FAQs: NM Diagnosis and Treatment of *C. difficile* Infection (May 14, 2021)

Q1: What is the best way to diagnose *Clostridioides difficile* infection (CDI)?

A: Diagnosis of CDI begins with recognizing your patient has the appropriate clinical gastrointestinal syndrome then sending a liquid stool sample for the appropriate laboratory test(s). The CDC, Infectious Disease Society of America (IDSA), and Society of Healthcare Epidemiology of America (SHEA) support two diagnostic strategies: 1) PCR-only testing with agreed-upon clinical criteria for testing and 2) a combination of tests including PCR and toxin.[1] There is growing evidence, however, that PCR-only testing over-diagnoses CDI. The updated Epic NMH Stool C diff PCR 2-step algorithm helps improve patient care and safety.

Q2: Why is NM changing from a PCR-only testing strategy to a 2-step algorithm to diagnose CDI?

A: Performing PCR-only testing for CDI is known to over-diagnose CDI. There are 2 major clinical negative consequences of treating for CDI when it is not present:

1. Unnecessary antibiotic treatment. Exposure to oral vancomycin has been associated with increased CDI recurrences, with prolonged microbiome disruption.
2. Incorrect attribution of gastrointestinal disease may result in missed diagnoses and missed treatment of another disease process. Consequences may include unnecessary hospital days, increased morbidity and mortality.

Q3: What are the appropriate clinical gastrointestinal syndromes for testing for CDI?

A: There are 2 major clinical presentations for testing stools for CDI. Both clinical presentations will soon be incorporated into the updated Epic order for Stool C diff PCR, which tentatively will roll-out in June, 2021:

1) New onset diarrhea with no other reasonable explanation such as recent laxatives or oral contrast or tube feeds. Patients may or may not have associated nausea, leukocytosis, abdominal tenderness or fever. This is the most common presentation of CDI.
    a. For hospitalized patients during calendar days 1-3: it is ideal to rapidly identify a patient for whom producing high-volume, frequent liquid stool is a new problem. Thus, if a patient or caregiver reports new onset, otherwise unexplained diarrhea and the health care team collects a large, liquid stool, CDI testing is likely indicated.
    b. For hospitalized patients after the third calendar day of hospitalization: the health care team should verify that the hospitalized patient has 3 or more large liquid stools (or new high-volume output from rectal tube) in the past 24 hours. In most instances, clinicians should avoid testing when there are other reasonable explanations such as recent laxatives or oral contrast or tube feeds.
2) Patients with abdominal distention, pain, tenderness, and/or colonic dilatation. These patients may present with ileus or scant liquid stools and are typically critically ill. This presentation is infrequent but usually warrants intensive care and consultation with Surgery and Infectious Diseases.

Q4: What is the NM 2-Step CDI testing strategy?

A: Samples must continue to meet laboratory criteria (liquid stool). Solid stool samples will be rejected by the Clinical Microbiology Lab**.** If no liquid stool is collected within 24 hours of the CDI Test order being placed, the ordering MD/APP will receive a Best Practice Alert (BPA) containing the recommendation to d/c the order.

Step 1: PCR. This is the same PCR test NMH has used previously, the Becton Dickinson (BD) MAX™ *C. difficile* Toxin B PCR[2]. The assay tests for the presence of *C. difficile* bacteria that carry the gene for Toxin B. Because C Diff PCR has a high negative predictive value, if the PCR is negative, no additional testing is done and CDI treatment is not indicated.

Step 2: Reflex Toxin EIA. For those stool samples that are PCR positive, the sample will be reflexed to the second test, the Toxin EIA. Reflex testing for toxin is fast, adding an estimated hour to the time to result reporting. PCR+ tests will be withheld until the reflex test result is available; both test results (PCR & Toxin EIA) will be reported simultaneously.

Q5. What is the toxin EIA test used in this 2-step algorithm?

A: The toxin EIA test used presently is TechLab C. Diff QUIK CHECK COMPLETE[3]. This assay tests for the presence of *C. difficile* toxin A and B. As an internal control, Glutamate Dehydrogenase (GDH), a *C. difficile* constitutive enzyme, is also tested by immunoassay. All *C. difficile* organisms make GDH, including organisms that carry the genes for toxin production and those that don't. To be Toxin EIA positive, indicating CDI, both GDH and toxin B must be present.

Q6: What are the 3 potential results of the 2-step algorithm?

- PCR(-): CDI is unlikely – because CDI is a toxin-mediated disease.
- PCR+/Toxin EIA(-): This is an indeterminate result. In most cases, do not treat for CDI. Stop unnecessary antibiotics. Reevaluate for alternative causes of diarrhea. If strong clinical suspicion of CDI still persists, treat for CDI and consider ID consultation. Place patient on Contact Plus isolation.
- PCR+/Toxin EIA+: CDI likely – Treat for CDI and stop unnecessary antibiotics. Place patient on Contact Plus isolation.

Q7: What do we know about patients who are C Diff PCR +/Toxin EIA (-) and how do they differ from PCR- patients and PCR +/Toxin EIA+ patients?

Patients who have PCR+/Toxin EIA(-) stools do have some increased risk of developing CDI compared to PCR- patients, so stopping or reducing inciting antibiotics is advised. These patients shed *C. difficile* spores and should be placed on Contact Plus isolation, which results in special terminal cleaning procedures in order to reduce transmission to others. Most of these patients present clinically as *C. difficile*-colonized patients, meaning that if they have diarrhea, there is another cause.

C. difficile-colonized patients are defined as patients whose gastrointestinal tracts carry *C. difficile* organisms that carry the genetic code for *C. difficile* toxin yet the patient does not have toxin-induced diarrhea. PCR+/Toxin EIA(-) results indicate that the gastrointestinal tract is colonized with bacteria with the toxin gene but toxin is not being produced, thus CDI, a toxin-mediated disease, is not present. An alternative explanation for these tests results, though, is possible. The amount of toxin produced in the stool could be lower than the threshold level of the assay. Thus, the toxin result would be a false negative, but this occurs rarely and is of unknown clinical significance. Reducing selection pressure (i.e., avoiding or stopping unnecessary antibiotics) is advised for Toxin EIA (-) patients as well as their Toxin + counterparts.

Multiple studies suggest that these PCR+/Toxin EIA (-) patients do not benefit from CDI treatment and rarely experience CDI complications. Polage, et al.[4] reviewed 7046 in-patients who were tested solely for toxin at a single tertiary medical center between 2005 and 2009. Charts were reviewed for evidence of CDI symptoms

and complications for toxin (+) patients vs. toxin (-) patients. Toxin (-) patients had shorter duration of diarrhea. Fewer toxin (-) patients had 6 or more stools per day or needed a rectal tube, and had lower WBCs. No toxin (-) patients had colectomy or toxic megacolon. One toxin (-) patient had pseudomembranous colitis. Subsequently, Polage, et al.[5] reviewed cases of hospitalized patients at a single tertiary medical center with hospital-onset diarrhea (n=1416) that were tested with PCR. Two hundred ninety-three patients had PCR+ samples. Of these, 162 of these were toxin negative. These 162 patients had milder symptoms and had shorter episodes of diarrhea than those with PCR+/Toxin+, with clinical presentations similar to PCR-/Toxin (-) patients. There were no complications although only 6 PCR+/Toxin (-) patients received CDI-targeted antibiotics. PCR+/Toxin+ patients had more antibiotic exposure, higher WBC, higher *C. difficile* bacterial load, higher toxin concentration. Results suggest that most hospitalized patients with PCR+/Toxin (-) results do not need to be treated for CDI. In a multicenter study, Planche, et al.[6] compared outcomes of multiple testing methods to a gold standard but time-consuming test, the cell cytotoxicity neutralization assay (CCNA). A subset of patients had clinical outcome data that found that PCR+/Toxin EIA (-) patients behaved like and had similar outcomes to CCNA-negative patients, including no deaths due to CDI complications, suggesting that they should not be treated for CDI. Guh, et al.[7], in a multicenter study, found no difference in 30-day mortality but identified PCR+/Toxin + cases as more likely to have classic risk factors for CDI, qualify by clinical criteria for testing, have severe disease, and be associated with almost two times the risk of recurrence, although both groups received high amounts of CDI treatment. Early information is building about the outcomes of patients with various immunosuppressed states[16-30] including patients with hematology-oncology, transplantation and inflammatory bowel disease diagnoses.

Q8: What is *C. difficile* colonization?

A: *C. difficile* colonization is presence of *C. difficile* organisms that carry the genes for *C. difficile* toxin but do not present with clinical signs or symptoms of CDI. For further information, see Crobach et al 2018.[8]

Q9: Should one send stool for CDI to "rule-out" CDI, when there is another reasonable explanation for observed liquid diarrhea such as recent laxatives, tube feeds or enemas?

A: Testing to "rule-out" CDI is incorrect medical decision-making because many persons can be colonized with *C. difficile* organisms (PCR+/toxin EIA+ or even PCR+/EIA+) but have other etiologies of diarrhea. Discontinuing high diarrheal risk medications for at least 24 hours then reassessing diarrheal output before testing is good practice. The NM order has a side bar that lists recent high diarrheal risk medications and/or tube feeds administered in the past 24 hours to assist medical decision-making.

Q10: Once the modified CDI test order rolls out at NMH early this summer, what are the changes to expect?

1. Patient-specific data to help clinicians decide whether CDI testing is appropriate will be located in the side bar of the order.
    a. Recent CDI tests, dates and results
    b. Medications that frequently cause diarrhea administered in the past 24 hours
2. Ordering clinicians will attest to one of 2 clinical presentations for appropriate C difficile testing that are outlined in **Q3**.
3. Ordering a CDI test will be blocked if a C diff prior test was sent within the previous 7 days. Repeat testing during this time period is unlikely to give a different result as well as unlikely to alter medical decision-making.

a. For a negative PCR result, repeat testing is unnecessary. Due to the high sensitivity of the C. Diff PCR, there is a high negative predictive value of the first test within the same episode of diarrhea.

b. b. For those who are PCR+, there is no reason to repeat the test in this brief time frame. If the test is PCR+/EIA+ in the past 7 days, there is no reason to repeat the test – either for a test-of-cure or to explain ongoing diarrhea. Because the PCR test is exquisitely sensitive and the toxin test is quite sensitive, testing stool can still be positive for a prolonged period, well beyond a week, so repeat testing does not supply a meaningful result. If the first stool sample is PCR+/Toxin EIA (-), clinicians should use clinical judgement, not repeat testing, to decide about CDI treatment in this brief time frame.

c. Repeating a C diff test is discouraged between day 8-30 after a PCR+/toxin EIA+ test (see **Q11** immediately below.) For logistical reasons, temporarily, this is not blocked by electronic decision support.

Q11: In late July, 2021, when NMH converts to Epic Beaker, the new laboratory information system, what are the changes to expect?

1. The name of the test will change throughout the NM System: eventually, C diff PCR/reflex toxin EIA will be the one test available.
2. Repeat testing will continue to be blocked if a C diff test was sent within the previous 7 days.
3. Repeat test will be blocked for PCR+/Toxin EIA+ results between 8-30 days after the first positive result. Clinical judgement, not repeat testing, is indicated because testing is likely to remain positive within this time frame, regardless of the cause of persistent or renewed diarrhea; furthermore, recurrent disease is common after a toxin+ CDI episode.

Index Result	CDI Test Performed in Past 7 days	CDI Test Performed in Past 8-30 days
PCR-	Retest blocked	Ok to retest
PCR+/toxin EIA-	Retest blocked	Ok to retest
PCR+/toxin EIA+	Retest blocked	Retest blocked

General Information about CDI

Q12: How common is CDI among hospitalized patients? How common is *C. difficile* colonization among healthy adults? How common is *C. difficile* colonization among hospitalized adults?

A: CDI is the top cause of infectious diarrhea among hospitalized patients – but most nosocomial diarrhea is not due to CDI. Studies estimate that 4-15% of healthy adults may be colonized with *C. difficile* organisms. Among hospitalized patients, this rate may be as high as 20%. Thus, using antibiotics only when necessary, carefully selecting patients for CDI testing, and avoiding CDI testing for patients with obvious causes of non-CDI diarrhea is important in order to avoid unnecessary CDI diagnosis and treatment.

Q13: What is the strongest risk factor for developing CDI?

A: Concurrent or recent exposure to antibiotics is the strongest risk factor for CDI. The CDC states that antibiotics in the past 28 days is the strongest risk factor for developing CDI.

Q14: What are major risk factors for relapsed CDI or recurrent CDI?

- Continuing inciting antibiotics after CDI diagnosis
- History of PCR +/toxin + disease
- Age >65 years
- Co-morbidities
- Residency in a long-term care facility

CDI Treatment Recommendations[1]

Disease	Clinical Presentation	Medication	Comment
C. difficile infection (CDI)	Initial episode, non-severe and severe	Inpatients: Oral vancomycin 125mg every 6 hours Outpatients: fidaxomicin is an alternative recommended oral therapy. Prior authorization is necessary.	Fidaxomicin*:* *Inpatient use is restricted to the treatment of CDI, restricted to ID consultation only, for inpatients who have had CDI recurrence after standard vancomycin followed by extended pulse dose oral vancomycin therapy. Prior authorization is necessary to ensure continuity of care following discharge.*
	Fulminant CDI, Initial episode: defined as CDI with hypotension, shock, ileus and/or toxic megacolon.	Oral vancomycin 500mg every 6 hours plus metronidazole IV 500mg every 8 hours +/- vancomycin enema per rectum	
	Recurrent episode		ID consult recommended

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