

## Update on the Testing, Treatment, and Isolation of Patients with *Clostridium difficile* Infection (CDI)

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*Clostridium difficile*, the leading cause of nosocomial enteric infection, is a gram-positive, spore-forming anaerobe. CDI can develop if the normal gastrointestinal flora is disrupted by antibiotic therapy and a person acquires toxin-producing *C. difficile*, typically via the fecal-oral route. Almost every antibiotic has been associated with CDI, and the use of antibiotics is the major risk factor for CDI. The incidence, severity and mortality due to CDI have been steadily increasing over the last decade. This is likely due to the spread of a new strain of *C. difficile* termed the NAP1/B1/O27 strain, which produces much higher levels of toxin than previous strains and is resistant to fluoroquinolone antibiotics. This strain has been detected at The Nebraska Medical Center, but the overall prevalence at The Nebraska Medical Center is unknown.

The diagnosis of CDI has been difficult in the past as the most commonly used test, the toxin enzyme immunoassay (EIA), has suboptimal sensitivity (70-90%). Clinicians have attempted to overcome this poor sensitivity by repeat testing. Other tests are available for CDI such as culture, cytotoxic assay, tests for a “common antigen” called glutamate dehydrogenase (GDH), and polymerase chain reaction (PCR) tests. In July of 2009, The Nebraska Medical Center introduced a new testing method for the detection of CDI utilizing detection of both GDH and toxins A and B.

Recommendations of how best to utilize this new assay were published by the institution, and the use of the new assay was analyzed over a 2-month period. The findings of this review suggested that repeated testing of stools for CDI was frequent, and the yield of repeat testing was quite low. Of 147 episodes of repeat testing of initially negative stools, only 2 patients (1.4%) were subsequently identified as having positive toxin assays, and patient charges were roughly \$37,000 per positive toxin assay. It is unknown if either of these 2 patients actually had CDI as the likelihood of a false positive test result increases dramatically with each repeated test due to lower pretest probability in the test population. Repeat testing typically results in more false positives than true positives.

Based on the above data and a review of the literature, institutional guidelines have been developed by the Antimicrobial Stewardship Program and Department of Healthcare Epidemiology regarding the testing, treatment, and isolation of patients with CDI. **Table 1** describes the interpretation of test results.

**Table 1. Interpretation of *C. difficile* testing**

<b>GDH Result</b>	<b>Toxin Assay Result</b>	<b>Interpretation</b>	<b>Recommendations</b>
<b>Negative</b>	<b>Negative</b>	No <i>C. difficile</i> present	No further action. Repeat testing is discouraged.
<b>Positive</b>	<b>Positive</b>	Toxigenic <i>C. difficile</i> is present	Isolate patient and begin therapy according to management algorithm. Repeat testing is discouraged.
<b>Positive</b>	<b>Negative</b>	Non-toxigenic <i>C. difficile</i> or false-negative toxin assay	Utilize contact isolation precautions if the patient has diarrhea. Treat if clinically indicated. Repeat testing is discouraged.
<b>Negative</b>	<b>Positive</b>	Indeterminate	Repeat test x 1.

**Testing:**

Patients should only be tested for CDI when a significant clinical suspicion exists (i.e. the patient has a clinical syndrome consistent with CDI). The laboratory will only accept liquid stool (conforms to the shape of the container) specimens for testing. **Do not order multiple CDI tests at once.** The current assay has a very high negative predictive value (99%); thus, a negative GDH and toxin effectively rules out CDI, and the test should not be repeated unless several days have passed and the clinical syndrome has changed. The current assay also has a very high positive predictive value (99%) when both the GDH and toxin are positive. Patients with this result have CDI and should be appropriately treated and isolated. There is no indication for “test of cure” testing. The interpretation of a positive GDH and negative toxin assay is difficult. Patients with GDH positive and toxin negative stools may have CDI and should be evaluated clinically. If a syndrome consistent with CDI is present (fever, elevated WBC count, abdominal pain, diarrhea, etc), treatment is indicated. Further investigation to improve diagnostic testing in this group of patients is ongoing. These patients should not undergo repeated testing as this has not resulted in increased diagnosis of CDI.

**Treatment:**

Patients diagnosed with CDI should have all unnecessary antibiotics and anti-diarrheal medications discontinued immediately. In patients with mild to moderate CDI, treatment can be withheld while awaiting test results. If CDI is diagnosed in patients with mild to moderate disease, oral metronidazole at a dose of 500mg orally every 8 hours should be instituted and continued for 10 days. In patients with severe CDI (WBC>20,000 or serum creatinine increased 1.5X baseline) vancomycin 125mg orally every 6 hours for 10 days is preferred. Some patients develop complications due to CDI including ileus,

hypotension, shock, toxic megacolon, and fulminant colitis. In cases with these complications both the gastroenterology and infectious disease service should be consulted and a regimen combining both oral vancomycin and intravenous metronidazole is recommended. Early colectomy can be life saving in patients with severe disease. Little data exists to guide treatment in refractory disease. If CDI recurs after treatment, the same agent used to initially treat the infection should be used again for 10 days. If further relapses occur, vancomycin should be used as prolonged courses of metronidazole have been associated with neurotoxicity.

### **Isolation:**

Vigilant hand washing, isolation precautions, and environmental cleaning are keys to controlling *C. difficile*. All patient care areas will use the same procedures for testing, treatment and isolation. Universal glove use, the use of gowns for any substantial patient or environmental contact, and hand hygiene with soap and water are key components to controlling the spread of *C. difficile*. Patients with a negative GDH and toxin assay do not need to be isolated. Patients with GDH positive, toxin negative stools may or may not have CDI. If patients have any symptoms consistent with CDI (i.e. diarrhea, fever, abdominal pain) they should remain in isolation as if they had a positive toxin assay. If patients with this result are completely asymptomatic (no diarrhea) then there is no need for isolation. Patients with CDI will remain in isolation for 1 week after treatment is completed and they are asymptomatic (no diarrhea).

For more information regarding any of these topics please refer to our recently revised guidelines and treatment pathway at: [www.nebraskamed.com/asp](http://www.nebraskamed.com/asp).

### **Example Cases:**

**Case #1:** A 68 year-old male is admitted with community-acquired pneumonia. He is started on piperacillin/tazobactam. On hospital day 2 he develops diarrhea. 3 stools are ordered and sent for *C. difficile* and all are negative for both GDH and toxin. Diarrhea resolves when piperacillin/tazobactam is changed to ceftriaxone. **Routine ordering of multiple *C. difficile* assays is unnecessary.**

**Case #2:** A 46 year-old female is admitted from home with diarrhea. Her only risk factor is receipt of a single dose of prophylactic cefazolin 2 weeks ago during an orthopedic procedure. She has a stool positive for both GDH and toxin, is started on metronidazole, and improves. **Any antibiotic can place a person at risk for CDI.**

**Case #3:** An 85 year-old male is admitted for diarrhea and abdominal pain. He had a WBC of 14,000 and a temperature of 38.4°C. His stool is positive for GDH, but negative for toxin. No other cause of his symptoms is noted upon evaluation and workup. He is treated with metronidazole and improves. **GDH positive, toxin negative patients should receive treatment based upon the syndrome present.**

**Case#4:** A 58 year-old female recently treated for pyelonephritis is admitted with severe diarrhea. She has a WBC of 25,000, a temperature of 38.6°C, minimal bowel sounds and severe pain upon palpation of the left lower quadrant. Abdominal X-ray shows evidence of an ileus. Stool is positive for both GDH and toxin. The patient is started on oral vancomycin but continues to deteriorate. Intravenous metronidazole and vancomycin enemas are added. The abdomen becomes rigid, surgery is consulted, and a total colectomy is performed. The patient improves slowly and is discharged to a rehab facility. **Patients with severe disease should be treated initially with vancomycin. Patients with severe, complicated disease may benefit from the addition of intravenous metronidazole and vancomycin enemas, and early surgical therapy can be lifesaving.**

#### **References:**

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