with 1 or more risk factors for *C. difficile* recurrence (ie, age >65 years, immunocompromise, prior severe episode of *C. difficile*) are most likely to benefit. Several risk factors have been associated with *C. difficile* diarrhea, although prior studies to develop clinical prediction scores that may support earlier empiric treatment of patients at high risk of severe or recurrent disease have modest predictive value and have not been widely adopted [24].

The ACG also concluded that the data were strong enough to support consideration of conventional fecal microbiota transplant (FMT) for treatment of adult patients who are hospitalized with fulminant *C. difficile*, and who are not responding to conventional therapies. These recommendations were recently expanded in an AGA clinical practice guideline on fecal microbiota therapies [25]. We concur with the risk-based guidance developed by the AGA, which suggests the consideration of FMT for prevention of additional recurrences after antibiotic treatment of immunocompetent adults with recurrent *C. difficile* infection. In mildly or moderately immunocompromised adults with recurrent *C. difficile* infection, the AGA suggests use of conventional FMT based on observational data for this group, but lack of data for fecal microbiota spores live-brpk (a donor stool-derived spore suspension, formerly SER-109) or fecal microbiota live-jslm (a donor stool-derived microbiota suspension, formerly RBX2660). We also agree with the AGA recommendation against the use of fecal microbiota therapies to prevent recurrent *C. difficile* in severely immunocompromised adults, due to the current paucity of data in this high-risk group.

The American Academy of Pediatrics issued a statement regarding the applications of fecal microbiota therapies for children. Studies suggested that FMT is an option for management of children with moderate to severe or recurrent *C. difficile* infection but cautioned that the post-treatment effects of FMT are not well described in children [26]. In September 2024, a nonprofit stool bank voluntarily suspended distribution of their investigational FMT product for the treatment of recurrent *Clostridioides difficile* infections. This action will result in limited access to FDA-approved microbiota products for FMT, with indications that currently exclude children with any form of *C. difficile* infection and adults with severe or fulminant *C. difficile* infection.

In 2022, the FDA approved the first fecal microbiota product, fecal microbiota, live-jslm (Rebyota®) [27] and in 2023 approved the first oral fecal microbiota spore product, fecal microbiota spores, live-brpk (VOWST™) [28]. Both were approved for the broad indication of prevention of recurrent *C.*

difficile for patients who have had at least one recurrence (ie two or more episodes), following a course of *C. difficile* directed antibiotics. This indication differs from prior guideline recommendations to consider FMT for patients with two or more recurrences (three or more episodes).

Post-marketing safety and efficacy cohort studies may be feasible in some situations and are needed to monitor equitable access to these therapies and to determine comparative effectiveness of the expanding number of prevention and treatment strategies for *C. difficile* and recurrent *C. difficile* infections in adults and children. Review of the FDA Adverse Event Reporting System (FAERS) Public Dashboard (<https://www.fda.gov/drugs/surveillance/fdas-adverse-event-reporting-system-faers>) may provide safety signals, however it is not an indicator of the safety profile of a drug or biologic, and causality cannot be derived from FAERS reports.

Non-Antimicrobial Management

A 2019 Cochrane review of probiotic use for treatment of acute infectious diarrhea included 82 studies published with 12,127 participants, 97% of whom were children [29]. The authors concluded that probiotic supplementation likely makes little difference in clinical outcomes in participants with diarrhea for ≥ 48 hours and on duration of diarrhea. Of note there was variability in how “acute diarrhea” and “the end of diarrhea symptoms” were defined, and there was heterogeneity in the probiotic products that were included. A Bayesian network meta-analysis of 28 clinical studies conducted in children residing in India (9), Pakistan (6), Turkey (6), Mexico (2), Italy (1), Iran (1), Brazil (1), Bolivia (1), and Argentina (1) published in 2021 demonstrated that *Saccharomyces boulardii* may be the most effective in reducing both duration of diarrhea and risk for diarrhea of greater than or equal to two days compared with placebo, with moderate evidence [30]. It is important to note that the profile of enteropathogens endemic in these countries may differ from the ones than might be expected in North America. In the United States, probiotics are regarded not as drugs but as supplements, which are not held to the same requirements for potency, manufacturing controls, or strain characterization that might be expected in a pharmaceutical product. Considerations for optimizing product standards for preterm neonates, one at-risk population, have been described [31]. Interestingly, a study suggested that in vitro, *Lactobacillus*-secreted soluble factors contributed to a delayed return to baseline microbiota composition compared to observation alone or FMT after antibiotic exposure [32].

There is biological plausibility and clinical trial evidence supporting the use of non-toxigenic strains of *C. difficile* and therapeutic microbial consortia (groups of characterized strains with complementary or emergent functions not observed with administration of individual strains), particularly for

prevention of recurrent *C. difficile* infection [33, 34]. These products are likely to be regulated and marketed as live biotherapeutic products, which have stricter manufacturing and potency requirements than dietary supplements.

Anti-diarrheal therapeutics should generally be avoided for patients with suspected infectious diarrhea. An exception is in management of traveler's diarrhea in adults, where loperamide has a role in symptom management when dysentery or toxigenic etiologies are not suspected [16]. However, given the frequency of post-infectious irritable bowel syndrome (IBS) [35], antimotility agents may reduce the duration of symptoms in adults who have undergone a thorough diagnostic evaluation for persistent diarrhea without identification of another etiology.

FOLLOW-UP, GOALS OF TREATMENT, MANAGING EXPECTATIONS, AND SHARED DECISION MAKING

The diagnosis and management of persons with diarrhea is frequently based on a synthesis of the history and presentation of the person with symptoms and the experience of the clinician. The over-arching goal of the management of a person with diarrhea is to maintain fluid and electrolyte balance to prevent the morbidity and mortality associated with dehydration and malnutrition. A companion goal is to eliminate the discomfort associated with diarrhea, facilitating a lifestyle that is functional. In certain situations, initial management will be definitive, while in others, post-infectious symptoms may require a multifaceted approach. To effectively deliver care to an individual patient, it is essential to incorporate shared decision-making so that both patient and clinician are aligned with goals of care. It is also important that goals are frequently reassessed to ensure that management and treatment plans continue to meet the needs of patients and their families. This is especially relevant when caring for patients with chronic or recurrent symptoms of diarrhea that may be dynamic.

When setting expectations, it is important to acknowledge that despite a unifying diagnosis, due to variations in host response, some patients may experience complete resolution of symptoms, whereas others might continue to experience a prolonged course with waxing and waning symptoms. Understanding the applications and limitations of diagnostic testing in situations of non-response and discussing them with patients in a shared decision-making conversation will optimize and promote judicious use of diagnostics and will facilitate interpretation and application of these diagnostic methods.

Future directions for the diagnosis, management, and prevention of infectious diarrhea include opportunities to:

- Further develop diagnostics and biomarkers that are able to differentiate between colonization and clinically significant infection and predict risk of progression

- Gain a deeper understanding of the role of live biotherapeutic and fecal microbiota products in the management of patients with infectious, post-infectious, and non-infectious diarrhea
- Develop effective therapies for currently recalcitrant and persistent enteric infections impacting persons who are immunocompromised
- Support research to develop effective vaccines to enteropathogens and novel preventative measures including bacteriophage therapy for the prevention of enteric infections
- Facilitate access to diagnostics and therapeutics, to all eligible people

Notes

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