Gastrointestinal Pathogen Panel Guidance

Authors: Trevor Van Schooneveld, MD, Kiri Rolek, PharmD, BCPS, Paul Fey PhD, Mark Rupp, MD

Background:

Many pathogens, including bacteria, parasites, and viruses can cause infectious diarrhea. Previously, many of the pathogens responsible could only be isolated using traditional techniques such as stool culture or ova and parasite exam that were often time consuming and lacked sensitivity. To improve the detection of intestinal pathogens, the microbiology lab has introduced multiplex PCR testing using the FilmArray Gastrointestinal (GI) panel, which detects 22 common viruses, bacteria, and parasites that cause infectious diarrhea. Results are typically available in about one hour.

Testing:

This panel has replaced traditional stool culture (STOCU) and the *Giardia* and *Cryptosporidium* antigen (OVPSC) screen. Stool cultures with isolation and susceptibility will now only be obtained reflexively when *Shigella* and *Campylobacter* are detected by the GI panel. The stool Ova & Parasite microscopic test (OVPAR), used primarily for individuals with a history of travel to foreign countries, will still be available but should be reserved for those who have **both** clinical symptoms and an epidemiologic exposure strongly suggestive of a parasite not detected by the GI Panel.

C. difficile PCR testing is part of the panel but will not be reported. The reason for this is the microbiology lab and antimicrobial stewardship team have determined that PCR testing alone is inadequate for accurately identifying those with *C. difficile* infection (CDI) who require treatment.[1,2] If CDI is suspected the *C. difficile* toxin assay is recommended as it is the preferred method for diagnosis. In cases where the GI panel *C. difficile* PCR is positive and no *C. difficile* test has been ordered the microbiology lab will contact the clinician so they can decide if further testing for CDI is warranted.

Restriction:

There are no restriction on outpatient use of the GI panel, but testing should only be performed in those where pathogen identification would result in a change in management. Repeat testing is not recommended due to the high sensitivity of the test.

For inpatients, the GI panel is restricted and may only be ordered once per admission. In addition it will only be allowed within the first 3 hospital days. Use outside these criteria requires approval by the microbiology director (or their designee) who may consult with antimicrobial stewardship or infectious diseases. These restrictions are based on data showing that routine stool cultures from patients with diarrhea that develops after 72 hours of hospitalization are low yield for the pathogens detected by the panel.[3,4] Specific PCR tests for norovirus and adenovirus are available for diagnosis or follow up testing to confirm clearance. Please contact the microbiology lab if follow up testing is needed for any single bacterial or parasitic pathogens.

Interpretation:

Results of PCR testing for stool pathogens must be taken into clinical context when making treatment decisions. Previously treatment decisions were made based upon either clinical presentation or traditional microbiologic diagnostic techniques. PCR testing is more sensitive than traditional techniques and allows for the detection of low numbers of pathogens.[5,6,7] The clinical correlation of PCR results with the need for treatment and clinical outcomes has not been established. Studies evaluating stool PCR testing frequently detect more than one enteric pathogen in patient's stool and data are not available to determine the causative organism in these situations.[5,7] Additionally low levels of stool pathogens have been detected in healthy persons and all decisions regarding need for treatment must be taken into clinical context of the patient.

Treatment Recommendations:

Taking all this into account most gastrointestinal infections due to common bacterial and viral causes are self-limited in nature and do not require antimicrobial therapy. Symptoms typically resolve within 7 days in a normal host and therapy should focus on providing supportive care by replacing fluid and electrolyte losses. The use of antimicrobial therapy must be carefully weighed against unintended and potentially harmful consequences, including antimicrobial-resistant infections, side effects of treatment with antimicrobial agents, super-infections when normal flora are eradicated by antimicrobial agents, the prolongation of a carrier state (particularly in *Salmonella*) and the possibility of induction of disease-producing phages by antibiotics (such as Shiga-toxin phage induced by quinolone antibiotics).

The role of antimicrobial therapy depends on the implicated pathogen. Misuse and overuse of antibiotics in the treatment of diarrheal illness has played an important role in the development of drug resistance, which complicates treatment of those infections in which antibiotics are indicated. Included below are suggested criteria for the treatment of specific pathogens. These recommendations apply to generally healthy persons unless otherwise noted. There is a paucity of data regarding the efficacy of antimicrobials in a number of the pathogens detected on the panel and in these cases antibiotics are generally only recommended in severe or non-resolving cases or those at risk for severe disease such as immunocompromised patients. Areas where antibiotics are always indicated have been delineated as have areas where data are less clear. In cases where data are lacking, clinical judgment and the assessment of the risk verses benefit ration must be considered.

Table 1 – Etiology and Treatment Recommendations[8,9,10,11]

Pathogen	Common Presentation	Commonly Implicated Sources and Seasonality	Treatment Recommendations	Antibiotics (If Indicated)
Bacteria				
Campylobacter	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present	Poultry, unpasteurized milk and dairy products Peak season – spring, summer	Most patients recover without antimicrobial therapy. Antibiotics have been shown to reduce symptom duration by 1.3 days and are recommended for severe illness (high fever, bloody, severe, or worsening diarrhea) or risk factors for complications (elderly, pregnant women, immunocompromised).	Azithromycin 500 mg daily x 3 days Fluoroquinolone x 3 days* Immunocompromised patients may require prolonged therapy (7-14 days)
Clostridium difficile (toxin A/B)	More than 3 watery, loose, or unformed stools within 24 hours; lab findings may include leukocytosis and elevated creatinine	Recent antibiotic use, especially broad spectrum agents	Test not reported on panel. If CDI is suspected, order the *C. difficile* toxin assay.	Metronidazole 500 mg TID x 10-14 days Vancomycin 125 mg QID x 10-14 days See CDI treatment algorithm Discontinue antibiotics if possible www.nebraskamed.com/asp
Plesiomonas shigelloides	Severe abdominal cramps, and diarrhea within 6-48 hours	Fresh water, shellfish, international travel	Most patients recover without antimicrobial therapy. Unclear if antibiotics shorten the duration of illness. Consider in severe diarrhea, extremes of age, and immunocompromised.	Fluoroquinolone x 3 days* Azithromycin 500 mg daily x 3 days TMP/SMX DS BID x 3 days
Salmonella	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present	Poultry, eggs, dairy products, produce, reptile contact Peak season – summer, fall	Antibiotics have no significant effect on the length of illness and may prolong carriage of the organism in the stool. Antibiotics should generally be avoided but recommended for severe illness (>8 stools/day, high fever, hospitalized) or risk for complications (age <1 or > 50, immunocompromised)	Antibiotics typically not indicated Fluoroquinolone x 7 days* Azithromycin 500 mg daily x 7 days TMP/SMX DS BID x 7 days Immunocompromised patients require 14 days of therapy or longer if relapsing
Yersinia enterocolitica	Fever and abdominal cramps within 1-11 days, with or without diarrhea, fecal leukocytes often present	Unpasteurized milk, undercooked pork, chitterlings Peak season – winter	Most patients recover without antimicrobial therapy. Unclear if antibiotics shorten the duration of illness.	Antibiotics typically not indicated as there is no benefit For severe infections: Fluoroquinolone*, TMP/SMX DS BID, or doxycycline 100 BID X 5 days

*Levofloxacin 500 mg daily or ciprofloxacin 500 mg BID

Vibrio species (if positive and *V. cholera* negative *V. vulnificans* or *V. parahaemolyticus* present)	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present	Shellfish	Most patients recover without antimicrobial therapy. Unclear if antibiotics shorten the duration of illness. Consider in severe or prolonged diarrhea.	Azithromycin 1 g x 1 dose Doxycycline 300 mg x 1 dose
Vibrio cholerae	Abdominal cramps and large volume watery diarrhea within 16-72 hours	Shellfish, travel to Haiti or other areas where cholera is endemic	Oral rehydration is the key intervention. Antibiotics shorten the duration of illness and are recommended.	Azithromycin 1 g x 1 dose Doxycycline 300 mg x 1 dose Levofloxacin 500 mg x 1 dose Ciprofloxacin 500 mg x 1 dose
Diarrheagenic E. coli/Shigella				
Enteroaggregative *E. coli* (EAEC)	Abdominal cramps and watery diarrhea within 16-72 hours, can be prolonged	International travel, infantile diarrhea in developing countries	Limited data in EAEC and EPEC. Many patients recover without antimicrobial therapy. Antibiotics have been shown to shorten the duration of illness in ETEC and are generally indicated for moderate to severe diarrhea (>4 stools/day, fever, or blood or pus in stool).	Fluoroquinolone x 3 days* Rifaximin 200 mg TID x 3 days Azithromycin 1 g x 1 dose or 500 mg daily x 3 days
Enteropathogenic *E. coli* (EPEC)				
Enterotoxigenic *E. coli* (ETEC) *lt/st*				
Shiga-like toxin-producing *E. coli* (STEC) *stx1/stx2* (shiga-toxin producing *E. coli* is present)	Bloody diarrhea with minimal fever within 3-8 days	Unpasteurized milk, fresh produce, ground beef, petting zoos	**Antibiotics and antimotility agents should be avoided.** Antibiotics have no effect on duration or severity of symptoms and certain antibiotics may increase the risk for hemolytic-uremic syndrome.	Supportive care only
E. coli O157 (the shiga-toxin producing *E. coli* is type O157)				
Shigella/Enteroinvasive *E. coli* (EIEC)	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes present	Egg salad, lettuce, day care	Treatment is recommended if detected.	TMP-SMX 160-800 mg BID x 3 days Fluoroquinolone x 3 days* Immunocompromised patients with *Shigella* require 7-10 days of therapy

*Levofloxacin 500 mg daily or ciprofloxacin 500 mg BID

Table 1 (cont.) – Etiology and Treatment Recommendations[8,9,10,11]

Parasites				
Cryptosporidium	Prolonged watery diarrhea	Contaminated water (recreational and drinking), unpasteurized apple cider	Most patients recover without antimicrobial therapy but antibiotics may decrease the duration of illness. Immunocompromised patients often develop prolonged symptoms and respond poorly to therapy.	May use antimotility agents and/or nitazoxanide 500mg BID x 3 days for prolonged or severe illness ID consult recommended for immunocompromised patients
Cyclospora cayetanensis		Imported fresh produce	Treatment indicated if symptomatic.	TMP/SMX DS BID x 7-10 days ID consult recommended for immunocompromised patients
Entamoeba histolytica		Returning travelers	Treatment recommended if detected.	Metronidazole 500 mg TID x 7-10 days OR Tinidazole 2 g daily x 3 days OR Nitazoxanide 500 mg PO BID x 3 days followed by paromomycin 25 mg/kg/day in 3 divided doses x 7 days
Giardia lamblia		Contaminated recreational water, daycare, international travelers	Treatment indicated if symptomatic.	Tinidazole 2 g x 1 dose Nitazoxanide 500 mg PO BID x 3 days Metronidazole 500 mg TID x 5-7 days
Viruses				
Adenovirus F 40/41	Vomiting and non-bloody diarrhea within 10-51 hours	Children <2 yrs, day care	No therapy available. Treat symptomatically.	Antibiotics not indicated
Astrovirus		Children <1 yr, day care		
Norovirus GI/GII		Salads, shellfish, cruise ships, epidemic foodborne disease Peak season – winter		
Rotavirus A		Infants Peak season – winter		
Sapovirus		Children		

Table 2 – Pediatric Dosing Recommendations

Agent	Recommended Dosing
Azithromycin	10 mg/kg daily
Ciprofloxacin*	20-30 mg/kg/day in 2 divided doses (max 1.5 g/day)
Doxycycline*	≥ 8 years: 2-4 mg/kg/day divided every 12-24 hours (max 200 mg/day)
Levofloxacin*	< 5 years: 8-10 mg/kg/dose twice daily ≥ 5 years: 10 mg/kg/dose once daily (max 750 mg/day)
Metronidazole	Giardiasis: 15 mg/kg/day in divided doses every 8 hours (max 250 mg/dose) *C. difficile*: 30 mg/kg/day in divided doses every 6 hours (max 2000 mg/day)
Nitazoxanide	1-3 years: 100 mg every 12 hours 4-11 years: 200 mg every 12 hours ≥ 12 years: 500 mg every 12 hours
Paromomycin	25-35 mg/kg/day divided every 8 hours
Rifaximin	3-11 years: 100 mg four times daily (limited data) ≥ 12 years: 200 mg three times daily
Tinidazole	50 mg/kg single dose or daily (max 2000 mg/day)
TMP/SMX	≥ 2 months: 8-10 mg/kg/day (TMP component) in divided doses every 12 hours
Vancomycin (oral)	40 mg/kg/day PO divided every 6-8 hours

*Fluoroquinolones and doxycycline are not routinely used as first line therapy in pediatrics

References:

1. Dionne LL, Raymond F, Corbeil J, et al. Correlation between *Clostridium difficile* bacterial load, commercial real-time PCR cycle thresholds, and results of diagnostic tests based on enzyme immunoassay and cell culture cytotoxicity assay. *J Clin Micro*. 2013;51:3624-30.
2. Planche TD, Davies KA, Coen PG, et al. Differenes in outcomes according to *Clostridium difficile* testing method: a prospective multicentre diagnostic validation study of *C. difficile* infection. *Lancet Infect Dis*. 2013;13:936-45.
3. Rohner P, Pittet D, Pepey B, et al. Etiological agents of infectious diarrhea: implications for requests for microbial culture. *J Clin Microbiol* 1997; 35:1427.
4. Bauer TM, Lalvani A, Fehrenbach J, et al. Derivation and validation of guidelines for stool cultures for enteropathogenic bacteria other than Clostridium difficile in hospitalized adults. *JAMA*. 2001;285(3):313-319.
5. Khare R, Espy MJ, Cebelinski E, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. *J Clin Micro*. 2014;52:3667-73.
6. Liu J, Kabir F, Manneh J, et al. Development and assessment of molecular diagnostic tests for 15 enteropathogens causing childhood diarrhoae: a multicentre study. *Lancet Infect Dis*. 2014;14:716-24.
7. Kabayiza JC, Andersson ME, Nilsson S, et al. Real-time PCR identification of agents causing diarrhea in Rwandan children less than 5 years of age. *Pediatr Infect Dis J*. 2014;33:1037-42.
8. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis.* 2001;32:331-50.
9. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, eds. *The Sanford Guide to Antimicrobial Therapy*, 39th ed. Sperryville, VA: Antimicrobial Therapy, Inc; 2014.
10. Bobak DA, Guerrant RL. Nausea, vomiting, and noninflammatory diarrhea. In: Mandell GL, Bennett JC, Dolin R, eds. Mandell, Douglas, and Bennets's: Priniciples and Practice of Infectious Disease. Vol 2. 8th ed. Philadelphia, PA: Elsevier;2014:1253-1262.
11. Mody RK, Griffin PM. Foodborne disease. In: Mandell GL, Bennett JC, Dolin R, eds. Mandell, Douglas, and Bennets's: Priniciples and Practice of Infectious Disease. Vol 2. 8th ed. Philadelphia, PA: Elsevier;2014:1283-1296.

Updated: October 2018