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Diagnosis and Management of Infectious Diarrhea

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GUIDELINE TITLE Diagnosis and Management of Infectious Diarrhea

DEVELOPER Infectious Diseases Society of America (IDSA)

RELEASE DATE December 15, 2017

PRIOR VERSION February 2001

FUNDING SOURCE IDSA

TARGET POPULATION Children and adults with suspected or confirmed infectious diarrhea

MAJOR RECOMMENDATIONS

- Stool testing (molecular or culture-based methods) should be performed for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Clostridium difficile*, and Shiga toxin–producing *Escherichia coli* in patients with diarrhea and fever, bloody or mucoid stools, severe abdominal pain, or sepsis (strong recommendation; moderate level of evidence).
- A stool culture may be needed in situations in which antibiotic susceptibility testing would affect clinical care of a patient or public health responses (strong recommendation; low level of evidence).
- Diagnostic testing is not recommended in most cases of uncomplicated traveler's diarrhea unless treatment is indicated or the traveler has had diarrhea lasting 14 days or longer (strong recommendation; moderate level of evidence).
- Antibiotics should be avoided in most immunocompetent patients with bloody diarrhea but without sepsis (strong recommendation; low level of evidence).
- Probiotics may be used to reduce the symptom severity and duration of infectious diarrhea in immunocompetent adults and children (weak recommendation; moderate level of evidence).

Summary of the Clinical Problem

Infectious diarrhea is the fifth leading cause of death worldwide.[1] In the United States, 179 million cases of acute diarrhea occur per year.[2,3] Most diarrheal illnesses are self-limited and do not require evaluation or treatment beyond supportive care such as rehydration. Some infections do require antimicrobial therapy, and appropriate use of diagnostic tests and treatments may potentially minimize unnecessary costs, decrease adverse events, optimize clinical outcomes, and limit antibiotic resistance.

Characteristics of the Guideline Source

The guideline was developed and funded by the IDSA, which assembled a panel of experts in infectious diseases, microbiology, gastroenterology, nutrition, epidemiology, and public health (**Table**). Panel members disclosed potential conflicts of interest regardless of perceived relevancy. No panel members were recused based on conflicts. Several panel members received grants and honoraria from pharmaceutical companies, and 1 panelist received travel subsidies from the International Scientific Association for Probiotics and Prebiotics. The guideline was externally peer reviewed and approved by the IDSA Standards and Practice Guidelines Committee and Board of Directors, the Society of Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society. The panel performed a systematic review to provide guidance on diagnosis and management of infectious diarrhea.[4]

Evidence Base

The guideline recommends against testing in uncomplicated cases of suspected infectious diarrhea, including traveler's diarrhea, in immunocompetent patients because the likelihood of isolating bacterial pathogens is low and use of antibiotics is almost always unnecessary.[4] The guideline recommends testing for specific pathogens by molecular or culture-based methods in patients with fever, bloody or mucoid stools, severe abdominal pain, or sepsis. This recommendation is based on improved outcomes of patients with severe infection.[4]

Molecular testing does not yield specimens that can be submitted to public health departments and cannot determine antimicrobial susceptibility. The guideline recommends submitting a specimen for culture in situations in which susceptibility results would inform clinical care and in which submission of a specimen to a public health laboratory would inform outbreak response. Using molecular typing, health departments can confirm an outbreak by determining whether organisms from different cases are of the

Table. Guideline Rating

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

same strain. A low level of evidence supports this recommendation, but practical concerns of increasing antimicrobial resistance and outbreak response make it a strong recommendation.[4] Broader testing, including for viral etiologies, may be indicated during an outbreak.

The guideline cites data, specific to typhoid fever, that show decreased mortality comparing treatment cohorts with historical controls as evidence of empirical antibiotic treatment of patients with infectious diarrhea and sepsis.[4] Several clinical trials and meta-analyses have demonstrated that patients with bacterial causes of diarrhea but without sepsis have only modest benefits from antibiotic treatment. Antibiotic choice in these studies is heterogeneous, and the studies also show increased risk of adverse events (odds ratio, 2.37; 95% CI, 1.50-3.75) and antimicrobial resistance associated with antibiotic treatment.[4]

The weak recommendation to use probiotics for acute infectious diarrhea is based on moderate strength of evidence, including a meta-analysis and several clinical trials. A reduction of 25 hours (95% CI, 16-34 hours) in total symptom duration and a reduction in stool frequency on the second day of symptoms were observed in the meta-analysis.[5] Data on probiotic use for infectious diarrhea are limited by heterogeneity (definitions of diarrhea, outcomes, probiotic selection, treatment duration, and setting). Almost all of the data in this meta-analysis were from pediatric patients, and the effects of probiotics were more favorable among study participants with a viral cause compared with a bacterial cause of diarrhea. In light of these limitations, this recommendation should be interpreted with caution, especially in adults.

Benefits and Harms

Notable in this guideline is the emphasis of multiplex molecular testing. The greater sensitivity of these tests and ability to detect multiple pathogens may have clinical utility[6] but, for a disease from which most patients recover without treatment, a more sensitive test will potentially lead to overtreatment. There are few data regarding how the availability of multiplex molecular testing will affect physician behavior, cost, and patient outcomes. To balance benefits and harms of testing, clinicians should consider patients' history, risk factors for severity of illness, and risk of complications.

Use of probiotics for acute diarrhea was not recommended in the prior version of the guideline. Although most probiotics have been shown to be safe in immunocompetent patients, there are concerns about the safety of some probiotics.[7] Because probiotics have been implicated in infections (such as *Saccharomyces* and lactobacilli) among immunocompromised and critically ill patients, clinicians should weigh the risks and benefits of probiotic use given the available data.[8]

Discussion

Developing uniform guidelines for testing in infectious diarrhea is challenging given low-quality data, variable epidemiologic risks, and emergence and spread of antimicrobial resistance. The IDSA and American College of Gastroenterology (ACG) guidelines are consistent in emphasizing that the decision to test for bacterial pathogens should be based on a combination of epidemiologic risks for specific pathogens, risk of complications, immunosuppression, risk of transmission, severity and duration of symptoms, and need for treatment.[4,8] Recommendations to treat patients with sepsis and more severe illness are based on favorable comparison with historical controls. Given these results, higher-quality studies are unlikely to be done.

The IDSA and ACG guidelines differ regarding the role of probiotics in acute infectious diarrhea.[4,8] The IDSA guideline states that probiotics may be used to reduce the symptom severity and duration of infectious diarrhea in immunocompetent adults and children, whereas the ACG recommends probiotics only in cases of antibiotic-associated diarrhea. Although the proven risks of probiotics are negligible in immunocompetent patients, the benefits are uncertain, with the most compelling data in pediatric patients and patients with antibiotic-associated diarrhea.

Areas in Need of Future Study or Ongoing Research

The optimal role of culture-based and molecular diagnostic testing has not been defined rigorously. Studies of specific algorithms with clinical end points are needed to guide diagnostic decisions and test selection. The question of whether probiotics mitigate acute infectious diarrhea has not been answered. Trials with less heterogeneous probiotic formulations are needed for specific targeted populations.

ARTICLE INFORMATION

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REFERENCES

1. Centers for Disease Control and Prevention. Diarrhea: common illnesses, global killer. 2018. https://www.cdc.gov/healthywater/pdf/global/programs/globaldiarrhea508c.pdf. Accessed August 17, 2018.

2. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality. *Lancet*. 2012;379(9832):2151-2161. doi:10.1016/S0140-6736(12)60560-1

3. DuPont HL. Persistent diarrhea: a clinical review. *JAMA*. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833

4. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45-e80. doi:10.1093/cid/cix669

5. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2010;(11):CD003048.

6. Gwinn M, MacCannell D, Armstrong GL. Next-generation sequencing of infectious pathogens [published online February 14, 2019]. *JAMA*. doi:10.1001/jama.2018.21669

7. Heikens E, Bonten MJM, Willems RJL. Enterococcal surface protein Esp is important for biofilm formation of *Enterococcus faecium* E1162. *J Bacteriol*. 2007;189(22):8233-8240. doi:10.1128/JB.01205-07

8. Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrhea infections in adults. *Am J Gastroenterol*. 2016;111(5):602-622. doi:10.1038/ajg.2016.126