REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

Acute Infectious Diarrhea in Immunocompetent Adults

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In the United States, approximately 179 million cases of acute diarrhea occur each year, amounting to 0.6 bouts per person per year. In one study, the estimated prevalence of diarrhea among adults the month before questioning was 3 to 7%, with the rate dependent on age, and 8% among children 5 years of age or younger.[1] A similar rate of acute diarrhea among adults was reported recently in Germany.[2] In the United States, 83% of deaths from acute diarrhea occur in adults 65 years of age or older. Hospital-associated *Clostridium difficile*–associated diarrhea is the most prevalent cause of fatal illness, followed by norovirus infection[3]; both are common in residents of nursing homes.[4]

Diarrhea is generally defined as the passage of three or more unformed stools per day, often in addition to other enteric symptoms, or the passage of more than 250 g of unformed stool per day. On the basis of its duration, diarrhea can be classified as acute (<14 days), persistent (14 to 29 days), or chronic (≥30 days). Gastroenteritis, which is often due to viral infection involving the stomach and small intestine, is associated with vomiting and diarrhea.

This review addresses the clinical approach to the diagnosis and management of acute diarrhea in immunocompetent adults, summarizes contemporary clinical controversies, and discusses research needed in the field.

Causes and General Host Factors

In the United States, noroviruses are the principal cause of gastroenteritis and they are responsible for approximately 50% of outbreaks of diarrhea,[5] 26% of cases of diarrhea in emergency departments,[6] and 13% of office visits for diarrhea.[7] Noroviruses are particularly common in closed populations such as cruise ships, nursing homes, dormitories, and hospitals. Data from the Centers for Disease Control and Prevention[8] indicate that infections with the following bacterial pathogens were detected in descending order of rates per 100,000 people in the United States in 2012: salmonella, 16.4 cases; campylobacter, 14.3 cases; Shiga toxin–producing *Escherichia coli* O157:H7 strain, 1.1 cases; vibrio, 0.4 cases; and yersinia, 0.3 cases. In 2011, the rate of shigella infection in the United States was 2.3 cases per 100,000 people.[9] The rates of reported infections are affected by outbreaks and investigations of outbreaks by public health authorities. Although they are not included in routine surveys, other diarrheogenic *E. coli*, particularly enteroaggregative *E. coli* and enterotoxigenic *E. coli*, are increasingly being recognized as causes of acute diarrhea.[10] Decreasing rates of rotavirus-associated gastroenteritis have been observed among adults, since rotavirus vaccine is being used in children.[11] Protozoal parasites are primarily identified in patients with persistent diarrhea. Most cases of diarrhea in adults who are not traveling lack an identifiable cause.

In the United States, the estimated 48 million cases of foodborne illness each year (36% of all cases of diarrhea) constitute an important area for disease-control

efforts.[12] Produce is the most common source of diarrhea due to foodborne infection (in 46% of defined cases), and contaminated leafy green vegetables are the most common single food item (in 22% of cases). Noroviruses are the most common pathogens in diarrhea due to foodborne infection,[13] and poultry is associated with the highest proportion of deaths (19%), which are mainly the result of infection by salmonella or listeria. Reference laboratories need to be fully developed to detect less commonly occurring pathogens such as *Vibrio cholerae* O1 (identified in U.S. workers in Haiti in 2010),[14] *E. coli* O104:H4 (identified in Europe in 2011),[15] and cyclospora (which accounted for a large U.S. multistate outbreak due to contamination of mixed salad during the summer of 2013).[16]

Host factors are important in the development of infectious diarrhea. Higher rates of infectious diarrhea occur among persons at extremes of age, among persons with altered immunity because of disease or drugs, and among persons with physiological features of the gut that are altered by medications, including acid-reducing agents such as proton-pump inhibitors and antibiotics that alter intestinal flora and gut homeostasis.

DOSE AND INFECTIVITY

Challenge experiments involving volunteers and epidemiologic studies show that infections with shigella, Shiga toxin–producing *E. coli*, noroviruses, rotaviruses, giardia, and cryptosporidium are easily spread by low inoculums of agents that often cause secondary spread of illness. Shigella and noroviruses, the most communicable pathogens, have a high potential for person-to-person spread,[17] which is related to the low amounts of inoculum required, the environmental stability of the organisms, and the common occurrence in young children who are likely to spread infection. Limited data from volunteer challenge studies suggest an intermediate dose response for most salmonella and campylobacter strains. Secondary spread occasionally occurs with salmonella strains, and the infection rate among infants is high, suggesting transmission at lower amounts of inoculum. The moderate-dose and high-dose pathogens cause illness most commonly after a person consumes contaminated food in which replicating organisms have reached a disease-producing amount of inoculum. The infectivity of enteric pathogens according to the amount of infectious inoculum is described in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

CLINICAL EVALUATION

Most people with acute diarrhea manage their illness and do not present for medical evaluation. In patients with severe diarrhea associated with colitis or fever, recent or current exposure to hospitals or nursing homes, or the previous use of antibiotics and in patients with persistent diarrhea, clinical and epidemiologic features may provide valuable information in the evaluation (Fig. 1).

Factors that are relevant to the cause of diarrhea include previous international travel; treatment with antibiotics, chemotherapy, or proton-pump inhibitors; unsafe sexual practices; work at a day-care center; and the presence of a known immunosuppressive disorder. When vomiting is the predominant finding, viral gastroenteritis or food poisoning with a preformed toxin is probably the cause. In an outbreak, the incubation period can be used to differentiate between viral infection (>14 hours, often 24 to 48 hours) and food poisoning (2 to 7 hours). The presence of severe abdominal pain in a patient older than 50 years of age or peritoneal signs or ileus on examination should lead to a workup for more serious intraabdominal disease.[18] The character of the stool, including odor, floatation in the toilet, and color (other than bright red from blood or black from melena) is not helpful in the evaluation of patients with acute diarrhea.

The patient's hydration status should be evaluated by examining vital signs, mucous membranes, and sensorium and looking for postural hypotension. The examination may reveal evidence of a systemic process. Painful hemorrhoids from frequent defecation may be detected in patients with colitis, proctitis, or both. A rectal examination should be performed to assess stool for gross and occult blood. Warning signs of complicated illness or bacteremia include systemic toxicity, high temperature (≥38.5°C [101.3°F]), and passage of grossly bloody stools.

DIAGNOSTIC TESTS AND PROCEDURES

BLOOD STUDIES

Levels of electrolytes and serum creatinine should be measured in cases of systemic toxicity or de-

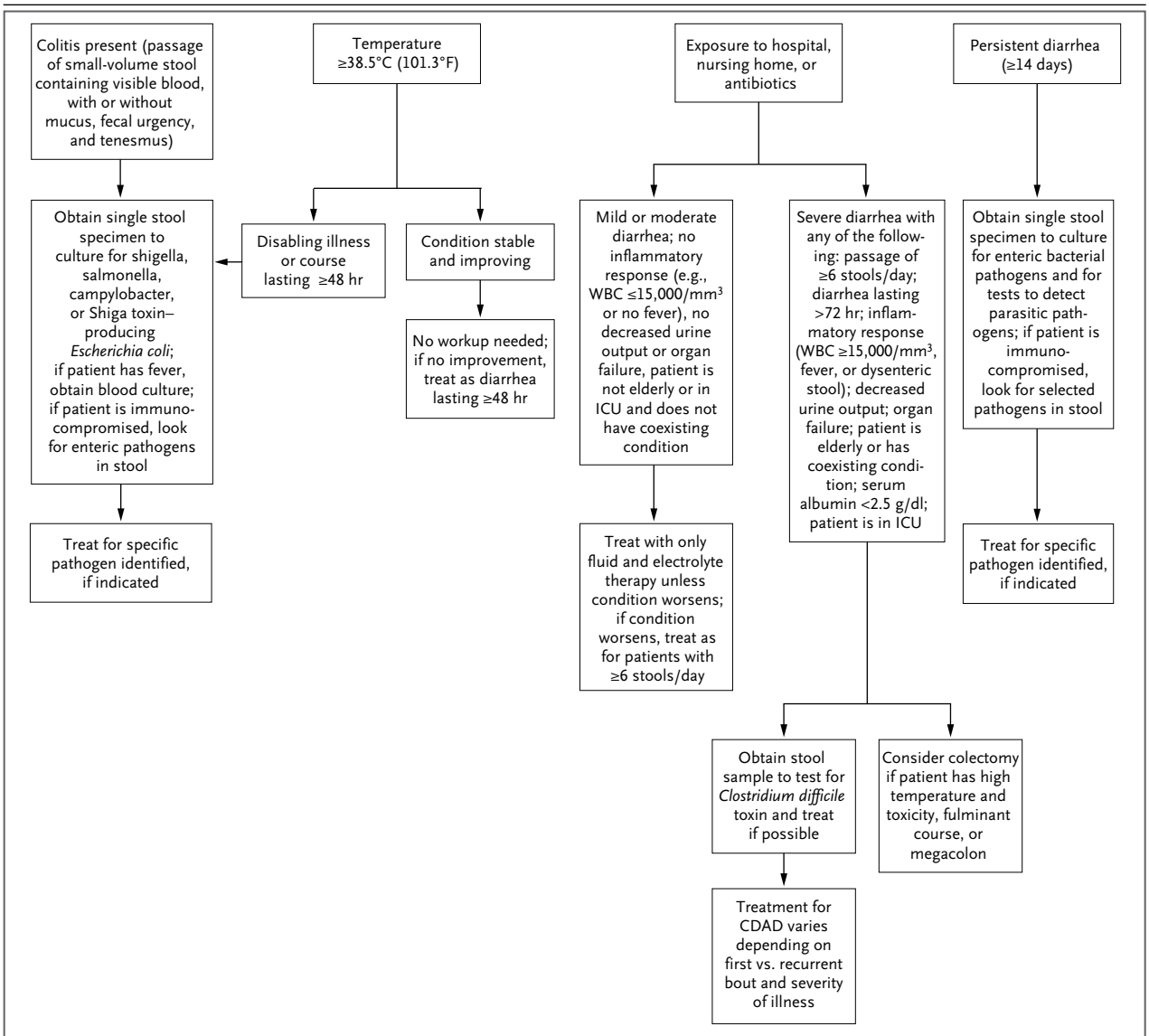

Figure 1. Evaluation and Treatment of Patients with Severe Diarrhea, According to Whether There Are Symptoms of Colitis, Fever, Exposure to Hospital, Nursing Home, or Antibiotics, and Persistent Diarrhea.

All patients with diarrhea should receive fluids and electrolytes and eat foods that are easy to digest such as bananas, toast, and broiled or baked meats and vegetables. CDAD denotes *Clostridium difficile*–associated diarrhea, ICU intensive care unit, and WBC white-cell count.

hydration, especially in elderly or infirm patients. A complete blood count may be indicated in patients with severe diarrhea accompanied by fever or toxicity, in whom leukocytosis or a shift to the left in neutrophils may indicate an inflammatory bacterial pathogen having prognostic significance in *C. difficile*–associated diarrhea. Eosinophilia may be seen in parasitic infections with an extraintestinal migration phase (e.g., strongyloidiasis).

STOOL EXAMINATION

The determination of the precise cause of diarrhea is costly, and in most cases of nonsevere diarrhea it is not necessary. Assessment of a stool sample to determine the cause of illness should be reserved for patients at high risk for diagnosable diarrhea or cases in which identification of the pathogen would be important. Stool samples should be obtained from patients with any of the following conditions: acute diarrhea that is se-

vere or associated with fever (≥38.5°C), diarrhea associated with a severe coexisting condition in a hospitalized patient who is receiving antibiotics (with testing only for *C. difficile* toxins), persistent diarrhea (≥14 days' duration), profuse cholera-like watery diarrhea, dehydration, and dysentery. In addition, samples should be obtained from elderly or immunocompromised patients with diarrhea and persons employed as food handlers, those confined to a nursing home, and those who work in a day-care center. Identification of the pathogen is also important in an outbreak of diarrhea.

When bacterial, viral, or protozoal causes of acute diarrhea are suspected, a single stool sample obtained from the patient and studied by a licensed laboratory is usually sufficient. The sample should be processed in the laboratory as soon as feasible, within 4 hours after passage if direct microscopic examination will be used to detect parasitic organisms and within 12 hours after passage if routine microbiologic methods will be used. In patients with acute diarrhea, performance of additional cultures adds to the cost, with little improvement in pathogen detection.[19] In patients with inflammatory bowel disease and possible *C. difficile*–associated diarrhea, multiple samples may be needed for diagnosis,[20] and in patients with persistent diarrhea due to a potential parasitic infection, three separate stool samples may be needed to detect the causative organism. All licensed laboratories are capable of detecting shigella, salmonella, campylobacter, Shiga toxin–producing *E. coli* O157:H7 strains, giardia, cryptosporidium, *Entamoeba histolytica*, and rotavirus. For evaluation of bloody diarrhea, a test for the presence of fecal Shiga toxin should also be performed to identify O157:H7 and non-O157:H7 Shiga toxin–producing *E. coli* strains. Reverse-transcriptase–polymerase-chain-reaction (PCR) assays for the detection of norovirus are available in local public health laboratories in the case of outbreaks.

PCR-BASED DIAGNOSTIC TESTS

Laboratories throughout the industrialized world are now using PCR-based diagnostic tests, which are often combined in a single test to detect multiple enteropathogens.[21] PCR offers the advantage of improved sensitivity, but it focuses on genes rather than on virulence factors. Also, PCR methods may detect DNA in patients with transient colonization by organisms containing targeted genes who are ill from another cause. PCR for the diagnosis of *C. difficile*–associated diarrhea has high sensitivity but lower positive predictive value when the rate of *C. difficile* infection is 10% or less among stools screened, with higher rates of asymptomatic infection in the general population.[22] Genome analysis,[23] testing for messenger RNA as a measure of protein expression or quantitative PCR,[24] more sensitive functional toxin assays,[25] or — in the case of colitis — subsequent identification of fecal inflammatory markers in PCR-positive cases of diarrhea[26] may improve the diagnostic value of nucleic acid–based diagnostic tests.

ENDOSCOPY AND ABDOMINAL COMPUTED TOMOGRAPHY

Flexible sigmoidoscopy or colonoscopy has limited value in the routine evaluation of patients with acute diarrhea.[27] Flexible sigmoidoscopy is a useful diagnostic procedure in cases of persistent diarrhea and in selected cases of acute diarrhea with clinical colitis in which the diagnosis is not clear, such as cases of suspected *C. difficile*–associated diarrhea with toxin-negative stool. Indications for endoscopy include suspected *C. difficile*–associated diarrhea and dysenteric diarrhea with negative results of stool toxin and microbiologic tests. Abnormalities observed during endoscopy may differentiate infectious colitis due to shigella, salmonella, campylobacter, invasive *E. coli*, Shiga toxin–producing *E. coli*, *C. difficile*, or cytomegalovirus from inflammatory bowel disease. Bowel preparation before endoscopy should be selected to minimize mucosal changes, and in patients with severe diarrhea, bowel preparation may be omitted. Proctoscopic examination may be helpful in diagnosing proctitis in patients who have had unprotected anal intercourse. Esophagogastroduodenoscopy may be useful in patients with persistent diarrhea if standard stool and serologic studies are not diagnostic.[28] This test may detect giardia infection, early-onset celiac disease, histopathological changes in the absorptive lining of the small bowel, and bacterial overgrowth in the small bowel.

Abdominal computed tomography (CT) may detect mucosal thickening or other changes of ischemic, hemorrhagic, or inflammatory colitis, and it is the preferred diagnostic study when both intraabdominal disease and intestinal disease are included in the differential diagnosis.[29]

Table 1. Recommendations for the Diagnosis and Treatment of Organism-Specific Enteric Infection in Adults.*

Enteric Illness	Diagnostic Method	Antimicrobial Therapy
Shigellosis	Stool culture	Ciprofloxacin, 750 mg once daily for 3 days, or azithromycin, 500 mg once daily for 3 days
Salmonellosis		
Nontyphoidal salmonellosis	Stool culture	No treatment in patients with nonsevere disease who are otherwise healthy. In patients with high-risk condition that confers predisposition to bacteremia[10] or with severe diarrhea, fever, and systemic toxicity or positive blood culture: levofloxacin, 500 mg orally (or other fluoroquinolone in corresponding dose) once daily for 7 to 10 days or slow intravenous infusion of ceftriaxone, 1 to 2 g once daily for 7 to 10 days (14 days in patients with immunosuppression)
Enteric fever, bacteremic salmonellosis (including typhoid fever)	Blood and stool cultures	Fluoroquinolone or intravenous cephalosporin for 7 days (≥14 days in patients with immunosuppression)
Chronic carriage of typhoidal salmonella	Stool culture (persistently positive stool cultures or single positive stool culture in a food handler, with detectable serum Vi antigen antibodies in an outbreak setting, is diagnostic)	Ciprofloxacin, 750 mg twice daily for 4 to 6 wk, or norfloxacin, 400 mg twice daily for 4 to 6 wk; in cases of treatment failure, evaluate for cholelithiasis and consider cholecystectomy
Intestinal campylobacteriosis	Stool culture	Azithromycin, 500 mg once daily for 3 days, or erythromycin, 500 mg four times daily for 5 days
Infection with Shiga toxin–producing *Escherichia coli* diarrhea	Stool culture on Sorbitol–MacConkey agar with O157:H7 antiserum for sorbitol-negative *E. coli* and test for Shiga toxin 1 and 2 in stool, broth, or culture plate[32]	No antibiotics; supportive treatment only, including dialysis for renal failure
Noncholeraic vibrio diarrhea	Stool culture with TCBS medium	Ciprofloxacin, 750 mg once daily for 3 days, or azithromycin, 500 mg once daily for 3 days
Vibrio cholerae infection (cholera)	Stool culture with TCBS medium	Doxycycline, 300 mg in a single dose
Clostridium difficile–associated diarrhea		
First or second bout	Fecal test for toxin A and toxin B (enzyme immunoassay, PCR, toxigenic culture, or cell-culture cytotoxic assay)	Mild cases: metronidazole, 500 mg thrice daily for 10 days; more severe cases: vancomycin, 125 mg four times daily for 10 days, or fidaxomicin, 200 mg twice daily for 10 days; fulminant cases: oral vancomycin, 500 mg every 6 hr for 7 to 10 days
Recurrent (≥3 bouts)	Repeat stool assay for toxin A and toxin B	Tapered or pulsed doses of vancomycin for 3 to 5 wk or fecal microbial transplantation, if available[33]
Travelers' diarrhea and enterotoxigenic *E. coli* diarrhea	None	Patients without fever or dysentery: rifaximin, 200 mg thrice daily for 3 days, or ciprofloxacin, 500 mg twice daily or 750 mg daily for 1 to 3 days; patients with fever or dysentery: azithromycin, 1000 mg in a single oral dose
Gastroenteritis		
Norovirus	Real-time reverse-transcriptase PCR assay of stool or emesis specimen	Fluid and electrolyte therapy; one study involving volunteers suggested that bismuth subsalicylate may improve symptoms
Rotavirus	Rapid antigen-detection test of stool specimen	Fluid and electrolyte therapy
Enteric adenoviruses, strain 40 or 41	Enzyme immunoassay of stool specimen	Fluid and electrolyte therapy
Giardiasis	Enzyme immunoassay or light-microscopic examination of stool specimen	Tinidazole, 2 g orally in a single dose, metronidazole, 250 mg thrice daily for 5 to 7 days, or nitazoxanide, 500 mg twice daily for 3 days

Table 1. (Continued.)

Enteric Illness	Diagnostic Method	Antimicrobial Therapy
Cryptosporidiosis	Enzyme immunoassay of stool specimen	Nitazoxanide, 500 mg twice daily for 3 to 14 days
Intestinal amebiasis	Fecal antigen-detection enzyme immunoassay, stool culture plus isoenzyme assay, or PCR-based assay	Metronidazole, 750 mg thrice daily for 5 days, plus either diloxanide furoate, 500 mg thrice daily for 10 days, or paromomycin, 25 to 35 mg/kg/day divided in 3 daily doses for 7 days
Cyclosporiasis	Stool acid-fast assay to detect oocysts, which appear as large cryptosporidia	TMP–SMX, 160 mg and 800 mg, respectively, twice daily for 7 days; longer treatment for patients with immunosuppression
Cystoisospora belli infection	Stool acid-fast assay to detect oocysts, which are larger than cyclospora oocysts	TMP–SMX, 160 mg and 800 mg, respectively, four times daily for 10 days
Enterocytozoon bieneusi or *Encephalitozoon intestinalis* infection	Light-microscopic examination of stool specimen with Weber's chromotrope-based stain or aniline blue stain to detect small spores	Albendazole, 400 mg twice daily for 14 to 28 days, or fumagillin, 20 mg thrice daily for 14 days†
Strongyloidiasis	Light-microscopic examination of stool specimen to detect larvae	Ivermectin, 200 μg/kg/day orally for 2 days, or albendazole, 400 mg twice daily for 7 days
Dientamoeba fragilis diarrhea	Light-microscopic examination and conventional and real-time PCR assay of stool specimen	Paromomycin, 25 to 35 mg/kg/day orally in 3 daily doses for 7 days, or iodoquinol, 650 mg thrice daily for 20 days
Blastocystis hominis diarrhea	Light-microscopic examination of stool specimen	Pathogenicity uncertain in most cases; in suspected cases, a 10-day course of metronidazole, TMP–SMX, or paromomycin in normal doses may be helpful
Cytomegalovirus colitis in immunocompromised persons	Mucosal biopsy or serologic test	Ganciclovir, 5 mg/kg intravenously every 12 hr for 14 days, or valganciclovir, 900 mg twice daily orally for 21 days; maintenance dose of either agent may then be needed

* PCR denotes polymerase chain reaction, SMX sulfamethoxazole, TCBS thiosulfate citrate bile salts sucrose, and TMP trimethoprim.
† Fumagillin is not available in the United States.

CT is particularly valuable for the detection of colonic mucosal thickening and pericolonic stranding, which may occur in cases of fulminant *C. difficile*–associated diarrhea.

MANAGEMENT

For patients with moderate-to-severe diarrhea, the first goal of treatment is to correct and maintain electrolyte and fluid balance, which can be lifesaving in the elderly, patients with coexisting conditions, and infants.

The antimotility drug loperamide (Imodium) is helpful in decreasing the passage of diarrheal stools in persons who are traveling or on a tight schedule. However, this class of drugs usually will not shorten the total duration of the illness. The maximum initial dose is 4 mg, followed by 2 mg after each unformed stool, with a total maximum dose of 8 mg per day for 48 hours. Loperamide should not be used in patients with febrile or dysenteric diarrhea. If it is used, the lowest effective dose should be administered to avoid constipation after diarrhea; often the initial 4-mg loading dose is sufficient. Antisecretory drugs are in development but remain untested in most forms of diarrhea. Crofelemer (Fulyzaq), a chloride-channel blocker, has been shown to reduce the number of stools in patients with travelers' diarrhea[30] and is approved for use in patients with human immunodeficiency virus infection complicated by diarrhea.[31] Probiotics have limited value for the treatment and prevention of specific forms of diarrhea, although they have some value in preventing antibiotic-associated diarrhea.

Empirical antibiotic therapy is recommended for sporadic cases of febrile dysentery, especially those associated with toxicity that suggests the possibility of systemic infection, as well as for severe cases of travelers' diarrhea or hospital-associated or antibiotic-associated diarrhea. Antibiotics are indicated in only a small percentage of patients with an established infectious cause of acute diarrhea (Table 1); in these patients, anti-

biotics can shorten the illness, decrease transmission, and prevent complications, including death. In selecting specific therapy for most cases of acute diarrhea, an etiologic diagnosis must be established. Antimicrobial therapy can be lifesaving in the case of bacteremic salmonellosis and *C. difficile* infection in the elderly.

ASSOCIATED CONDITIONS

Reactive arthritis can follow acute enteric infection by strains of salmonella, shigella, and yersinia because of autoimmune responses targeting epitopes common to both the infecting pathogen and the joint or periarticular tissues.[34]

Functional bowel disorders, including postinfectious irritable bowel syndrome (IBS), occur in 5 to 10% of patients after enteric infection by inflammatory bacterial pathogens and less commonly after infection by viruses and parasites.[35] In IBS, the infecting organism leads to persistent low-grade intestinal inflammation, air trapping in the intestine, and altered intestinal motility in the constipation form of the disease. Factors that increase the risk of this syndrome with a bout of diarrhea include greater virulence of the pathogen,[36] more severe illness, younger age, female sex, and preexisting psychological disturbances.[37] Postinfectious IBS may be associated with a better prognosis than idiopathic forms of IBS, but it may last 8 years or more.[38,39] Host genetic factors involving serotonin, epithelial function, and innate immunity play a role in the development of postinfectious IBS.[40]

The Guillain–Barré syndrome occurs in the 2 months after a bout of campylobacter infection in approximately 1 to 2 cases per 10,000 patients with campylobacteriosis,[41] as a result of cross-reactivity between the infecting organisms and neural ganglioside epitopes.[42] Risk factors include the virulence of infecting strains and host genetic factors.

AREAS OF UNCERTAINTY

Because very sensitive diagnostic tests may not differentiate between asymptomatic infection and pathogen-specific illness, testing for intestinal inflammatory biomarkers can be a useful addition to diagnostic tests for some pathogens. The presence of fecal leukocytes correlates with diffuse colitis but lacks sensitivity, since many forms of colitis occur focally. Fecal lactoferrin and calprotectin are more sensitive biomarkers and may correlate with the severity and extent of colonic inflammation.

Currently, antibiotic therapy is not helpful in cases of mild diarrhea caused by salmonella, and it lengthens shedding for 3 weeks or longer.[43] Some antibiotics induce Shiga toxin–encoding phage and may precipitate the hemolytic–uremic syndrome. Therefore, in an outbreak of bloody diarrhea, antibiotics are not currently recommended for patients with minimal or no fever who have Shiga toxin–producing *E. coli* infection. In general, single cases of acute febrile dysentery are likely to be due to treatable enteric bacterial pathogens such as shigella and campylobacter; in these cases, antibiotics shorten the illness and prevent complications.

Additional areas of uncertainty in the diagnosis and treatment of enteric infections are described in Table S2 in the Supplementary Appendix.

RESEARCH PRIORITIES

New molecular methods are needed to detect known enteric pathogens (bacterial, viral, and parasitic) as well as new viral genera, including astrovirus, sapovirus, bocavirus, polyomavirus, parechovirus, torovirus, and Aichi virus. Intestinal biomarkers should be sought for use in determining the cause of diarrhea. A comprehensive diagnostic approach, with the use of 16S ribosomal RNA mass metagenomic sequencing for novel sequences, DNA microarray technology with various amplification strategies, and other molecular methods, needs to be undertaken to look for new pathogens. Additional studies of strains of diarrheogenic *E. coli* are needed to better understand the biology of these pathogens, which are being detected more frequently. The large outbreak of diarrhea in Europe in 2011, which was due to a strain of *E. coli* O104:H4 involving a hybrid strain of enteroaggregative *E. coli* that had acquired a Shiga toxin–producing *E. coli* phage inducing Shiga toxin production, underscored the complexity of *E. coli* strains as causes of human illness. More studies are needed to define microbial and host factors in nontyphoidal salmonella sepsis, which is currently seen in sub-Saharan Africa. Sensitive methods are needed to screen for pathogens[44] in food products destined for human consumption; once developed, such screenings would be conducted routinely by the food industry.

Host factors have not been adequately studied to determine susceptibility to pathogen-specific illness and complications after enteric infection. Host genes that influence organism attachment, pathogen recognition, and intestinal inflammatory response have been associated with enhanced susceptibility to enteric infections.[45] The high risk of enteric infections among patients who have undergone solid-organ or hematopoietic stem-cell transplantation calls for prospective study of cases in which treatment or prevention may influence the outcome. Patients with enteric infection need to be monitored for the development of complications of chronic disease.

It is not known whether the more inflammatory forms of enteric infection can be prevented in persons who are susceptible to enteric infection and postinfectious complications such as IBS or whether these conditions are destined to develop in susceptible persons over time. If such conditions are preventable, the avoidance of high-risk foods and use of antimicrobial chemoprophylaxis during international travel, as well as the development of new enteric vaccines, may be important approaches to disease prevention.

More studies are needed to determine the importance of long-term use of proton-pump inhibitors, which are prescribed for myriad abdominal symptoms. This should lead to improved indications for the use of proton-pump inhibitors and a perspective on the cause of illness when patients present with enteric infection.

Currently, therapy for *C. difficile*–associated diarrhea is inadequate, with high rates of recurrent disease. There is strong clinical evidence, based on the high rate of recurrent infection after treatment, that 10-to-14-day courses of therapy are insufficient for the illness produced with this spore-forming organism. Recurrent disease has led to follow-up therapy or a second course of treatment. Clinicians should consider longer durations of therapy (20 to 30 days) for primary *C. difficile*–associated diarrhea.

Mechanisms of acute diarrhea according to the infecting pathogen should be studied to look for novel treatment targets. Antisecretory drugs such as crofelemer and ecadotril are in the pipeline; the forms of diarrhea for which these physiological treatments would be appropriate are not known. Azithromycin and rifaximin, which do not appear to induce Shiga toxin–encoding phage,[46,47] should be tested for their value in treating the more severe forms of Shiga toxin–producing *E. coli* infection.

Studies of intestinal flora in human disease may provide important therapeutic options after identification of the key members of the gut microbiota that can be harnessed as powerful probiotics delivered to the colon by means of enteric-coated capsules or retention enema after removal of colonic contents through purging. Studies of the mechanism underlying the efficacy of fecal microbiota transplantation are needed to refine strategies for improving the intestinal microflora in patients with chronic or recurrent diarrhea due to *C. difficile*, inflammatory bowel disease, and IBS.

Finally, vaccines are needed to provide protection against a number of enteric pathogens with outbreak potential, including *C. difficile*. Antibody production to prevent disease recurrence is important in *C. difficile*–associated diarrhea, and monoclonal antibodies to the toxins of the organism have been shown to prevent recurrence of *C. difficile*–associated diarrhea. Vaccines are also needed for noroviruses (genogroup I and genogroup II, especially genogroup GII, genotype 4), *V. cholerae* O1, enterotoxigenic *E. coli*, shigella, and campylobacter. Table S3 in the Supplementary Appendix describes additional research priorities in the field.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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