Evidence-Based Commentary: Testing for Clostridioides difficile Infection

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What Is Clostridioides difficile Infection, and Why Is It a Significant Healthcare Concern?

Clostridioides difficile infection (CDI) is a bacterial infection of the large intestine caused by the gram-positive, spore-forming bacterium, C. difficile. It is a significant healthcare concern due to low quality of life, an increasing incidence, high morbidity, recurrence rates, and economic burden. Furthermore, CDI is a leading cause of healthcare infection, affecting hospitalized and recently discharged patients. Its contagious nature poses a risk to healthcare facilities. C. difficile infection is associated with various risk factors, the most prominent being recent antibiotic exposure, particularly broad-spectrum antibiotics, which disrupt the normal gut microbiota and allow C. difficile to proliferate. Other risk factors include advanced age, longer length of stay, chemotherapy, immunosuppression, and gastrointestinal surgery. C. difficile infection presents with diarrhea, abdominal pain, and fever, and in severe cases, it can lead to pseudomembranous colitis, toxic megacolon, or even sepsis. Given the increasing prevalence and severity of CDI, timely and accurate diagnosis is crucial to guide appropriate therapy, reduce transmission, and improve patient outcomes.

What Are the Available Diagnostic Methods for C. difficile Infection, and How Do They Compare in Terms of Accuracy, Sensitivity, and Specificity?

There is no perfect test for the diagnosis of CDI and should be performed and interpreted in context of symptoms. Patients without risk factors or symptoms of CDI should not be tested. Several diagnostic methods are available for CDI, with varied sensitivity, specificity, advantages, and limitations (Table 1). These include nucleic acid amplification tests (NAATs), toxin detection tests, and culture-based assays. Culture-based methods are the gold standard, allowing for strain typing and antimicrobial susceptibility testing. They are slow and have lower sensitivity due to the requirement for viable C. difficile organisms. Cell culture cytotoxicity neutralization assay is not used in clinical practice as it is time consuming, cumbersome, and can lead to delayed results. It is generally used in research settings. While pseudomembranes have high sensitivity and specificity for CDI, endoscopy is invasive. If stool tests do not demonstrate CDI, and there is a high suspicion, endoscopic evaluation for pseudomembranes can be performed. If pseudomembranes are seen on endoscopic evaluation, treatment for CDI can be initiated in the appropriate clinical context. Polymerase chain reaction (PCR) is a form of NAAT, offers high sensitivity and specificity, and is preferred due to speed and accuracy in detecting the presence of C. difficile DNA. However, it does not detect presence of toxin, and therefore do not distinguish between colonization and active infection. This may lead to over diagnosis, especially in the absence of symptoms or symptoms explained by other causes.

Toxin detection tests, such as an enzyme immunoassays (EIA) for the presence of toxin A & B, are used to detect C. difficile toxins in stool samples. These are cost-effective and provide rapid results but have a lower sensitivity leading to missed cases. This low sensitivity is related to the performance of the assay (a higher lower limit of detection) or toxin degradation due to stool handling and delays in performing the test. In order to achieve the best diagnostic accuracy, a two-step approach is often recommended, starting with a sensitive test (but not specific) like an antigen

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(glutamate dehydrogenase/GDH) and confirming positive results with a toxin assay (Fig. 1).6

What Are the Advantages and Limitations of Nucleic Acid Amplification Tests (NAATs) in Diagnosing C. difficile Infection?

PCR has revolutionized the diagnosis of CDI, offering advantages, including high sensitivity and specificity, rapid results, and the ability to detect the presence of C. difficile DNA in stool samples.4 Despite limitations, NAATs have become increasingly popular in clinical practice due to their accuracy and speed. Advantages include their ability to detect cases missed by toxin-based tests, making them suitable for high-risk patient populations.7 Rapid turnaround times aid in timely clinical decision-making, which is crucial for infection control and management. The main limitation of NAATs is their inability to distinguish between colonization and active infection. They detect the presence of C. difficile DNA, but not necessarily the production of toxins causing symptoms. This leads to the potential overdiagnosis of CDI, particularly in patients without clinical symptoms. Overreliance on NAATs may contribute to unnecessary treatment and increased healthcare costs. Therefore, it is important for clinicians to interpret NAAT results in the context of clinical symptoms and risk factors. In summary, NAATs are highly sensitive and specific tools for CDI diagnosis, but clinical judgment is crucial to avoid overtreatment.6,7

What Are the Current Guidelines or Recommendations for C. difficile Testing?

Clinical societies including the American College of Gastroenterology, Infectious Diseases Society of America, and European Society of Clinical Microbiology and Infectious Diseases have established guidelines and recommendations for CDI testing to help clinicians make informed diagnostic decisions. There are several considerations when evaluating guidelines and using them in clinical practice:

- **Test selection:** Guidelines emphasize the importance of test selection based on the clinical context. NAATs have gained popularity due to their high sensitivity, but the guidelines stress the need for clinical correlation to avoid overdiagnosis.
- **Two-step testing:** Many guidelines suggest a two-step approach, beginning with a highly sensitive test like NAAT.
and confirming positive results with a toxin assay. This strategy balances sensitivity and specificity (► Fig. 1). 6

Asymptomatic carriers: Guidelines acknowledge that asymptomatic carriers exist and recommend against screening for C. difficile in the absence of clinical symptoms. 7

What Challenges and Controversies Exist in the Realm of C. difficile Testing, and How Do We Contextualize Evidence-Based Testing Strategies for CDI?

C. difficile testing faces several challenges and controversies that clinicians must navigate to improve diagnostic accuracy and patient care. Evidence-based testing strategies for CDI play a crucial role in improving patient outcomes, reducing healthcare costs, and promoting antimicrobial stewardship.

Overdiagnosis: NAATs have high sensitivity but do not differentiate between colonization and active infection. This leads to the overdiagnosis in asymptomatic carriers or patients with other causes of diarrhea. Clinicians must use judgment to avoid overtreatment.

Underdiagnosis: Toxin detection tests, such as EIAs, have lower sensitivity than NAATs and may miss cases of CDI, especially those caused by nontoxicigenic strains or new toxin variants. This can result in underdiagnosis and delayed treatment.

Improved patient outcomes: Accurate CDI diagnosis ensures that patients with genuine infections receive appropriate treatment promptly. This reduces morbidity and the risk of severe complications, such as pseudomembranous colitis or toxic megacolon.

Asymptomatic carriers: Asymptomatic C. difficile carriers may be a source of transmission in healthcare. The significance of detecting C. difficile in the absence of symptoms is debatable. Testing asymptomatic individuals can lead to unnecessary treatment and potential harm.

Antimicrobial stewardship: Reducing inappropriate antibiotic use is a fundamental aspect of CDI prevention. Evidence-based testing strategies help identify situations where CDI is less likely and suggest avoiding testing. This contributes to the broader goal of antimicrobial stewardship by curbing antibiotic resistance and the risk of CDI.

Reduced healthcare costs: Evidence-based testing strategies help prevent the overdiagnosis of CDI, reducing the financial burden associated with unnecessary treatment and hospital isolation. Additionally, by guiding appropriate therapy, these strategies can lead to cost-effective patient management.

When Should and Should Not a Patient Be Retested for C. difficile Infection?

Testing for CDI should be performed in the context of clinical symptoms of the disease keeping the syndrome in mind. As is well known in the field, the risk of recurrent CDI after a primary infection can be 20 to 30% and this rate of recurrence can be more than 50% in patients with multiple infections. There is also a risk of postinfection irritable bowel syndrome that ranges between 20 and 30% after CDI has resolved.

1. Patients who do not exhibit symptoms of CDI after antibiotic treatment is completed should never be retested. The risk of false positive test can be up to 50%. Treatment of a false-positive test or a carrier state can lead to future CDI and does not confer any clinical benefit.

2. Patients who exhibit symptoms of postinfection irritable bowel syndrome after antibiotics for CDI are stopped should not be tested for CDI. The detailed symptom history to exclude postinfection irritable bowel syndrome is important period; these patients typically present with

Fig. 1 Interpretation of a two-step testing algorithm for C. difficile (Clostridioides difficile) infection. EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction. A negative GDH by itself is not used to rule out C. difficile infection and is followed by an EIA for toxin A/B as the diagnostic kits check for both GDH and the C. difficile toxins. Reprinted with permission. 6
diarrhea, alternating constipation or formed stools with or without abdominal cramps, with symptoms generally related to food intake.

3. Patients who have recurrence of CDI symptoms, that is, otherwise unexplained recurrent diarrhea would benefit from repeat testing for CDI.

**Are There Any Emerging Technologies in C. difficile Testing That Show Promise for Improving Accuracy of Diagnosis?**

The field of testing for CDI is evolving, with emergence of technologies showing promise for improving diagnostic accuracy. These emerging trends and technologies offer exciting opportunities to enhance CDI diagnosis. However, their clinical utility and cost-effectiveness need further evaluation before widespread adoption.

**Ultrasonic toxin detection**: Tests are being developed to improve sensitivity of toxin bases assays.

**Phenotypic testing**: Phenotypic testing, which measures the metabolic activity of *C. difficile*, may help distinguish between colonization and active infection. It is an area of ongoing research.

**Metagenomic sequencing**: Metagenomic sequencing, which analyzes the entire gut microbiome, is gaining attention for its potential to detect *C. difficile* and other pathogens. This approach may offer higher sensitivity and specificity, as well as the ability to identify antibiotic resistance genes.

**Potential Competing Interests**

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**Ethical Statement**

Not applicable.

**References**