Microbiology Clinical Brief:  
*Clostridium difficile* Diarrhea and Colitis

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**KEY POINTS/LABORATORY POLICY**

1. Two tests are available at Children’s Hospital Colorado to detect toxigenic *C. difficile*
   a. *C. difficile* PCR (Xpert® *C. diff*, Cepheid.)
   b. *C. difficile* in the Gastrointestinal Pathogen Panel (FilmArray® GIP, Biofire)
2. Formed stools are not acceptable for testing unless patient has an ileus or megacolon.
3. Testing is generally discouraged in children <1 year of age due to high rates of asymptomatic carriage. Positive *C. difficile* results on the GIP panel are not reported for children <1 year of age unless released by Infectious Disease, Gastroenterology, or Antimicrobial Stewardship. Positive results of the *C. difficile* PCR are reported for children of any age.
4. Due to the high sensitivity of PCR tests, one stool specimen is sufficient to detect the pathogen.
5. Specimens will not be tested if sent within 2 weeks of a previous positive result because *C. difficile* DNA can persist long after successful treatment. Testing can be repeated 2 days after a previous negative result.

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*Clostridium difficile* is a spore-forming, anaerobic, Gram-positive bacillus that is primarily acquired from the environment or by the fecal-oral route. Asymptomatic infection with non-toxin bearing strains is common in the general population. Disease is primarily caused by new infection or overgrowth of strains that elaborate toxins A and B, which damage intestinal epithelial cells. Clinical disease due to toxigenic *C. difficile* ranges from mild or moderate watery diarrhea, to pseudomembranous colitis with bloody diarrhea, fever, and abdominal pain. Rare patients may present with ileus or toxic megacolon.

*C. difficile* is now the most common cause of antimicrobial-associated diarrhea. It is also a common health-care associated pathogen, with the incidence of *C. difficile* infection (CDIs) in hospitalized children increasing dramatically over the past decade. Community-acquired CDIs in children are also rising and now represents most CDIs in the pediatric population. The primary risk factor for development of CDI is previous antibiotic exposure. Other risk factors include contact with a healthcare environment, receipt of cytotoxic chemotherapy, use of gastric acid-suppressing agents, inflammatory bowel disease, presence of a gastrostomy tube, and/or underlying immunocompromising conditions. Several laboratory tests can detect toxigenic *C. difficile*. Currently our laboratory offers two tests. If risk factors or clinical scenario warrants testing only for toxigenic *C. difficile*, the monoplex *C. difficile* PCR (Xpert® *C. diff*, Cepheid) should be ordered. If more comprehensive testing is indicated (i.e. *C. difficile* could be one of multiple possible pathogens) then the FilmArray®Gastrointestinal Pathogen Panel (GIP, Biofire) is recommended. The GIP is a multiplex PCR assay which detects the 22 most common bacterial, parasitic, and viral causes of gastroenteritis/colitis, including *C. difficile*. The PCRs target the toxin A (*tcdA*) and/or the toxin B genes (*tcdB*), although *tcdB* is considered the major virulence factor. The sensitivity of the *C. difficile* component of the monoplex *C. diff* PCR and multiplex GIP assays are comparable and estimated at 99% and 97%, respectively. The charge for the monoplex *C. difficile* PCR is about one-half that for the multiplex GIP panel.

The specificity of either test varies by the type of patient being tested. Patients may have positive test results unrelated to the cause of their diarrhea due to asymptomatic carriage of toxigenic strains of *C. difficile*. Asymptomatic carriage in some patient populations creates considerable difficulty interpreting positive *C. difficile* PCR results. This is particularly problematic in pediatrics. The rate of asymptomatic colonization in children under 1 year of age ranges from 30-60%. By 2-3 years of age, colonization rates begin to decline to rates in adult populations (3-10%). Colonization rates are also elevated in certain high-risk patient populations, such as those with underlying gastrointestinal disorders or malignancies. For example in a study conducted at CHCO, 30% of our pediatric oncology patients were found to be asymptomatic carriers of *C. difficile* (positive *C. difficile* PCR without any gastrointestinal symptoms.) Currently there is no test to distinguish asymptomatic carriage from true disease.
RECOMMENDATIONS FROM THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA, THE INFECTIOUS DISEASE SOCIETY OF AMERICA, AND THE AMERICAN SOCIETY OF GASTROENTEROLOGY FOR DIAGNOSIS AND TREATMENT OF CDI

Testing Recommendations:
1. Only test diarrheal stools (stools that assume the shape of the container).
2. Unless there are compelling clinical reasons or risk factors, do not test children < 1 year of age due to the high rate of asymptomatic colonization in this age group.
3. Repeat testing is not recommended if an initial specimen is PCR-negative.
4. Testing for cure should not be done as C. difficile PCR assays may remain positive for several weeks after treatment. Cessation of symptoms is the best test of cure.
5. Diarrhea developing after admission to the hospital (≥ 3 days) or in conjunction with the use of antibiotics should be tested for C. difficile.

Treatment Recommendations:
1. If possible, any inciting antibiotics should be discontinued.
2. The use of anti-peristaltic agents should be limited or avoided.
3. Patients with C. difficile should be placed on strict contact precautions.
4. Children with mild to moderate CDI should be treated with oral metronidazole for 10 days, (30 mg/kg/day in 4 divided doses.) Adults: 500 mg 3 times a day or 250 mg 4 times a day.
5. Children with severe CDI should be treated with oral vancomycin for 10 days (40 mg/kg/ day; maximal dose 125 mg 4 times a day) in 4 divided doses. Adults: 125 mg 4 times a day.
6. For hospitalized patients with severe CDI, an ID and/or GI consult is warranted.
7. Unfortunately, recurrent CDI is common, with 15-25% of patients experiencing a recurrence. After one recurrence, the risk of a second recurrence increases to 35-50%. Recurrent CDI can be treated with the same regimen used to treat the first regimen, but vancomycin is recommended if symptoms are severe. For a second recurrence, most experts would recommend a pulsed or tapered regimen of oral vancomycin.
8. For a third recurrence, consider fecal microbiota transplantation (FMT). Clinical trials in adults have demonstrated a > 90% cure rate of FMT for the treatment of recurrent C. difficile. CHCO started a FMT clinic in 2015 for the treatment of pediatric patients with recurrent C. difficile. Our protocol utilizes a rigorously screened, commercially available stool source (OpenBiome) that is administered via a nasogastric tube. Children should be referred to ID or GI for consultation.

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