Gastrointestinal Pathogen Panel Guidance

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 utilizes a multiplex PCR testing (FilmArray Gastrointestinal panel (GIP)), which detects 22 common viruses, bacteria, and parasites that cause infectious diarrhea. Results are typically available in about 1-2 hours after receipt in the lab.

Testing:

Most diarrheal illness are self-limited and so most patients with diarrhea do not need testing for enteric pathogens. Current guidelines recommend that stool testing for enteric pathogens be reserved for patients with diarrhea with fever, bloody or mucoid stools, severe abdominal pain, or signs of sepsis. The threshold for testing should be lower in immunocompromised patients with diarrhea and testing may be indicated in the setting of a suspected outbreak even when the high-risk symptoms are not present. A recent study found restricting GIP testing to patients meeting the above criteria would reduce testing volume 32% while preserving pathogen detection (sensitivity 97%, NPV 99.5%).[1]

Stool culture is no longer available, but culture and susceptibility will reflexively be obtained when *Shigella* and *Campylobacter* are detected by the GI panel and results reported in One Chart if the pathogen is grown. The microbiology lab does try to isolate Salmonella when detected by the GIP and clinicians can contact the lab to request susceptibility testing. Invasive enteric pathogens (those isolated from sterile sites and blood) will always have susceptibility testing performed. The stool Ova & Parasite microscopic test (OVPAR), is 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.

Patients where significant concern for *C. difficile* infection (CDI) exists should be tested using the *C. difficile* toxin assay, not the GIP. *C. difficile* PCR testing is now reported as part of the panel, but the GIP alone is not a very useful tool for evaluating for CDI as PCR testing alone is inadequate for accurately identifying those with *C. difficile* infection (CDI) who require treatment.[2,3] In cases where the GIP *C. difficile* PCR is positive and CDI testing has not been ordered the lab will reflexively perform the *C. difficile* toxin assay. This should be interpreted based on the guidance published in the CDI Guidance document.

Restriction:

Outpatients: Use should be reserved for those patients where pathogen identification would result in a change in management. Repeat testing is not recommended due to the high sensitivity of the test.
Inpatients: Due to the community acquisition of the pathogens on the panel and its high sensitivity 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 institutional data showing that use of the GIP outside of these restrictions was of exceedingly low yield. Other studies of both stool culture and GIP use in patients with diarrhea that develops after 72 hours of hospitalization corroborate the low yield for the pathogens detected by the panel.[4-6] 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. PCR testing is more sensitive than traditional techniques and allows for the detection of low numbers of pathogens.[7-9] The clinical correlation of PCR results with the need for treatment and clinical outcomes has not been well 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.[6,8] 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.

In particular, GIP results positive for Campylobacter or Enteropathogenic *E. coli* (EPEC) alone should be evaluated closely for other causes of diarrhea as these specimens are often culture negative and often do not represent enteric pathogen infection.[10] In patients with typical enteric infection symptoms (fever, bloody diarrhea, severe abdominal pain, or sepsis) these results may be significant or if Campylobacter is isolated in culture. In other settings they should be looked at with some skepticism. Clinicians should seek other causes of diarrhea and generally await culture confimration before treatment is considered.

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.

Cost of test: The GIP is a relatively expensive test and costs around $200 with patient charges significantly higher.

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Table 1 – Etiology and Treatment Recommendations

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 <u>severe illness</u> (high fever, bloody, severe, or worsening diarrhea) <u>or risk factors for complications</u> (elderly, pregnant women, immunocompromised).	Azithromycin 500 mg daily x 3 days (preferred) Fluoroquinolone x 3 days* (20% resistance at NM) 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	Do not start therapy until C. difficile toxin assay results are available. See CDI guideline on test interpretation treatment recommendations. Discontinue other antibiotics if possible. www.nebraskamed.com/asp	Vancomycin 125 mg QID x 10 days Fidaxomicin 200mg BID X 10 days (outpatient only)
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* TMP/SMX DS BID x 3 days
Salmonella	Fever, abdominal cramps, and diarrhea within 6-48 hours, fecal leukocytes often present Typhoidal strains do not cause diarrhea but associated with fevers in returning travelers	Poultry, eggs, dairy products, produce, reptile contact Peak season – summer, fall Travel to central Asia	Antibiotics have no 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 due to diarrhea) or risk for complications (age <1 or > 50, immunocompromised) Typhoidal Salmonella infection should always be treated	**Antibiotics typically not indicated** <u>Severe disease/bacteremia:</u> Ceftriaxone 2g IV daily x 7 days <u>Non-severe/oral transition:</u> TMP/SMX DS BID x 7 days (preferred) Fluoroquinolone x 7 days* Azithromycin 500 mg daily 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 not indicated in mild disease. <u>Immunocompromised or sepsis:</u> Ceftriaxone 2g IV daily +/- gentamicin 5 mg/kg/day <u>Oral transition:</u> TMP/SMX DS BID x 5 days Fluoroquinolone x 5 days* Doxycycline 100mg BID x 5 days
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 and/or prolonged diarrhea.	Doxycycline 300 mg x 1 dose (preferred) Azithromycin 1 g 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.	Doxycycline 300 mg x 1 dose (preferred) Fluoroquinolone x 1 dose* Azithromycin 1 g 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. Most patients recover without antimicrobial therapy. Treatment not generally indicated, particularly if multiple pathogens detected. Antibiotics have been shown to shorten the duration of illness in travelers diarrhea due to 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 TMP/SMX DS BID 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 always recommended.	Fluoroquinolone x 3 days* Azithromycin 500 mg daily x 3 days Ceftriaxone 2g IV daily x 5 days (hospitalized/bacteremia) Immunocompromised patients with *Shigella* require 7-10 days of therapy
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 of exposure	Children <2 yrs, day care	No therapy recommended. Treat symptomatically.	Antibiotics not indicated. Place in contact isolation for all infections except for norovirus which requires enteric isolation.
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

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