

Brittany Jackson, MD
Department of Internal Medicine,
Mayo Clinic, Jacksonville, FL

Sabrina Billings, MD
Department of Internal Medicine,
Mayo Clinic, Jacksonville, FL

Dana M. Harris, MD
Department of Internal Medicine,
Mayo Clinic, Jacksonville, FL

Jane Hata, PhD
Department of Laboratory Medicine
and Pathology, Mayo Clinic,
Jacksonville, FL

Mary S. Hedges, MD
Department of Internal Medicine,
Mayo Clinic, Jacksonville, FL



Q: Which patients with presumed acute infectious diarrhea in an outpatient setting should undergo gastrointestinal pathogen panel testing?

A 65-year-old man presents to the clinic with a 7-day history of diarrhea. His medical history is significant for psoriasis treated with abatacept, hypertension, and gastroesophageal reflux disease. A polymerase chain reaction (PCR) gastrointestinal pathogen panel was ordered, which returned positive results for Salmonella.

A: Advances in multiplex PCR assays have significantly improved the diagnosis of diarrhea in patients in whom testing is appropriate. These assays enable simultaneous detection of multiple pathogens from a single stool sample, including bacteria, viruses, and parasites, in as little as 1 hour. Most cases of acute diarrhea are mild and self-resolving. Conditions that warrant gastrointestinal pathogen panel testing include fever, visible blood in the stool, sepsis, severe abdominal pain, hospitalization, persistent diarrhea (≥ 7 days), advanced age, and immunocompromise.¹⁻³ Inflammatory bowel disease should be considered in patients with persistent diarrhea who have negative results on testing.^{1,2}

ACUTE DIARRHEA DEFINED

Diarrhea occurs when the normal physiologic processes of the small and large intestines are disrupted. These organs typically absorb ions, substrates, and water. Diarrhea results from either reduced water absorption or increased water secretion in the intestines, leading to excessive fluid in the stool.

doi:10.3949/ccjm.92a.24084

The American College of Gastroenterology¹ describes acute diarrhea as passage of unformed, loose, or watery stool for a duration of less than 2 weeks. In contrast, chronic diarrhea lasts more than 4 weeks. Acute diarrhea is often caused by viruses, bacteria, or parasites.²

Chronic diarrhea is less likely to be infectious but may be related to parasitic infections.¹ Distinguishing between infectious and noninfectious causes of diarrhea is crucial for guiding the clinical approach and determining appropriate management strategies.

WHAT ARE COMMON INFECTIOUS CAUSES OF ACUTE DIARRHEA?

Common bacterial causes of acute diarrhea include *Salmonella*, *Campylobacter*, *Escherichia coli*, *Shigella*, and *Clostridioides difficile*. Bacterial infections are associated with travel, food ingestion, and antibiotic use.³ A specific cause can often be found based on the exposure history.

Common viral causes include norovirus and rotavirus. Norovirus causes acute diarrhea outbreaks worldwide, often in close-containment settings such as dormitories, nursing facilities, cruise ships, and hospitals. Rotavirus is commonly found in children younger than 5 years. However, cases have decreased in high-income countries due to increased rotavirus vaccination rates.²

TABLE 1
Organisms detected on multiplex gastrointestinal molecular panels

	Panels					
	Verigene system ^a	xTAG panel ^b	Biofire panel ^c	BD Max assays ^{d,e}	BioCode panel ^f	QIAstat-Dx panel ^g
Bacteria and bacterial toxins						
<i>Campylobacter</i> species	X	X	X	X	X	X
<i>Clostridioides difficile</i> toxins A and B		X	X		X	
<i>Plesiomonas shigelloides</i>			X	X		X
<i>Salmonella</i> species	X	X	X	X	X	X
<i>Yersinia enterocolitica</i>	X		X	X	X	X
<i>Vibrio cholerae</i>	X	X	X	X		
<i>Vibrio parahaemolyticus</i>	X		X	X	X	
<i>Vibrio vulnificus</i>			X	X		
Enterotoxigenic <i>Escherichia coli</i>			X		X	
Enteropathogenic <i>E coli</i>			X			X
Enterotoxigenic <i>E coli</i>		X	X	X	X	X
Shiga-like toxin–producing <i>E coli</i>	X	X	X	X	X	X
<i>E coli</i> O157		X	X		X	X
<i>Shigella</i> and enteroinvasive <i>E coli</i>	X	X	X	X	X	X
Parasites						
<i>Cryptosporidium</i> species		X	X	X	X	X
<i>Cyclospora cayentanensis</i>			X			X
<i>Entamoeba histolytica</i>		X	X	X	X	X
<i>Giardia duodenalis</i> ^h		X	X	X	X	X
Viruses						
Adenovirus 40/41		X	X	X	X	X
Astrovirus			X			X
Norovirus genogroups I and II	X	X	X	X	X	X
Rotavirus	X	X	X	X	X	X
Sapovirus			X	X		

^aDiasorin. Verigene enteric pathogens test. <https://us.diasorin.com/en/molecular-diagnostics/kits-reagents/verigene-enteric-pathogens-test>. Accessed January 16, 2025.

^bDiasorin. xTAG gastrointestinal pathogen panel. <https://us.diasorin.com/en/molecular-diagnostics/kits-reagents/xtag-gastrointestinal-pathogen-panel-gpp>. Accessed January 16, 2025.

^cBiomerieux. Biofire Filmarray gastrointestinal panel. www.biomerieux.com/us/en/our-offer/clinical-products/biofire-gastrointestinal-panel.html. Accessed January 16, 2025.

^dThe BD Max Enteric assays include an enteric bacterial panel, extended enteric bacterial panel, enteric parasite panel, enteric viral panel, and an enteric viral panel that tests for only norovirus and rotavirus.

^eBD. Gastrointestinal infections portfolio. www.bd.com/en-no/products-and-solutions/solutions/gastrointestinal-infections-portfolio. Accessed January 16, 2025.

^fApplied BioCode. Gastrointestinal pathogen panel. www.apbiocode.com/products/assays/gi-panel/. Accessed January 16, 2025.

^gQiagen. Syndromic testing for GI infections with QIAstat Dx. www.qiagen.com/us/applications/syndromic-testing/syndromic-testing-benefits/diagnosing-gastrointestinal-infections-with-qia-stat-dx. Accessed January 16, 2025.

^hAlso known as *G lamblia* or *G intestinalis*.

Based on information from assay manufacturer websites^{a–g} and reference 6.

Parasitic and protozoal causes of acute diarrhea are typically acquired through ingesting contaminated water or food or person-to-person transmission. Parasites and protozoans are a significant cause of morbidity and mortality, specifically in low-income countries. Common organisms in the United States include *Giardia duodenalis* (also known as *G lamblia* or *G intestinalis*), *Cryptosporidium* species, *Cyclospora*, and *Entamoeba histolytica*.²

Gastrointestinal infections in immunocompromised persons

Acute diarrhea is prevalent among all individuals but poses a significant risk among those with a compromised immune system, often leading to considerable morbidity. The etiologic agents that cause diarrhea in immunocompromised persons may be the same as those in immunocompetent persons, but, due to impaired

immunity, the former are more susceptible to infection and may not recover as quickly.

C difficile is the most common cause of antibiotic-associated diarrhea.⁴ In the community or healthcare setting, it can cause severe colitis in both immunocompetent and immunocompromised patients. *Salmonella* species, *Cryptosporidium* species, and *Cyclospora cayentanensis* cause severe diarrhea, particularly in patients with immunocompromised states.⁵ Cryptosporidiosis is self-limited in immune-competent individuals but causes severe, prolonged diarrhea in immunocompromised patients, especially those with impaired cell-mediated immunity.⁵

■ CONSIDERATIONS WHEN ORDERING A GASTROINTESTINAL PATHOGEN PANEL

Six multiplex PCR gastrointestinal pathogen panels are approved by the US Food and Drug Administration (Table 1).⁶ These panels test for up to 22 enteropathogens (bacteria, viruses, parasites) and, compared with traditional culture methods, have increased sensitivity of organism detection as well as a faster turnaround time.⁷ The ability to detect a broad range of pathogens helps clinicians tailor treatment more effectively, particularly in patients with complex clinical presentations.^{1,7}

Considerations when ordering a multiplex panel include clinical history and presentation, the type and number of organisms to be tested for, treatment implications based on diagnostic results, test cost for the patient, and the patient population tested. Although recommendations from the Centers for Medicare & Medicaid Services generally guide insurance providers, some insurance plans may limit coverage to panels with fewer than 5 targets.⁸ The lack of consistency across insurance plans accentuates the need for clinicians to be aware of limitations in coverage when recommending diagnostic tests.

Also, multiplex pathogen panels detect the toxin genes in *C difficile*, a result that needs to be correlated clinically and confirmed by an additional test such as the antigen test for *C difficile* toxin.² When bacte-

rial pathogens are detected, bacterial culture may be needed for susceptibility testing and to fulfill public health reporting requirements and provide epidemiologic data.⁶

Gastrointestinal pathogen panels play an essential role in public health surveillance. They also can improve clinical management and reduce healthcare costs.⁶ A retrospective observational study assessed diagnostic methods for acute infectious gastroenteritis using data from 36,787 outpatients with this diagnosis who had a traditional workup (eg, bacterial culture, antigen testing, microscopy), multiplex PCR panel testing with less than 12 target pathogens, or multiplex PCR panel testing with 12 or more target pathogens.⁹ This study supported the cost-effectiveness and clinical utility of large multiplex PCR panels (> 12 targets) in diagnosing acute infectious gastroenteritis, finding that such panels were associated with greater diagnostic yield, lower 30-day follow-up cost, and reduced hospitalization risk compared with a traditional workup.

In the case example, multiplex testing for 22 enteropathogens was positive for *Salmonella* species. The patient was immunocompromised and was successfully treated with antibiotics. The possible source of his diarrheal illness was cucumbers that had been recalled due to *Salmonella* contamination.¹⁰

■ THE BOTTOM LINE

Timely diagnosis and treatment of diarrhea are essential in specific patient populations, including those who are immunocompromised and are at increased risk of complications. Testing using multiplex gastrointestinal pathogen panels, available in most microbiology laboratories, provides accurate detection of a broad range of pathogens in a timely, cost-effective manner and can improve patient outcomes. ■

■ DISCLOSURES

Dr. Hata has disclosed serving as a research principal investigator for Roche Molecular and teaching and speaking for Seegene. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

■ REFERENCES

1. Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. *Am J Gastroenterol* 2016; 111(5):602–622. doi:10.1038/ajg.2016.126
2. 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
3. Randal A. Infectious diarrhea: IDSA updates guidelines for diagnosis and management. *Am Fam Physician* 2018; 97(10):676–677. PMID:29763277
4. Shin JH, Chaves-Olarte E, Warren CA. *Clostridium difficile* infection. *Microbiol Spectr* 2016; 4(3):10.1128/microbiolspec.E110-0007-2015. doi:10.1128/microbiolspec.E110-0007-2015
5. Krones E, Högenauer C. Diarrhea in the immunocompromised patient. *Gastroenterol Clin North Am* 2012; 41(3):677–701. doi:10.1016/j.gtc.2012.06.009
6. Hata DJ, Powell EA, Starolis MW. Utility and recommendations for the use of multiplex molecular gastrointestinal pathogen panels. *J Appl Lab Med* 2023; 8(6):1148–1159. doi:10.1093/jalm/jfad009

7. **Miller JM, Binnicker MJ, Campbell S, et al.** Guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2024 update by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). *Clin Infect Dis* 2024; Published online March 5, 2024. doi:10.1093/cid/ciae104
8. **US Centers for Medicare & Medicaid Services.** CMS.gov. Mol:Dx Molecular Syndromic Panels for Infectious Disease Pathogen Identification Testing. <https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39044>. Accessed January 17, 2025.
9. **Moon RC, Bleak TC, Rosenthal NA, et al.** Relationship between diagnostic method and pathogen detection, healthcare resource use, and cost in US adult outpatients treated for acute infectious gastroenteritis. *J Clin Microbiol* 2023; 61(2):e0162822. doi:10.1128/jcm.01628-22
10. **Centers for Disease Control and Prevention.** *Salmonella* outbreak linked to cucumbers-June 2024. www.cdc.gov/salmonella/outbreaks/africana-06-24/index.html. Accessed January 17, 2025.

.....
Address: Brittany Jackson, MD, Department of Internal Medicine, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32257; Jackson.Brittany3@mayo.edu