Review

Persistent Diarrhea
A Clinical Review

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IMPORTANCE Diarrheal disease is commonly encountered in clinical practice. Persistent diarrhea (≥14 days) can be caused by pathogens that differ from those commonly seen in acute illness; proper etiologic diagnosis is important for appropriate therapeutic management. This review provides an overview of the epidemiology, etiology, diagnosis, and management of persistent diarrhea caused by infectious agents in immunocompetent individuals worldwide.

OBSERVATIONS Much of the data on persistent diarrhea comes from studies of residents in or expatriates of developing countries and travelers to these regions where follow-up studies have been performed. Persistent diarrhea occurs in approximately 3% of individuals traveling to developing countries. *Schistosoma mansoni* (and rarely *Schistosoma haematobium)* intestinal infection is also not very common and is found only in endemic areas. The microbiologic causes of protracted diarrhea include detectable parasitic (eg, *Giardia*, *Cryptosporidium*) and bacterial (eg, enteroaggregative *Escherichia coli*, *Shigella*) pathogens. Available diagnostic tests include culture-dependent for bacterial pathogens and culture-independent methods for bacterial, viral, and protozoal infections (eg, polymerase chain reaction [PCR]), including multiplex PCR, as well as and microscopy for protozoal infections. Antimicrobial therapy can be given empirically to patients returning from the undeveloped to the developed world. Otherwise, antibiotics should be given based on the results of laboratory testing.

CONCLUSIONS AND RELEVANCE Persistent diarrhea is a poorly recognized syndrome in all populations that requires proper assessment and diagnosis to ensure that affected individuals receive the treatment needed to experience improvement of clinical symptoms.

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Although acute infectious diarrhea (ie, diarrhea lasting hours or days) is common in the United States, affecting 179 million individuals annually, less attention is given to the problem of persistent diarrhea (diarrhea ≥14 days).[1] Chronic diarrhea is typically defined as diarrhea lasting longer than 4 to 6 weeks and is rarely caused by infectious agents. This review includes an overview of the epidemiology and etiology of persistent diarrhea in otherwise healthy individuals in developing and industrialized regions of the world, including both infectious and noninfectious causes of persistent diarrhea. Clinical symptoms for different etiologies are presented, followed by a discussion of the proper assessment and diagnosis of persistent diarrhea. Suggested treatment options are reviewed based on findings from clinical studies, systematic reviews, and meta-analyses.

Methods

A review of PubMed and Google Scholar was conducted on February 12, 2016, for English language articles on the epidemiology, etiology, and management of persistent diarrhea in immunocompetent individuals using the search terms *persistent diarrhea*, *infectious diarrhea*, *enteric infection*, *epidemiology*, *treatment*, *management*, *guidelines*, and *immunocompetent*. A search of all articles was performed (ie, no limitations by date). Bibliographies of review articles were used to identify additional sources. Websites for the US Centers for Disease Control and Prevention, US Food and Drug Administration, and World Health Organization were also accessed for any additional information related to this topic.

In a database search on the epidemiology of persistent diarrhea conducted on February 12, 2016, of the 491 references initially identified, 38 articles were selected for inclusion in this review. Of the 309 primary articles focused on the management of persistent diarrhea, systematic reviews and meta-analyses, and guideline articles identified, 76 articles were selected for inclusion. Systematic reviews related to the treatment of *Clostridium difficile* infection were limited to publications since 2013, resulting in identification of 81 reviews, of which 11 were selected for inclusion. Articles were excluded for a number of reasons, including a

lack of relevance to persistent diarrhea (eg, duration of diarrhea not defined), inclusion of populations not considered as healthy (eg, immunocompromised), a primary focus on a pharmaceutical agent or vaccine, etiology not included in this review (eg, surgery), or a description of methods for conducting epidemiologic studies (eg, modeling, transmission). Further, articles detailing molecular and phylogenetic characterization of infectious agents were excluded. Primary articles included in more recent systematic reviews were excluded on the basis that they were summarized in the systematic review.

Countries and regions were characterized as developing or industrialized using information from the Department of Economic and Social Affairs of the United Nations Secretariat (2012).[2] Suggested management strategies for persistent diarrhea were evaluated using the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence (ie, evaluation of articles selected for inclusion), and the OCEBM 2009 Levels of Evidence (ie, grading of suggested treatments).[3,4] When guideline recommendations were available, these levels of evidence were used. Otherwise, the evidence was graded by considering the type of study and publication (ie, systematic review of randomized trials [level 1], randomized study with dramatic effect [level 2], nonrandomized controlled study or follow-up study [level 3], case report or case-control study [level 4], mechanism-based reasoning [level 5]), and consistency of evidence presented in available studies (ie, A [consistent level 1 studies], B [consistent level 2 or 3 studies, or extrapolations from level 1 studies], C [level 4 studies, or extrapolations from level 2 or 3 studies], and D [level 5 evidence, or inconsistency across studies]).

Results

Epidemiology and Etiology of Persistent Diarrhea

Persistent diarrhea typically results from protracted infection (eg, parasites), recurrent infection (eg, *C difficile*), noninfectious causes (eg, lactase deficiency, ingested osmotic substances), or continuing noninfectious pathology after the infectious agent has cleared (eg, postinfectious irritable bowel syndrome). Because of differing populations and hygienic conditions in the world and the limited number of studies available, it is not possible to provide a specific pathogen breakdown in cases of persistent diarrhea (**Table 1**).[5-19] Parasites are the most common infectious agents causing persistent diarrhea, of which protozoa are the most important: *Giardia*, *Cryptosporidium*, *Entamoeba histolytica, Cyclospora, Cystoisospora belli, Dientamoeba fragilis, Strongyloides stercoralis,* and Microsporidia species (ie, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*). A less common parasitic cause of persistent diarrhea is *Blastocystis hominis.* Its role as a pathogen is unclear, since many individuals colonized with *B hominis* do not require or benefit from treatment. However, for patients excreting the organism with persistent diarrhea not attributable to other pathogens, treatment for *B hominis* is warranted.[20] *Schistosoma mansoni* (and rarely *Schistosoma haematobium)* intestinal infection is also not very common and is found only in endemic areas (**Box**).

Bacterial diarrhea usually has a duration of 1 week or less but may be persistent when specific bacterial species are involved, including enteroaggregative *Escherichia coli*, *Shigella*, *Campylobacter*, *Salmonella*, *Vibrio parahaemolyticus* (a noncholera *Vibrio* usually associated with persistent diarrhea in immunocompromised individuals), *Arcobacter butzleri*, and *Aeromonas* species. *C difficile* causes recurrent diarrhea among patients taking antibiotics in health care settings. Viral agents (eg, norovirus) and helminths (eg, *Schistosoma* species, *Strongyloides*) can cause persistent diarrhea in immunocompetent patients, although this occurs less commonly than parasitic or bacterial infections. Persistent diarrhea may occur with celiac disease, carbohydrate malabsorption, or cancer exclusive of any infectious etiology.[21]

Persistent Diarrhea in Developing Regions

Parasites are more common in the developing world. Consequently, persistent diarrhea is more common in these areas and in local populations or people traveling to these locations. Persistent diarrhea in infants and young children in developing nations is associated with high mortality,[22] attributable to underlying host diseases such as malnutrition and zinc or vitamin A deficiency.[23-26] *Giardia* was positively associated with persistent diarrhea in a meta-analysis of 5 studies that included children or adults in developing countries.[27] Persistent diarrhea occurs in approximately 3% of international travelers to developing regions.[28] People from the United States living in a developing region (eg, Guatemala) in close proximity to local residents frequently acquire parasitic infections.[29] Studies conducted in developing countries that include residents, expatriates, and travelers to the countries show the importance of protozoal, bacterial, and viral infections in persistent diarrhea (Table 1). Coinfection with more than 1 pathogen was reported in a wide range of patients from developing nations with persistent diarrhea (14% to 54% of patients studied).[30-32]

Persistent Diarrhea in Industrialized Regions

Studies of persistent diarrhea are less common in the industrialized countries, where parasitic infection is less common and there are few studies of diarrhea in adults with sufficient follow-up to classify illness as persistent. Foodborne and waterborne pathogens and *C difficile* have been implicated in persistent diarrhea affecting nontravelers (Table 1).[14,15,17]

Noninfectious Causes of Persistent Diarrhea

Diarrhea may persist after an infectious cause has been cleared, resulting from the continued presence of noninfectious pathologies. Celiac disease may present as persistent diarrhea associated with exposure to an infectious agent.[18] Other noninfectious explanations for persistent diarrhea include postinfectious irritable bowel syndrome and other forms of functional bowel disease,[33] inflammatory disease unmasked by enteric infection, ischemic colitis, microscopic colitis, cancer, and other forms of idiopathic illness.

Brainerd diarrhea is presumably of infectious origin because it follows exposure to unpasteurized milk or untreated water, and patients may have diarrhea for up to 3 years before recovery.[19] The diagnosis of Brainerd diarrhea is made by exclusion based on lack of an identifiable pathogen in individuals with self-limiting, nonspecific diarrhea after bouts of prolonged illness, especially in patients with a history of consuming raw milk or untreated water.

Table 1. Epidemiology of Persistent Diarrhea

Etiology	Pathogens	Individuals Affected, %	Population
Infectious Etiology in Developing Regions			
Residents			
China[5]	Persistent diarrhea	4.6	Children <5 y
	Rotavirus A	8.7	
	Norovirus GII	8.7	
	Adenovirus	4.3	
Nepal[6]	Protozoa	35.5	Children <5 y
	Bacteria	12.6	
Iran[7]	*Cryptosporidium*		Children 1 mo to 10 y
	Persistent diarrhea	12.5	
	Acute diarrhea	1.2	
Travelers to and Expatriates Residing There			
Nepal[8]	Persistent diarrhea	19	Travelers and expatriates
	Giardia	27	
	Enterotoxigenic *Escherichia coli*	19	
	Campylobacter	16	
	Shigella	5	
Iraq or Afghanistan[9]	Not specified	10	US military personnel
Unspecified tropical regions[10]	Persistent diarrhea	68	Travelers from Belgium and the Netherlands
	Giardia lamblia	16.4	
	Blastocystis hominis	9.6	
	Campylobacter jejuni	6.1	
	Shigella species	3.5	
	Cyclospora	3.5	
Tropical and subtropical regions[11]	*Aeromonas* species	2	Travelers from Spain
	Persistent diarrhea	50	
Infectious Etiology in Industrialized Regions			
Residents			
Japan[12]	Cytomegalovirus		Adults
United States[13]	Persistent diarrhea	0.18[a]	Children, mean age, 15.2 mo
Milwaukee, Wisconsin (1993)[14]	Waterborne *Cryptosporidium*	83[b]	Immunocompetent children and adults
California (April 1998 to March 1999)[15]	Chronic diarrhea[c] *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio*, *Cryptosporidium* species, or *E coli* O157:H7	83	Individuals with laboratory-confirmed infection with foodborne pathogens
Belgium[16]	Persistent diarrhea		Children and adults
	Arcobacter butzleri	16.4	
	C jejuni	4.7	
	Odds of developing persistent diarrhea (*A butzleri* vs *C jejuni*)	4.0 (95% CI, 1.4-11.3)	
Denmark (2009 to 2011)[17]	Community-acquired *Clostridium difficile*[d]	73[e]	Children and adults
Noninfectious etiology			
United States[18]	Celiac disease in individuals with history of infectious gastroenteritis	Overall, 3.6 cases/100 000 person-years Increase from 1999-2008, from 1.3 to 6.5 cases/100 000 person-years	Active duty military personnel
United States[19]	Brainerd diarrhea	5000-8000 Individuals annually	Children and adults

Abbreviation: GII, Bristol virus, Lordsdale virus, Toronto virus, Mexico virus, and Snow Mountain virus.

[a] Episodes per person-year (median, 22 d per episode).

[b] Mean 12 d (range, 1-55 d).

[c] Three or more loose stools in 24 h for 3 or more months.

[d] The mean annual incidence is 34 per 100 000 persons.

[e] Persistent diarrhea for more than 15 d.

Clinical Presentation

Recognition of clinical symptoms is necessary for the proper diagnosis and treatment of infectious pathogens associated with persistent or recurrent diarrhea (**Table 2**).[34] Malnourished children in the developing world can develop severe diarrhea and dehydration associated with high mortality rates. None of the causes of persistent diarrhea occurring in children in the United States and in international travelers have unique clinical features except for amoebic colitis, which is associated with bloody stools. Because the diarrhea is protracted, patients with persistent diarrhea usually present with generalized weight loss and are often very disabled by their illness.

Assessment and Diagnosis

Clinical assessment of patients with persistent diarrhea should include a complete history and physical examination. Patients should be asked about symptoms, including the time of their onset and their duration, the length of time out of the country and proximity to local populations, and potential exposures (eg, raw milk, untreated water; **Figure**). Evaluation of patients with persistent diarrhea of unknown etiology should be initiated after patients have experienced symptoms for more than 14 days. Some diagnoses can be made from the clinical history (eg, lactase deficiency or ingested substances) or by blood test (eg, celiac disease).[35] If the diagnosis is unclear, at least 1 stool sample should be obtained from patients with persistent diarrhea for laboratory analysis for a pathogen that might be responsible for the symptoms. The initial evaluation is the same for patients with dysentery or watery diarrhea who have persistent diarrhea, since both may be caused by mucosal-inflammatory bacterial (eg, *Shigella*) or parasitic agents (eg, *E histolytica*). If the initial stool sample results are unrevealing and the patient has continued illness, further evaluation is necessary. This includes sequential collection of stool samples every 2 to 3 days for study to increase the likelihood that a pathogen can be identified. In some patients, multiple pathogens may be responsible for persistent diarrhea. Patients who develop persistent or recurrent diarrhea after hospitalization or during a nursing home stay or patients receiving or having recently used antibiotics should have their stool samples tested for *C difficile* toxin.

A number of different laboratory tools are available for detection and identification of pathogens associated with diarrheal disease (**Table 3**).[30,34] Historically, bacterial pathogens were identified using culture-based methods.[36] In most US laboratories, *Giardia*, *Cryptosporidium*, and *E histolytica* are currently detected by commercial enzyme immunoassay testing. Other protozoa have traditionally been detected by microscopy; however, *E histolytica* cannot be diagnosed by microscopy because it cannot be differentiated from avirulent *Entamoeba dispar*. For microscopic identification of other protozoal pathogens, the expertise of laboratory personnel in identifying the broad range of agents is essential. Antigen detection or polymerase chain reaction (PCR) methods are helpful for identifying pathogenic strains of *E histolytica*.

Culture-independent sequencing diagnostic methods are now available and include a multiplex approach that allows a number of bacterial, viral, and parasitic enteropathogens to be detected in a single test simultaneously. This method identifies unique DNA sequences to detect pathogens. Two multiplex platforms are commercially available: the xTAG Gastrointestinal Pathogen Panel (Luminex Corp), which tests for 14 viruses, bacteria, and parasites and the FilmArray GI panel (Biofire Diagnostics) that tests for 22 viruses, bacteria, and parasites. These methods are faster and have greater sensitivity than culture-based methods facilitating identification of the many pathogens that must be considered when trying to find the cause of persistent diarrhea. These new tests are easy to use, are capable of detecting a broad range of pathogens,[30,36] and represent a significant improvement over culture-based diagnostic approaches. The major limitation of PCR testing is that positive results do not distinguish between pathogenic and nonpathogenic organisms.[37] Polymerase chain reaction–based diagnostic tests for pathogenic DNA may be limited when the frequency of asymptomatic infection in the study population is high. Until more accurate diagnostic platforms are available, false-positive test results will remain problematic, resulting in unnecessary treatments.

Box. Take-Home Messages

Persistent diarrhea (≥14 days) is a common and underappreciated clinical condition in all areas of the world, occjurring in residents of developing countries, in travelers to less industrialized nations, in individuals exposed to foodborne or waterborne pathogens, and in health care settings. Health care workers should determine duration of diarrheal illness to help identify patients who may need extensive evaluation.

Persistent diarrhea of infectious etiology is usually caused by protozoal or bacterial pathogens. In certain hosts, viruses and helminths are identified. When infectious agents are not identified, noninfectious causes should be considered (eg, irritable bowel syndrome, inflammatory bowel disease, celiac disease, lactase deficiency, ingested substances, or cancer).

The evaluation for persistent diarrhea includes a complete history, physical examination, and diagnostic testing for the treatable infectious agent(s) or noninfectious etiologies responsible for symptoms.

Treatment

Oral rehydration therapy containing electrolytes and glucose can be used to prevent or treat dehydration associated with persistent diarrhea. The fluid therapy includes consuming soups and other liquid drinks, eating saltine crackers, and, in more severe cases, using pediatric hydration solutions that can be found in pharmacies. Elderly patients are especially prone to dehydration. Severe dehydration may require hospitalization and intravenous fluid administration. Medications used for symptom control, such as antimotility and antisecretory agents, are not advisable for use when there is an infectious cause of persistent diarrhea for patients not yet receiving specific anti-infective treatment. Use of the antimotility agent loperamide alone is not recommended for patients (adults or children) with fever or abdominal pain or for those with dysenteric diarrhea associated with infectious diarrhea, inflammatory bowel disease, or ischemic bowel disease. For diarrhea caused by a specific bacterial pathogen, loperamide may be used in all cases of persistent diarrhea to decrease stool frequency in combination with specific antibiotic therapy.

Once adequate hydration status is addressed, the cause of the diarrhea should be determined by laboratory studies. Adult patients with persistent diarrhea occurring after traveling to the

Table 2. Clinical Symptoms of Pathogens Associated With Persistent or Recurrent Diarrhea[a]

Pathogen[b]	Timing		Symptoms					
	Incubation Period	Duration of Untreated Illness	Diarrhea	Nausea	Vomiting	Fever	Cramping	Other
Bacteria								
Aeromonas species	>24 h	d-wk	✓ Mild to dysenterylike, including stool with passage of blood or mucus					Consider this organism in particular, in persistent diarrhea in tropical and subtropical areas Dysentery
Campylobacter	1-5 d	Colitis may persist or recur	✓ Stools with blood, pus, or mucus		✓	✓	✓	Abdominal pain Fecal urgency Tenesmus
Recurrent *Clostridium difficile*	<30 d of primary infection	wk-mo	✓	✓	✓	✓		Abdominal pain
Enteroaggregative *Escherichia coli*	8-52 h	2-4 d in young children in developing countries; may last for several weeks	✓ Watery stool, often with mucus, bloody stool possible	✓	✓	✓ Low-grade		Abdominal pain Tenesmus Borborygmi Anorexia
Enteropathogenic *E coli*	4 h	21-120 d	✓ Watery stool		✓	✓ Low-grade		Cause of outbreaks in newborn nurseries and in developing countries; serious problem in infants; may lead to death
Salmonella species (typhoid fever) complicated with diarrhea	1-3 wk, up to 2 mo	2-4 wk without treatment	✓			✓ (103°F to 104°F)	✓	Tenesmus Fatigue Constipation Headache Loss of appetite Rash Achiness
Shigella	8-50 h	Few d common, but may persist for 2-3 wk	✓ Stools with blood, pus, or mucus		✓	✓	✓	Abdominal pain Fecal urgency Tenesmus
Viruses								
Norovirus	24-48 h (<12 h has been reported)	In immunocompromised patients, infection may be chronic	✓ Watery, nonbloody stools	✓	✓ Explosive, projectile	✓ Sometimes low-grade	✓	Chills and achiness possible Headache Thirst Vertigo
Protozoa								
Blastocystis hominis	Like *Giardia*	Usually nonpathogenic, may occasionally cause illness resembling *Giardia* infection	✓	✓	✓		✓	Abdominal pain Fatigue Anorexia Flatulence
Cryptosporidium	7-10 d	2-14 d; longer duration or chronic in immunocompromised patients	✓ Abundant, watery stools	✓	✓	✓ Possible	✓	
Cyclospora cayetanensis	7-10 d	Days- months, if untreated, with possibility of relapse	✓ Frequent, watery stools; sometimes explosive	✓			✓	Loss of appetite Weight loss Bloating Fatigue Flu-like symptoms Occasional cause of foodborne outbreaks in United States
Cystoisospora belli	1 wk	2-3 wk	✓ 6-10 Watery stools/d			✓ Low-grade	✓	Weight loss Abdominal pain Important cause of diarrhea in patients with AIDS in developing countries
Dientamoeba fragilis	1-2 wk, can be longer	Acute disease: 1-2 wk; chronic disease: 1-2 mo	Some patients asymptomatic while others experience nausea, vomiting, diarrhea with mucus, and abdominal discomfort					
Entamoeba histolytica	1-4 wk (range, few days to years)	May last weeks- months, usually with intermittent symptoms	✓ Watery stools, with blood or mucus possible			✓ Possible	✓	Abdominal pain Loss of appetite Weight loss Important cause of liver abscess, especially in males

(continued)

Table 2. Clinical Symptoms of Pathogens Associated With Persistent or Recurrent Diarrhea[a] (continued)

Pathogen[b]	Timing		Symptoms					
	Incubation Period	Duration of Untreated Illness	Diarrhea	Nausea	Vomiting	Fever	Cramping	Other
Giardia	1-2 wk	3-4 d to mo	✓ Explosive, watery stools	✓		✓ Low-grade possible	✓	Flatulence Abdominal distention Anorexia Chills
Microsporidium species (including *Enterocytozoon bieneusi* or *Encephalitozoon intestinalis*)	Unknown	Prolonged duration has been reported	✓				✓	Dehydration Weight loss (>10% of body weight) Flatulence Loss of appetite
Helminths								
Schistosoma mansoni colitis	wk-mo	2-10 wk				✓	✓	Malaise Myalgia Headache Fatigue Abdominal pain, and may pass bloody stools
Strongyloides								
Acute infection		Up to several weeks	✓					Abdominal pain Rash Anorexia Constipation
Chronic infection	2 wk	Several decades	✓		✓			

[a] The check marks indicate that symptoms can occur with each pathogen.

[b] Higher doses are associated with shorter incubation periods.

developing world may receive a single dose of empirical azithromycin, 1000 mg, concurrent to the laboratory investigation because bacterial causes not normally identifiable by diagnostic laboratories are very common in this setting.[34] Antimicrobial agents are recommended for the treatment of infectious diarrhea caused by a number of different pathogens (Table 3).[26,34] However, the decision to administer a particular antibiotic in bacterial diarrhea should be based on the susceptibility of pathogens isolated. Development of antibiotic drug resistance following empirical antimicrobial therapy cannot be overlooked.[38] Antimicrobial resistance is common in bacterial enteropathogens. In a study of patients hospitalized in the United States, *E coli* resistance following fluoroquinolone use was found in 16% of patients whose fecal samples were initially susceptible to fluoroquinolones.[39] The first documented outbreak of azithromycin-resistant *Shigella* in the United States occurred in 2012. This is a very troubling development, given the importance of this drug for the treatment of multidrug-resistant *Shigella* infection.[40] However, once a specific organism is identified, antibiotic selection can be optimized (**Table 4**).[41]

Fecal microbial transplantation (FMT), which normalizes the gut microbiome, is effective for patients experiencing recurrent *C difficile* infection.[42,43] Fecal microbial transplantation may be tried for patients infected with *C difficile* who do not to respond to standard antibiotic therapy. However, although efficacious, a number of questions remain unanswered regarding FMT, including optimal mode of FMT preparation and delivery and posttreatment testing for a cure (ie, to measure response to therapy).

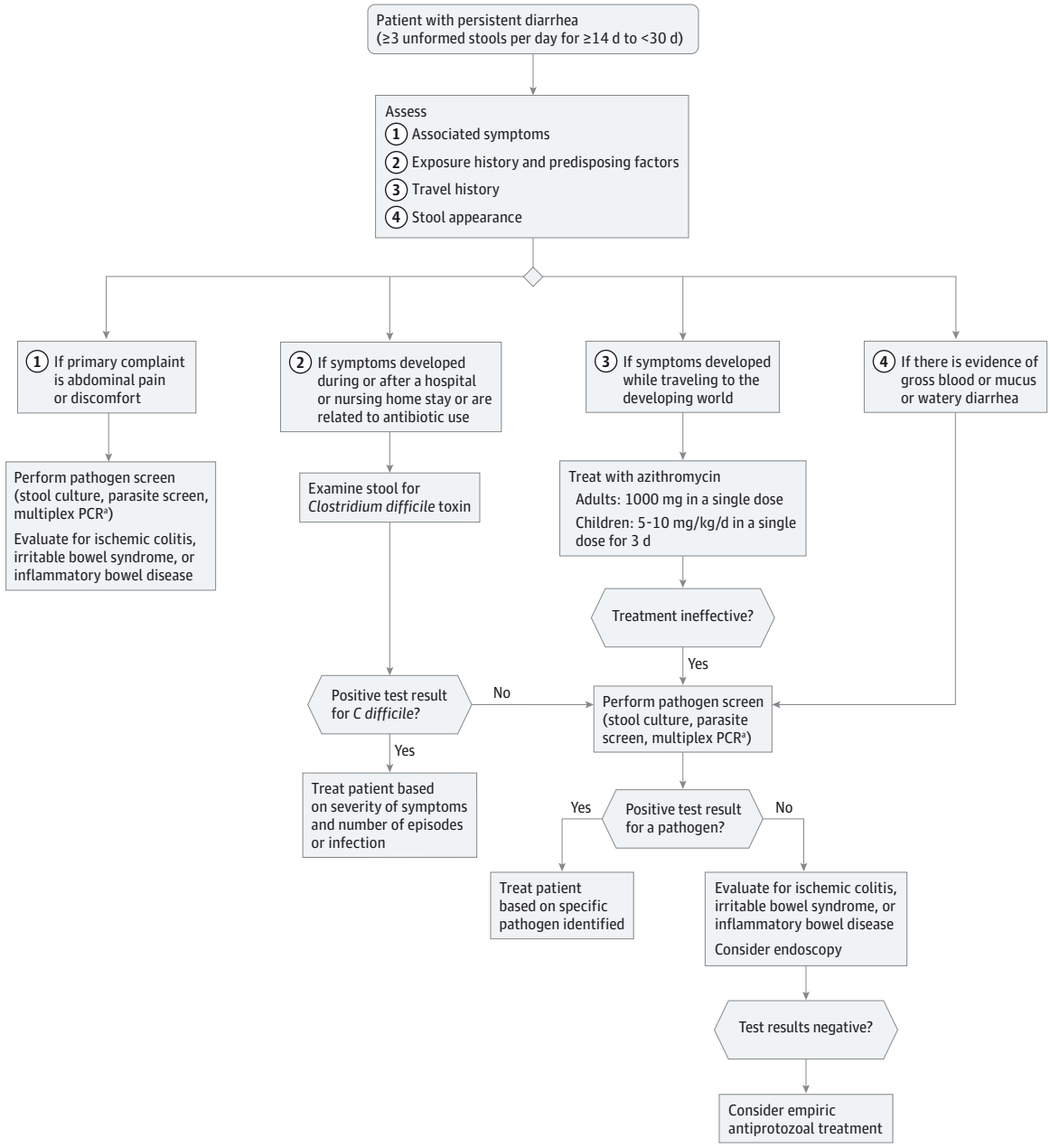
The treatment of protozoal infections is best tailored to the organism identified from a stool sample (Table 4). Nitazoxanide, an agent used for the treatment of diarrhea caused by *Cryptosporidium* and *Giardia*, has a broad range of antiparasitic activity, with activity against *Cryptosporidium*, *Giardia*, *E histolytica*, and *B hominis*.[44,45] In most cases when *B hominis* is found in stool, it is not a pathogenic organism, so treatment is not recommended.[20] Rarely, *B hominis* is pathogenic when part of a waterborne outbreak. When no other cause can be identified, the bacteria may respond to antiparasitic therapy.

Nitazoxanide has been suggested as a possible empirical treatment for children with persistent diarrhea because of its broad antiparasitic activity.[46] Once it is known that there are no bacterial pathogens, nitazoxanide may be considered for empirical therapy for adults because of the likelihood of a protozoal cause for persistent diarrhea in this setting.[47] Empirical antiprotozoal treatment is reasonable if laboratory testing for parasites is not available. A systematic review of 3 randomized, controlled trials of persistent diarrhea in young children in developing countries found no benefit of oral gentamicin or metronidazole relative to placebo.[48] Although there is no role for gentamicin, metronidazole should be restricted for use against recognized *Giardia* or *E histolytica* infections. Furthermore, a report from London found that an increase in resistance of *Giardia* to nitroimidazoles, including metronidazole, was observed between 2008 and 2013.[49] Nitazoxanide may be an option for selected patients with persistent diarrhea in a setting where AIDS is prevalent,[50] or in patients with known *Giardia* infection and those with no etiologic agent detected.[47,51]

Prognosis

Immunocompetent patients affected by persistent diarrhea in industrialized nations generally have a good prognosis because, in general, the disease is self-limiting.[28] Persistent diarrhea usually does not result in mortality but morbidity can be substantial. Proper diagnosis and treatment generally leads to a resolution of symptoms.[28,34] However, in some patients, infection with bacterial pathogens including *Campylobacter*, *Salmonella*, or *Shigella* may lead to chronic inflammation, resulting in the development of postinfectious irritable bowel syndrome[52] or reactive arthritis.[53] Patients with persistent diarrhea lacking an identified infectious etiology should undergo further evaluation because other conditions

Figure. Proposed Algorithm for Determining Etiology of Persistent Diarrhea in Adults in the United States



[a] *Giardia, Entamoeba,* and *Cryptosporidium* by enzyme immunoassay; others: *Cyclospora,* Microsporidia species, *Strongyloides, Dientamoeba fragilis, Schistosoma* species (only in endemic areas).

IBD indicates inflammatory bowel disease; IBS, irritable bowel syndrome; PCR, polymerase chain reaction.

(eg, cancer, inflammatory bowel disease, carbohydrate malabsorption) may be causing the diarrhea.

Discussion

The frequency of persistent diarrhea is unknown. Persistent diarrhea is often caused by protozoal infection, but bacteria and viruses should be considered as the causative agents in some settings such as among international travelers.[14,15,21] Physicians assessing patients with diarrhea should determine duration of diarrheal illness when developing an evaluation plan; the longer the duration of illness, the more likely it is that parasitic pathogens or noninfectious causes will eventually be identified.

A number of meta-analyses have examined the efficacy of FMT as treatment for patients infected with *C difficile* with multiple recurrences of disease. Because of the large number of studies and patients included in these analyses, as well as consistency in findings across analyses, a strong case can be made for FMT as a treatment for persistent diarrhea caused by *C difficile*.

Table 3. Diagnosis of Infectious Pathogens or Idiopathic Causes of Diarrhea

Pathogen/Cause	Diagnostic Method	Comments
Bacteria		
Aeromonas species	Stool or blood culture; stool culture on selective medium (eg, CIN)	
Campylobacter	Stool culture on selective medium Fecal EIA for *Campylobacter*-specific antigen	*Campylobacter* cultured under microaerophilic conditions (5% O_2, 5%-10% Co_2) at 42°C
Clostridium difficile	Detection of toxin A and toxin B (EIA, PCR, toxigenic culture, or cell-culture cytotoxic assay)	
Enteroaggregative *Escherichia coli*	Stool culture in Luria broth followed by Hep-2 cell adherence assay or PCR with virulence gene(s)	
Enteropathogenic *E coli*	Stool culture on MacConkey agar; isolates that induce focal attachment to tissue culture cell PCR detection of virulence factor genes	
Typhoid *Salmonella typhi* and *paratyphi*	Blood and stool culture	Serology testing aimed at O and H antigens (Widal test) may have some value in highly endemic areas but is of no value in industrialized regions due to its lack of specificity
Viruses		
Cytomegalovirus in an immunocompromised host	Mucosal biopsy, serologic testing (IgM and IgG), or PCR	
Human immunodeficiency virus	Immunoassay, Western blotting, RT-PCR	
Norovirus in an immunocompromised host	Serum, stool, or emesis samples: RT-PCR, which allows for viral genotyping	Greater severity of symptoms in patients who are immunocompromised, hospitalized, or elderly
Protozoa		
Blastocystis hominis	Stool sample examined by light microscopy (ie, wet-mount smears and permanent stains) Appearance by microscopy: 6-40 µm diameter; large central body with ≤6 small nuclei; central body stains red, green, or blue with trichrome stain	Usually not the cause of persistent diarrhea; consider after ruling out all other agents
Cryptosporidium	Stool samples evaluated by commercial EIA test. Oocytes can be seen by microscopy and acid-fast staining Appearance of oocysts by modified acid-fast staining: bright red spheres 4-6 µm with 4 crescent-shaped sporozoites visible	With limited experience of laboratory personnel, *Cryptosporidium* oocytes may be incorrectly identified as much larger *Cyclospora* cysts or yeast, or missed due to small size
Cyclospora cayetanensis	Stool sample examined by detection of immature oocysts (8-12 µm diameter) using microscopy and acid-fast staining Appearance of oocysts by microscopy: standard wet-mount under UV light, white-blue (330-365 nm excitation filter) or blue-green (450-490 nm excitation filter); modified safranin stain, reddish-orange PCR	*Cyclospora* oocysts are twice the size of *Cryptosporidium* oocysts
Cystoisospora belli	Stool sample examined by microscopy (acid-fast stain for detection of oocysts, which are larger than *Cyclospora* oocysts) PCR	
Dientamoeba fragilis	Stool sample examined by light microscopy, and conventional and real-time PCR Appearance of trophozoites by microscopy: 5-15 µm length, 9-12 µm width, with 1 or 2 fragmented nuclei	Diagnosis based on morphology is difficult
Entamoeba histolytica	Stool samples evaluated by commercial EIA test or specific antigen or DNA to differentiate from avirulent *Entamoeba dispar*. Where strongly suspected in endemic areas where diagnostic reagents are unavailable, ≥3 stool samples studied by microscopy: trophozoites detected using wet-mount smears (where they must be shown to contain ingested RBCs).	
Giardia	Stool samples evaluated by commercial EIA test. Stools can be examined by light microscopy (formalin-ether concentration or permanent trichrome stains) with trophozoites or cysts visible; visible by wet-mount smears; cysts visible (both are found in active diarrhea).	
Microsporidium species (including *Enterocytozoon bieneusi* or *Encephalitozoon intestinalis*)	Stool sample examined by light microscopy or transmission electron microscopy (detection of small spores using Weber chromotrope-based stain, aniline blue stain, or modified Giemsa, modified trichrome, or toluidine blue staining) PCR	

(continued)

Table 3. Diagnosis of Infectious Pathogens or Idiopathic Causes of Diarrhea (continued)

Pathogen/Cause	Diagnostic Method	Comments
Helminths		
Schistosoma mansoni colitis	Stool sample examined by microscopy to detect eggs (eg, Kato-Katz method, ethyl acetate- or formalin ether-based concentration techniques, Stoll's dilution, sedimentation, FLOTAC)	Molecular methods offer greater sensitivity than microscopy, but are limited by inconsistent distribution of eggs in samples Serologic methods can detect active infection but cannot differentiate active infection from prior exposure in individuals living in endemic regions
Strongyloides	Stool sample examined by light microscopy to detect larvae Stool culture on Koga agar, followed by microscopy to detect larvae	
Idiopathic		
Brainerd diarrhea	Stool sample: no enteric infectious pathogens present	
Postinfectious IBS	New symptoms of IBS based on Rome III criteria: symptoms ≥3 mo, with onset of abdominal pain or discomfort in previous ≥6 mo, following an episode of acute illness characterized by ≥2 of the following symptoms: fever, vomiting, diarrhea, stool culture positive for bacterial infection	
Unmasked early IBD	New-onset chronic diarrhea diagnosed as IBD based on colonoscopy and mucosal biopsy	Consider in patients with persistent diarrhea with no infectious etiology
Lactase deficiency, ingested substances (eg, metformin, toxins, pesticides, mushrooms), or food intolerances	Lactulose breath hydrogen test or diagnosis after exclusion of lactose-containing foods, drinks, or other substances associated with osmotic or intraluminal changes leading to diarrhea	
Sprue	Serologic testing of serum IgA or IgG antitissue transglutaminase antibodies (patients without or with IgA deficiency, respectively) Biopsy of small intestine is confirmatory	
Tropical sprue	Normal antitissue transglutaminase antibody levels, lack of antiendomysial antibodies, lack of HLA DQ2/8, lack of response to gluten-free diet Histology includes incomplete villous atrophy, ileal involvement, and increased eosinophils in lamina propria	

Abbreviations: CIN, cefsulodin-Irgasan-novobiocin; EIA, enzyme immunoassay; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; PCR, polymerase chain reaction; RBC, red blood cell; RT, reverse transcriptase; UV, ultraviolet.

There may not be much benefit of antimicrobial treatment for some forms of acute and persistent bacterial diarrhea (eg, nontyphoid *Salmonella* and *Shiga* toxin-producing strains of *E coli*). Limitations of studies examining treatment for pathogenic infections include adults with partial immunity, which is expected in a developing region compared with immunologically naive children found everywhere; and presence of comorbidities that may exist in some patients (eg, AIDS, malaria) but not others, which influences response to treatment. However, most of the treatments suggested in this review have demonstrated efficacy and safety in most patients examined. It should be noted that pathogen drug resistance is an emerging issue, underscoring the need for new therapies.

There is a limited body of evidence supporting the diagnosis and treatment of persistent diarrhea. This is because of inadequate recognition of the importance of persistent diarrhea in industrialized regions and the limited number of studies of the clinical problem that have been performed.[54] Most of the studies performed to date are from developing countries and of travelers and expatriates from industrialized regions that have helped to define this condition. Consequently, the etiology and epidemiology of persistent diarrhea is better characterized in the developing world than in industrialized nations. Findings from developing nations may not pertain to industrialized nations because developing nations have substandard hygienic conditions, a greater parasite burden, and a higher rate of malnutrition compared with industrialized nations.[13] Interest in this clinical problem is waning as evidenced by a declining number of articles published, a trend that began in the 1990s.[54] More research on the epidemiology and etiology of the disease is needed in both the developing world and in industrialized regions. Persistent diarrhea may be as common in children in the United States as in developing countries, but the prognosis is better for US children, for whom protein caloric malnutrition and vitamin A and zinc deficiencies are not present.

Standard culture-dependent microbiologic diagnostic methods are time-intensive, may require skills not frequently used in industrialized countries (such as identification of protozoa), and present difficulty in diagnosing viral etiologies due to the lack of testing reagents. These limitations may be overcome with molecular diagnostic tools such as multiplex PCR.[34] Multiplex PCR testing of stool samples may allow for the simultaneous examination of a full range of bacterial, viral, and parasitic agents in a single test.[55] Culture-independent diagnostic tests for bacterial infection are currently unable to provide subtype information or perform antimicrobial susceptibility testing. Stool culture will still be needed for disease outbreaks or when the illness is severe.[36]

Table 4. Recommended Treatment Options for Adults and Children With Persistent Diarrhea

Pathogen	Recommended Treatment[a] Adults	Children
Bacteria		
Aeromonas species or *Shigella* species	Ciprofloxacin 500 mg bid for 3 d Norfloxacin 400 mg bid for 3 d Trimethoprim/sulfamethoxazole 160 mg/800 mg bid for 3 d if susceptible in vitro (*Aeromonas*, B-3; *Shigella*, A-1)	Azithromycin 10 mg/kg/d qd for 3 d, or ceftriaxone 50 mg/kg/d qd for 3 d; short course (3 d) ciprofloxacin 20-30 mg/kg/d in 2 doses is being used in many areas
Campylobacter	Many acute diarrhea cases do not need treatment; persistent diarrhea is treated with azithromycin 500 mg qd for 3 d or 500 mg erythromycin qid for 5 d Many acute diarrhea cases do not need treatment; persistent diarrhea is treated with erythromycin 30 mg/kg/d in 3-4 divided daily doses for 5 d	Many acute diarrhea cases do not need treatment; persistent diarrhea is treated with erythromycin 30 mg/kg/d in 3-4 divided daily doses for 5 d
Clostridium difficile	Second bout: vancomycin 125 mg qid for 14 d (A-1), or fidaxomicin 200 mg bid for 10 d (A-1) ≥3 Bouts: oral vancomycin 125 mg qid for 14 d, followed by tapered or pulsed doses of vancomycin for 3-5 wk, or FMT (A-1), if available (most effective treatment) Nitazoxanide 500 mg bid for 3 d (B-2)	Most cases: vancomycin 40 mg/kg/d in 4 divided doses for 10-14 d
Enteropathogenic *Escherichia coli*	Supportive therapy to prevent dehydration Trimethoprim/sulfamethoxazole 160 mg/800 mg bid for 3 d, or Norfloxacin 400 mg bid for 3 d Ciprofloxacin 500 mg bid for 3 d (B-2)	Ceftriaxone 50 mg/kg/d, trimethoprim/sulfamethoxazole 10 mg/50 mg/d in 2 divided doses, or ciprofloxacin 20-30 mg/kg/d in 2 doses
Typhoidal *Salmonella* species	Bacteremic salmonellosis (including typhoid fever): Fluoroquinolone or IV ceftriaxone for 7 d (≥14 d in patients with immunosuppression; B-3) Chronic carriage of typhoidal salmonella: Ciprofloxacin 750 mg bid for 4-6 wk, or norfloxacin 400 mg bid for 4-6 wk (B-2); patients with treatment failure should be evaluated for cholelithiasis and cholecystectomy should be considered	IV ceftriaxone 100 mg/kg/d in 2 divided doses/d for 7 d Azithromycin 20 mg/kg/d for 7 d (A-1)
Vibrio parahaemolyticus (noncholeraic)	Doxycycline 100 mg qid for 5 d, ciprofloxacin 750 mg qd for 3 d, or MIC susceptibility testing should confirm best drug to use (C-3)	Doxycycline 2-4 mg/kg/d in 1-2 doses
Viruses		
Cytomegalovirus colitis in immunocompromised persons	Ganciclovir 5 mg/kg IV q12h for 14 d (B-2), or valganciclovir 900 mg bid PO for 21 d (D-5); maintenance treatment of either agent may be needed	Ganciclovir in adjusted doses
Human immunodeficiency virus (idiopathic, pathogen-negative diarrhea)	Antiretroviral drugs; crofelemer 125 mg bid for 24 wk can be used for diarrhea associated with antiretroviral therapy (B-2)	Antiretroviral drugs
Norovirus	Supportive care (fluid and electrolyte treatment); bismuth subsalicylate may improve symptoms, although evidence for this comes from 1 uncontrolled study[41] Nitazoxanide 500 mg bid for 3 d (C-3)	Supportive care
Protozoa		
Cryptosporidium	Nitazoxanide 500 mg bid for 3-14 d (A-1)	12-47 mo: Nitazoxanide 100 mg PO with food q12h for 3 d; 4-11 y: 200 mg PO q12h for 3 d; ≥12 y: treat like adult (A-1)
Cyclospora cayetanensis	Trimethoprim/sulfamethoxazole 160 mg/800 mg, respectively, bid for 7 d (A-1); longer treatment for patients with immunosuppression (A-2)	Trimethoprim/sulfamethoxazole 10 mg/50 mg/d in 2 divided doses PO for 3-7 d
Cystoisospora belli	Trimethoprim/sulfamethoxazole 160 mg/800 mg, respectively, qid for 10 d (A-1)	Trimethoprim/sulfamethoxazole 10 mg/50 mg/d in 2 divided doses PO for 10 d
Dientamoeba fragilis	Paromomycin 25-35 mg/kg/d PO in 3 daily doses for 7 d, or iodoquinol 650 mg tid for 20 d (C-4)	Paromomycin 25-35 mg/kg/d PO in 3 daily doses for 7 d (C-4), or iodoquinol 30-40 mg/kg/d (max 2 g) in 3 daily doses for 20 d (C-4)
Entamoeba histolytica (intestinal infection)	Metronidazole 750 mg tid for 5 d, plus either diloxanide furoate 500 mg tid for 10 d or paromomycin 25-35 mg/kg/d over 3 daily doses for 7 d (A-2) Nitazoxanide 500 mg bid for 3 d (B-2)	Metronidazole 35-50 mg/kg tid for 5-7 d (for patients with severe disease, 10 d), followed by iodoquinol 30-40 mg/kg/d (max 2 g) in 3 doses for 20 d or paromomycin 25-35 mg/kg/d in 3 daily doses for 7 d
Giardia	Single oral dose of tinidazole 2 g (C-3); metronidazole 250 mg tid for 5-7 d (A-1); or nitazoxanide 500 mg bid for 3 d (A-2)	Metronidazole 15 mg/kg tid for 5 d Or nitazoxanide, 12-47 mo: 100 mg PO with food q12h for 3 d; 4-11 y: 200 mg PO q12h for 3 d; ≥12 y: treat like adult (A-2) Or tinidazole ≥3 y: single dose of 50 mg/kg PO (B-2)
Microsporidium species (including *Enterocytozoon bieneusi* or *Encephalitozoon intestinalis*	Albendazole 400 mg bid for 14-28 d (B-1), or fumagillin 20 mg tid for 14 d (B-2)	Albendazole 15 mg/kg/d in 2 doses (max adult doses) for 7 d (C-2)

(continued)

Table 4. Recommended Treatment Options for Adults and Children With Persistent Diarrhea (continued)

Pathogen	Recommended Treatment[a] Adults	Children
Stramenopiles		
Blastocystis hominis	One of the following: metronidazole 750 mg tid for 10 d (B-2) Trimethoprim/sulfamethoxazole 320 mg/1600 mg qd for 7 d (C-3) Nitazoxanide 500 mg bid for 3 d (B-2) *Saccharomyces boulardii* 250 mg bid for 10 d (C-3)	Albendazole (D-2) Metronidazole 15 mg/kg bid for 10 d (C-4) Trimethoprim 6 mg/kg/d for 7 d (C-4) Nitazoxanide 100 mg to 200 mg bid for 3 d (B-2) Tinidazole 50 mg/kg/d for 5 d (patients <40 kg; C-4)
Helminths		
Schistosoma species (consider only in endemic areas in patients with colitis)	Praziquantel 40 mg/kg bid for 1 d (C-3)	Praziquantel 40 mg/kg bid for 1 d (C-3)
Strongyloides	Ivermectin 200 µg/kg/d PO for 2 d (B-3), or albendazole 400 mg bid for 7 d	Ivermectin 200 µg/kg/d PO for 2 d (for children >15 kg)
Idiopathic		
Brainerd diarrhea	Unresponsive to antibiotics or antiparasitic therapies, but some patients responsive to opioid antimotility agents	
Postinfectious IBS	Treat as idiopathic forms of IBS	
Unmasked early IBD	Treat as IBD	
Lactase deficiency	Reduce lactose consumption to <12 g/d	
Sprue	Gluten-free diet	
Tropical sprue	Tetracycline 250 mg qid for 1-6 mo, folic acid 5 mg bid for 90 d, and vitamin B_{12} 1000 µg/wk for 2-3 wk	

Abbreviations: bid, twice daily; FMT, fecal microbiota transplant; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IV, intravenous; MIC, minimum inhibitory concentration; PO, orally; qd, once daily; q12h, every 12 h; qid, 4 times per day; tid, 3 times per day.

[a] Recommendation and level of evidence presented for each treatment. Recommendation of A is consistent level 1 studies; B, consistent level 2 or 3 studies, or extrapolations from level 1 studies; C, level 4 studies or extrapolation from level 2 or 3 studies; and D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level. Level of evidence 1 represents systematic review of randomized trials; 2, randomized trial or observational study with dramatic effect; 3, nonrandomized controlled cohort and follow-up study (postmarketing surveillance) provided there are sufficient numbers to rule out a common harm; 4, case series, case-control studies, or historically controlled studies; and 5, mechanism-based reasoning.[3,4]

Conclusions

Persistent diarrhea (≥14 days) in otherwise healthy individuals usually is indicative of a protozoan or bacterial infection. Less commonly, helminths or viruses may be responsible for persistent diarrhea. The occurrence of persistent diarrhea among infants and children in less industrialized nations is associated with mortality. Travelers to developing nations, military personnel deployed overseas, and US expatriates frequently develop persistent diarrhea. Domestically acquired foodborne pathogens and health care–acquired infections (eg, *C difficile*) have also been implicated in persistent or recurrent diarrhea. Identification of a pathogen in freshly collected stools is important for identifying the proper therapy. Finally, more research is needed to identify new pathogens, improve diagnostic tools, and develop new therapies.

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