JAMA Clinical Guidelines Synopsis

Acute Diarrheal Infections in Adults

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GUIDELINE TITLE Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults

DEVELOPER American College of Gastroenterology (ACG)

RELEASE DATE April 2016

PRIOR VERSION 1997

FUNDING SOURCE ACG

TARGET POPULATION Immunocompetent adults with acute intestinal infections other than *Clostridium difficile*

MAJOR RECOMMENDATIONS (1) Empirical antimicrobial therapy is not recommended for routine acute diarrheal infection or mild traveler-associated diarrhea (TD) (strong recommendation; high level of evidence [LOE]). (2) Probiotics or prebiotics are not recommended for treatment of acute diarrhea in adults, except in cases of postantibiotic-associated illness (strong recommendation; moderate LOE). (3) Disabling TD with fever should be treated with azithromycin. (4) In patients receiving antibiotics for TD, use adjunctive loperamide therapy to decrease duration of diarrhea and increase chance of cure (strong recommendation; moderate LOE). (5) Culture-independent methods of stool testing (eg, polymerase chain reaction [PCR]) may be used to identify etiology in adult patients with dysentery, moderate to severe diarrhea, and symptoms lasting more than 7 days (strong recommendation; low LOE). (6) Persistent diarrhea (14-30 days) should be initially evaluated with culture and/or culture-independent microbiologic testing.

Summary of the Clinical Problem

Acute diarrhea is defined as lasting less than 14 days and can lead to significant morbidity and mortality. In the United States, approximately 179 million cases of acute gastroenteritis, including 47.8 million cases of foodborne illness, occur each year.[1,2] *Clostridium difficile* infections are the most common cause of diarrhea-associated mortality but are not addressed in this guideline.

Most adults who have not traveled abroad have no cause identified for their acute diarrhea.[2] Norovirus is the most common cause of gastroenteritis and is associated with 26% of cases of diarrhea in emergency departments,[1] with 90% of norovirus deaths occurring in people aged 65 years or older.[3] Immunocompromise and abnormal gastrointestinal physiology also increase the risk of severe diarrhea. Bacterial infections potentially amenable to antibiotics (*Shigella*, *Salmonella*, and *Campylobacter* species, Shiga toxin–producing *Escherichia coli* strains, *Vibrio parahemolyticus*, enterotoxigenic *Escherichia coli*) were identified in only 9% of acute diarrhea in a multicenter, emergency department–based study of adults.[2] In contrast, pathogens can be identified in 50% to 94% of patients with TD, most often bacterial.[4] Etiologic agents of persistent diarrhea for 14 days include intestinal parasites such as *Giardia*, *Cryptosporidium*, *Entamoeba histolytica*, and *Cyclospora*, Microsporidia species, and bacteria such as enteroaggregative *E coli*, *Shigella*, *Campylobacter*, *Salmonella*, and *V parahemolyticus*.[5]

Characteristics of the Guideline Source

The Practice Parameters Committee of the ACG produced this guideline. The literature searches were guided by a university reference librarian, and no financial support was provided to any author. Each author reported relationships with more than 1 pharmaceutical company within 2 years prior to guideline publication (**Table**).

Evidence Base

Multiple databases were used to identify literature published in the last 10 years. References from the database articles and from the authors' own archives were also examined. Strength of recommendations and quality of evidence were assessed using GRADE.

A Cochrane review from 2000 showed a clear benefit of antibacterials in shortening duration of moderate to severe TD. The Cochrane review and 9 randomized trials cited by the guideline examined use of fluoroquinolones vs placebo for TD treatment and found overall shortened duration of symptoms. Azithromycin was compared with fluoroquinolones in 4 clinical trials cited by the guideline and found to be as efficacious in a single dose or as 500 mg/d for 3 days. Five studies from 2001-2006 evaluated use of rifaximin as treatment for TD. Benefit from rifaximin was consistently shown over placebo, and it was generally equivalent to ciprofloxacin except for invasive pathogens such as *Salmonella*, *Shigella*, and *Campylobacter*, for which median time to last unformed stool was 24 hours with ciprofloxacin vs 44 hours for rifaximin. The guideline also addressed other therapies for diarrhea.

The potential value of probiotics in treating acute infectious diarrhea was suggested in a 2010 Cochrane systematic review, which found a reduction in the mean duration of diarrhea (mean difference, 24.8 [95% CI, 15.9-33.6] hours) and incidence of diarrhea lasting 4 or more

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Fair
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Fair
Implementation issues	Good

days (RR, 0.41; 95% CI, 0.32-0.53); evidence was insufficient to recommend a specific probiotic. Recent travelers to Mexico had significant symptom relief with bismuth subsalicylate (BSS) in a randomized trial, though loperamide was favored vs BSS in travelers to Latin America. Loperamide was more efficacious than BSS for symptom duration. In a systematic review and meta-analysis, loperamide plus antibiotics was found to rapidly reduce the number of diarrheal stools.[6]

In a 2005 review of 8 studies of personal hygiene precautions for TD prevention, 7 showed no relationship between types of food consumed and risk of TD. The guideline suggests that prophylactic use of antibiotics should be restricted to travelers outside of the United States and Europe, who are at high risk of TD, especially if illness may pose potentially serious health consequences or critically affect the intended purpose of travel. Both fluoroquinolones and rifaximin have been used for prophylaxis but both have coverage gaps; rifaximin is increasingly favored because of its greater safety and its lower risk of development of *C difficile* infection and extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL-PE).[4]

Benefits and Harms

The guideline recommends an empirical, algorithmic approach depending on (1) presence of dysentery (grossly bloody stools); (2) severity of illness (moderate: forced change in activities; severe: total disability due to diarrhea); (3) presence of fever of 101°F or higher; and (4) travel abroad. The guideline recommends treatment of acute diarrhea with oral rehydration in all cases, especially in elderly individuals with severe diarrhea or any traveler with severe, watery diarrhea. Bismuth subsalicylate is recommended for travelers with mild to moderate diarrhea to somewhat reduce stool frequency. The guidelines do not recommend empirical antibacterial therapy for adults with acute diarrhea except in travelers with moderate to severe diarrhea who have a high enough likelihood of bacterial infection to justify the risks of antibiotics, such as those with fever or dysentery. Loperamide should be given along with antibiotics to patients with TD. The guideline aims to dissuade clinicians from offering antibiotics to patients with community-acquired diarrhea since it is usually caused by viruses.

Although treatment of acute diarrhea may benefit selected travelers and patients with specific parasitic infections, there are risks associated with antibiotic treatment of acute diarrhea. *Clostridium difficile* colitis may occur in patients receiving antibiotics, and fluoroquinolones may increase this risk substantially. A retrospective cohort study in Quebec found an adjusted hazard ratio of 3.44 (95% CI, 2.65-4.47) for patients receiving fluoroquinolones who developed *C difficile* colitis.[7] Moreover, antibiotic treatment of mild TD is typically not required clinically and may lead to more severe and resistant infections in contacts. A recent review found that 12% to 69% of returning travelers had become colonized by ESBL-PE, with place of travel and use of antimicrobial therapy for TD common independent risk factors for acquisition and colonization, which can persist for 6 to 9 months.

Discussion

Epidemiologic data on the incidence and etiology of acute diarrhea in adults are limited. Therefore, the guideline's strong recommendation against empirical antibiotic therapy for community-acquired diarrhea or mild TD, while based on very low-level evidence, merits respect at a time of increasing concern about emerging drug resistance.

While PCR is more sensitive and rapid than traditional stool testing, its net benefits remain to be established. Despite low evidence, the guideline recommends use of culture-independent methods for diagnosis in cases of dysentery, moderate to severe disease, and symptoms lasting longer than 7 days at least as an adjunct to traditional methods, given the frequent failure of traditional methods to identify a pathogen. Polymerase chain reaction cannot distinguish between live and dead organisms, and several pathogens may be identified, risking needless treatment given uncertainty about the truly causative pathogen(s). Yet if only culture-independent methods are used for diagnosis in acute diarrhea, antibiotic susceptibilities will not be known, precluding modification of antibiotic selection and limiting public health guidance regarding bacterial resistance patterns and proper therapy.

Areas in Need of Future Study or Ongoing Research

Additional studies are in progress on newer formulations of oral rehydration. Further study is needed regarding the effect of PCR-based assays for diagnosis on patient outcomes. While more sensitive, rapid diagnostics may limit antibiotic exposure if clinicians withhold antibiotic therapy, this has yet to be clearly shown. Finally, pragmatic guidelines would be of value for institutions considering contact precautions for travelers treated with antibiotics abroad, including when to screen them for colonization by various multidrug-resistant bacteria.

Related guidelines and other resources

ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Page 603—guideline algorithm. *Am J Gastroenterol*. doi:10.1038/ajg.2016.126

Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. doi:10.1038/ajg.2013.4

Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. *Gastroenterology*. doi:10.1053/j.gastro.2016.12.039

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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