

## Guidelines for Diarrheal Pathogen Testing in Patients Presenting to the Marshfield Clinic Health System (MCHS)

These guidelines are intended for use throughout the MCHS and pertain to inpatients and outpatients. They are appropriate for adults and children outside the neonatal period. They are meant to assist in selecting microbiologic studies in patients with diarrhea. Many patients with diarrhea (especially in the subacute/chronic category) have non-infectious causes of their symptoms. How to evaluate non-infectious causes of diarrhea is beyond the scope of this document.

### Definitions

- **Diarrhea** is defined as at least 3 loose or watery stools occurring in a 24-hour period.
- **Acute diarrhea** is generally defined as lasting less than 14 days, although patients often present for care much earlier than that, typically within 3 days of symptoms. **Subacute diarrhea** is defined as that lasting 14 to 28 days, while chronic diarrhea is present for greater than 28 days. For simplicity, subacute and chronic diarrhea are often combined into a single category.
  - Acute diarrhea is most commonly caused by infection, whereas non-infectious causes are more likely in patients with subacute/chronic diarrhea. In determining which microbiology tests to order, it is helpful to first distinguish between acute diarrhea and subacute/chronic diarrhea based on the duration of symptoms. For patients with acute diarrhea, one should determine whether the diarrhea is **inflammatory** (characterized by the presence of blood and/or mucus in the stool and often in patients with fever) or **non-inflammatory** (which manifests as watery diarrhea and usually in a patient without fever). Studies have shown that a microscopic exam for fecal leukocytes is neither sensitive nor specific for bacterial diarrhea, and that test is no longer offered.[1]

### Bacterial causes of diarrhea

The most common causes of acute inflammatory diarrhea are bacterial: *Clostridioides difficile*, *Salmonella*, *Shigella*, *Campylobacter*, and Shiga-toxin-producing *E. coli* (including *E. coli* O157:H7).[2] If the patient has recently used antibiotics or has a history of *C. difficile* infection in the past, consider ordering *C. difficile* by PCR (CDNAT) only, otherwise testing for *C. difficile* by PCR (CDNAT) and for fecal bacterial pathogen panel by PCR (SSCSNAT) is suggested. Unless the patient is immunocompromised or has signs of sepsis, antimicrobial therapy should generally be withheld in patients with acute inflammatory diarrhea pending test results. This is because antibiotics increase the risk of hemolytic-uremic syndrome in patients with Shiga-toxin-producing *E. coli* infection, and it is not possible to distinguish bacterial causes of diarrhea by clinical features.

Studies have shown that the yield of tests for bacteria in the stool (except for *C. difficile*) among patients hospitalized for over 3 days is extremely low. Thus, testing for *Salmonella*, *Shigella*, *Campylobacter*, and Shiga-toxin-producing *E. coli* should not be ordered for a patient who has been in the hospital for more than 3 days. [3]

### *Clostridioides difficile*

*C. difficile* has emerged as a common cause of diarrhea in both outpatient and inpatient settings. Although about two-thirds of patients will have a history of recent antibiotic use, approximately one-third will not. In addition, the clinical manifestations are variable, from mild watery diarrhea without fever to severe

bloody diarrhea with high fever and systemic toxicity. Thus, *C. difficile* infection should be **considered** in a patient with unexplained diarrhea (at least 3 loose or watery stools in a 24-hour period), whether in the hospital or in the outpatient setting, whether the diarrhea is acute or subacute, and whether it is inflammatory or non-inflammatory. Note: patients whose diarrhea can be explained by medications, such as laxatives, should not be tested for *C. difficile*.

PCR tests for *C. difficile* are highly sensitive. In a patient with a *negative* test, retesting is not indicated for the same episode of diarrhea, but if the patient is having a new episode of diarrhea greater than 7 days since the last time the patient tested negative, it may be reasonable to retest. In a patient with a *positive* test for *C. difficile*, repeat tests are not indicated unless the patient re-develops diarrhea after completing a course of therapy. [4] It is not appropriate to perform a test-of-cure on a patient in therapy or on a patient who has recently completed therapy.

For *C. difficile* management details, refer to: [Inpatient and Ambulatory Clostridioides difficile Antimicrobial Guideline \(mfldclin.org\)](https://www.mfldclin.org/inpatient-and-ambulatory-clostridioides-difficile-antimicrobial-guideline)

### **Parasitic causes of diarrhea**

In the United States, the most common parasitic causes of gastroenteritis are *Giardia lamblia* and *Cryptosporidium parvum*, which are protozoans that cause subacute onset of watery diarrhea and abdominal cramping, usually without fever. The test with the greatest sensitivity in detecting these pathogens is polymerase chain reaction (PCR), which can be ordered by requesting test code EPPNAT. In addition to having greater sensitivity than microscopic examination for ova and parasites (O&P exam), this test has a much shorter turnaround time.

The yield of traditional O&P exams is very low and should only be considered for returning travelers and immigrants. The O&P exam is a send-out test to Mayo and is orderable only by GI and ID providers.

### **Extended fecal pathogen panel by PCR**

An extended fecal pathogen panel by PCR is available in-house (test code EGIPNAT). The assay is restricted to patients who have been admitted to the hospital with acute diarrhea and may occasionally be helpful in the immunocompromised host with persistent diarrhea of unknown cause. Although there will still be no treatment available, knowing the cause of the diarrhea may enable a less extensive evaluation. Detecting an organism in the stool does not guarantee that the organism is causing the patient's symptoms—or that it is the sole cause of the patient's symptoms; immunocompromised patients often have more than one contributing problem.

### **Lack of utility of abdominal CT for patients with diarrhea**

In the absence of significant abdominal pain, in which an acute abdomen is a consideration, most patients with diarrhea (whether inflammatory or non-inflammatory) do not require computed tomography of the abdomen as the yield is extremely low. If an acute abdomen is being considered, surgical consultation should be requested.

### Consulting specialty services

In patients with diarrhea, indications for GI consultation include bloody diarrhea with negative testing for bacterial pathogens on the fecal bacterial pathogen panel by NAT (SSCSNAT) and non-bloody diarrhea that has persisted for more than 14 days.

Indications for ID consultation in the patient with diarrhea include recent travel to the developing world, significant eosinophilia (absolute eosinophil level greater than 500 per  $\mu$ l), worms present in the patient's stool, and diarrhea for greater than 7 days in an immunocompromised host.

### Accompanying tables and figures

[Figure 1](#) provides an algorithm for ordering microbiologic tests on stool in patients with acute diarrhea. [Table 1](#) shows the tests available at MCHS when considering infectious causes of diarrhea.

Although this document primarily concerns what tests to order and when to order them, it also includes a chart of recommended therapies for the most common infectious causes of diarrhea ([Table 2](#)). This is added for convenience; there are many other excellent antimicrobial guides to which the reader may want to refer.

### References

1. Chitkara YK, McCasland KA, Kenefic L. Development and implementation of cost-effective guidelines in the laboratory investigation of diarrhea in a community hospital. *Arch Intern Med* 1996;156:1445.
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:e45e80.
3. Barbut F, Leluan P, Antoniott G, et al. Value of routine stool cultures in hospitalized patients with diarrhea. *Eur J Clin Microbiol Infect Dis* 1995;14:346-9.
4. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA* 2015;313:398-408.

Table 1: Tests for Diarrheal Pathogens at MCHS

Test	Enteric Bacterial Panel PCR	Clostridioides difficile Toxin PCR	Enteric Parasites Panel PCR	Enteric Viral Panel	Ova and Parasite, Microscopy (MAYO Send out)	Extended Gastrointestinal Panel PCR
Test Code	SSCSNAT	CDNAT	EPPNAT	EVPNAT	OPE	EGIPNAT
<b>Pathogens Detected</b>	<ul style="list-style-type: none"> <li>• <i>Salmonella</i> spp.</li> <li>• <i>Campylobacter</i> spp. (jejuni and coli)</li> <li>• <i>Shigella</i> spp. / Enteroinvasive <i>E. coli</i> (EIEC)</li> <li>• Shiga toxin 1 &amp; 2</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Clostridioides difficile</i> Toxin</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Giardia lamblia</i></li> <li>• <i>Cryptosporidium</i> (<i>C. hominis</i> and <i>C. parvum</i>)</li> <li>• <i>Entamoeba histolytica</i></li> </ul>	<ul style="list-style-type: none"> <li>• Norovirus GI &amp; GII</li> <li>• Rotavirus A</li> <li>• Adenovirus F40/41</li> <li>• Sapovirus (I, II, IV, V)</li> <li>• Human Astrovirus</li> </ul>	Detecting and identifying parasitic protozoa and eggs and larvae of parasitic helminths	<ul style="list-style-type: none"> <li>• <i>Campylobacter</i> species</li> <li>• <i>Plesiomonas shigelloides</i></li> <li>• <i>Salmonella</i> species</li> <li>• <i>Vibrio</i> species</li> <li>• <i>Yersinia</i> species</li> <li>• Enteroaggregative <i>Escherichia coli</i> (EAEC)</li> <li>• Enteropathogenic <i>E. coli</i> (EPEC)</li> <li>• Enterotoxigenic <i>E. coli</i> (ETEC)</li> <li>• Enteroinvasive <i>E. coli</i> (EIEC)</li> <li>• Shiga-like toxin-producing <i>E. coli</i> (STEC) <i>stx1/stx2</i> including <i>E. coli</i> O157</li> <li>• <i>Shigella</i> species</li> <li>• <i>Cryptosporidium</i> species</li> <li>• <i>Cyclospora cayetanensis</i></li> <li>• <i>Entamoeba histolytica</i></li> <li>• <i>Giardia</i></li> <li>• Adenovirus F 40/41</li> <li>• Astrovirus</li> <li>• Norovirus GI/GII</li> <li>• Rotavirus A</li> <li>• Sapovirus (I, II, IV, V)</li> </ul>
<b>Specimen Type</b>	Unformed/liquid feces	Unformed/liquid feces	Unformed/liquid feces	Unformed/liquid feces	Various specimen types including feces	Unformed/liquid feces
<b>Transport Media</b>	Fresh feces in a leak-proof container	Fresh feces in a leak-proof container	Fresh feces in a leak-proof container	Fresh feces in a leak-proof container	Ecofix	Fresh feces in a leak-proof container or Cary-Blair
<b>Turnaround Time</b>	24-36 hours	24-36 hours	24-36 hours	24-36 hours	48-72 hours	24-36 hours
<b>Relative Charge to Patient</b> (Rejection of insurance claims have occurred)	\$1,500	\$400	\$1,500	\$1,500	\$70	\$3,400

**Table 2. Preferred antimicrobial therapy for the most common diarrheal pathogens**

Organism	Antimicrobial agent	Adult dosing	Pediatric dosing*	Comments
Campylobacter	Azithromycin	1000 mg PO once	10 mg/kg PO once daily x 3 days	Mild cases may not require treatment
	Alternative: Ciprofloxacin	500 mg PO BID x 5 days	15 mg/kg PO BID x 5 days	
C. difficile (please see <a href="#">MCHS C. diff guideline</a> )	Vancomycin	125 mg PO QID x 10 days	10 mg/kg PO QID x 10 days	Stop offending antibiotic if possible; (please see <a href="#">MCHS C. diff guideline</a> )
	Fidaxomicin	200 mg PO BID x 10 days	4-7 kg: 80 mg BID x 10 days; 7-9 kg: 120 mg BID x 10 days; 9-12.5 kg: 160 mg BID x 10 days; ≥12.5 kg: 200 mg BID x 10 days	
Salmonella (nontyphoid fever serotypes)	Usually none: Antimicrobial therapy for Salmonella prolongs fecal shedding and increases the relapse rate. Please see comments for few exceptions.	Ciprofloxacin: 500 mg PO BID x 7-10 days (14 days if immunocompromised)	Ciprofloxacin: 15 mg/kg PO BID x 5 days	Consider treatment only for invasive disease, infants less than 3 months old, and immunocompromised hosts. Alternative treatments: cefixime, ceftriaxone
	For Exceptions: Ciprofloxacin			
	For Exceptions: Azithromycin	Azithromycin: 500 mg PO daily x 7 days (14 days if immunocompromised)	Azithromycin: 10 mg/kg PO once daily x 3 days	
Shiga-toxinproducing E. coli	None: antibiotics result in increased toxin production and higher risk of development of hemolytic-uremic syndrome (HUS)	Antibiotics are contraindicated	Antibiotics are contraindicated	Monitor CBC and creatinine 5-7 days after onset of diarrhea; intravenous normal saline has been shown to decrease the risk of developing HUS
Shigella	Azithromycin	500 mg PO once daily x 3 days	10 mg/kg PO once daily x 3 days	Mild cases may not require treatment
	Alternative: Ciprofloxacin	750 mg PO BID x 3 days	15 mg/kg PO BID x 5 days	
Cryptosporidium	Nitazoxanide	Standard risk host: 500 mg PO BID x 3 days; Immunocompromised host: 500 to 1000 mg PO BID for at least 14 days	Standard risk host: 1-3 yr: 100 mg PO BID x 3 days; 4-11 yr: 200 mg PO BID x 3 days; ≥12 yr: 500 mg PO BID x 3 days; Immunocompromised host: Same doses as above but treat for at least 14 days	For patients on immunosuppression, consider reducing doses of immune suppressing drugs, if possible
Giardia	Tinidazole	2 grams PO once	Age ≥3 yr: 50 mg/kg PO once	High incidence of GI side-effects
	Alternative: Metronidazole	250 mg PO TID x 5 days	Any age: 5 mg/kg PO TID x 5 days	

\*Do not exceed the recommended adult dose when treating children.

Figure 1 – Algorithm for performing microbiologic stool testing in patients with diarrhea

