5 *Clostridium difficile* Diagnostics in Long-Term Care Facilities

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Introduction

Clostridium difficile (*C. difficile*) infection (CDI) is the most common nosocomial infection and disproportionally affects our elderly patients, with 80% of *C. difficile* infections occurring in patients 65 years of age and older [1]. As described in other chapters of this book, patients with CDI can have multiple loose or watery stools in 1 day causing extreme dehydration, electrolyte disarray, sepsis, toxic megacolon, and even death. With the increasing prevalence and severity of CDI over the past decade,

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T. Chopra (ed.), *Clostridium Difficile Infection in Long-Term Care Facilities*, https://doi.org/10.1007/978-3-030-29772-5_5

clinicians are understandably concerned when suspecting CDI in one of their patients and keen to test to see if *C. difficile* is present in the stool. However, the presence of *C. difficile* in the stool is not sufficient to diagnose CDI, and the diagnostic tests currently commercially available for testing are complex. In 1935, Dr. Ivan Hall and Elizabeth O'Toole first identified and named *Clostridium difficile* (originally *Bacillus difficilis*) because the organism was difficult to isolate and grow in culture [2, 3]. CDI is a toxin-mediated infection and, therefore, diagnostic assays often focus on the presence of toxin as a necessary component to develop infection, as opposed to colonization with non-toxigenic *C. difficile* strain.

Clinical Manifestations of CDI

Patients with CDI must have loose and unformed stools. However, patients can also be asymptomatic carriers of *C. difficile*, and therefore, the clinical scenario in which a clinician decides to test for CDI is paramount to appropriate diagnosis. While CDI is common in the elderly and LTCF patients and the most common bacterial cause of acute diarrhea in this population, so too is asymptomatic carriage either upon facility admission or acquired during their stay [8].

Recent clinical guidelines for CDI cite that patients with suspicion of CDI must first have ≥3 unexplained and new-onset unformed stools in 24 hours [4]. There are many important pieces of this guideline statement to highlight here. First, patients much have diarrhea to be considered for CDI testing. Diarrhea is defined as an unformed stool that occurs at least three times within 1 day. Patients who are having formed stool should not be considered as having CDI, and therefore, clinical laboratories will refuse to test a formed stool specimen for *C. difficile.* A second notable part of the guidelines is that the unformed stool must be new and unexplained to be appropriate to consider for CDI testing. Therefore, a patient with a history of chronic diarrhea with no change from baseline is not appropriate for testing for CDI. As specifically detailed in the guideline, "If a patient has diarrheal symptoms not clearly attributable to underlying conditions (inflammatory bowel disease (IBD)

and therapies such as enteral tube feeding, intensive cancer chemotherapy, or laxatives), then testing to determine if diarrhea is due to *C. difficile* is indicated. Alternatively, testing may be indicated if symptoms persist after stopping therapies to which diarrhea may be otherwise attributed (e.g., laxatives)" [4]. Therefore, all medical conditions, medications, and baseline stool history must be reviewed prior to consideration of *C. difficile* testing. Notably, patients with IBD and on enteral feeds are at increased risk for CDI, and thus, true infection should be suspected when these subgroups of patients have new or worsening diarrhea.

As described in previous chapters, it is critical to determine whether a patient has recently been exposed to antibiotics, as antibiotic disruption of microbiome remains the top risk factor for developing CDI. However, no recent history of antibiotic exposure has precluded the possibility of CDI in a patient with appropriate symptoms and other relevant risk factors for infection (e.g., age, recent hospitalization or stay in LTCF). Severe signs and symptoms of colitis could also aid in the diagnosis and often include lower quadrant pain, distension, and fevers. Typical laboratory evaluation reveals WBC > 15,000 and elevated serum creatinine >1.5 for severe disease. Fulminant disease is often characterized by hypotension, ileus, and megacolon. Lastly, CDI cause recurrent infections in which symptoms recur from days to months after completing appropriate CDI treatment.

Laboratory Testing

C. difficile is not typically cultured in the clinical laboratory, like other bacterium, due to the difficulty of culturing – hence the name *difficile*! [2, 3]. Instead, there are generally multiple types of diagnostic tests available to detect the *C. difficile.* Specifically, there are currently two reference standard assays commercially available for *C. difficile* testing; however, the utility for these testing is limited as they require a very high level of technical expertise. Cell cytotoxicity assay (CCTA) measures the presence of free *C. difficile* toxin (A or B) in the stool by detecting abolishment of cytopathic effect in cell culture by anti-toxin. This test has been shown to have a sensi-

tivity of 67–90% and is not often used due to the technical expertise required to properly conduct the assay. Cytotoxigenic culture (CC) requires culturing the bacterium from stool; if present, then it determines if the *C. difficile* strain present produces cytotoxins. This is considered the "gold standard" for testing in laboratory; however, it has limited utility in the clinical setting as isolating the bacterium is difficult and the turn-around time is not compatible with clinical need. Stool cultures alone – without toxin confirmation – has a low specificity due to prevalent asymptomatic carriage, especially in LTCFs [6, 8].

Enzyme immunoassay (EIA) testing has been commercially available for decades. These assays are rapid and do not require extensive technical expertise. These assays look for the presence of *gdh* or *tcd A/tcd B* – the genes that encode for glutamate dehydrogenase (GDH, *gdh*) [6]. GDH is a universal protein that is found in all strains of *C. difficile*. While this test is sensitive and useful to detect *C. difficile*, it is not able to differentiate between the toxigenic and non-toxigenic strains of *C. difficile*. GDH assays have a low specificity of 75–92% and a high sensitivity of 94.5% for true infection, necessitating it be used in combination with other assays [6].

There are numerous commercial tests available for CDI that look for the presence of one or both of the cytotoxins produced by *C. difficile* toxin B gene (*tcdB*) or toxin proteins. While EIA for *C. difficile* toxins A and B has a sensitivity of 69–99%, the test does have a very high specificity of 94–100% [6]. NAAT assay uses polymerase chain reaction (PCR) to identify the gene that encodes of toxin B (*tcdB*). Research has shown that clinically relevant CDI is caused by strains that produce either toxins A and B or toxin B alone [1]. However, while NAAT can determine the presence of toxin producing strain, it is not able to determine if there is active toxin production. Therefore, while this assay has a high specificity of 94–100% [6], it is unable to distinguish CDI from asymptomatic carriage. This limitation highlights the need to test stool only in appropriate clinical settings and scenarios.

Due to the diagnostic limitations of each individual testing modality, current *C. difficile* diagnostic guideline recommends using a multistep, algorithmic approach to *C. difficile* diagnosis [4]. Based on current guideline, the first step in CDI diagnosis is that clinicians and laboratory personnel should first agree on the

appropriate patients and stool samples on which to do *C. difficile* testing – patients not on laxatives who have ≥3 new and unexplained unformed stools within 24 hours of testing [4]. If this agreement can be reached, then the recommended algorithm is NAAT alone (PCR for toxin) or stool toxin test (EIA) that has highest sensitivity reported [4], instead of toxin test alone. However, if clinicians and laboratory personnel do not have institutional agreement on diagnostic criteria, the guidelines instead recommend stool toxin assay as part of a multistep algorithm that can include GDH plus toxin if NAAT is positive or NAAT plus toxin assay, instead of just NAAT alone [4]. With proper diagnostic algorithm, repeat testing within 7 days of initial sample is not indicated [4].

To simplify these recommendations, optimal diagnostic testing for CDI is to use combined assay for GDH plus toxin with or without NAAT or use NAAT plus toxin assay. NAAT alone is not recommended without institutional criteria for stool specimen submission based on clinical criteria.

Consequences of False-Positive/-Negative Testing

It is necessary to choose the proper laboratory testing due to the consequences of false-positive or false-negative results.

False-positive testing – a patient tests negative for CDI but the laboratory tests are positive – will likely lead to a patient having increased and unnecessary CDI treatments with antibiotic that will further increase the patient's risk of ultimately developing CDI as well as developing antimicrobial resistance.

False-negative testing – a true case of CDI where the laboratory tests are negative – may lead to inappropriate discontinuation of CDI treatment and increased risk of poor outcome from infection, especially in a vulnerable elderly population.

Surveillance

Diagnostic surveillance for CDI in patients without diarrhea in LTCFs should not be done.

Clinicians and clinical staff must remain vigilant to determine if our patients develop diarrhea. CDI should be considered in our high-risk, LTCF, and elderly patients with appropriate clinical exposure who develop new diarrhea (defined as ≥3 unformed new and unexplained stools within 24 hours of testing). For these patients, prompt clinical and laboratory evaluation with appropriate testing should be performed.

Laboratory testing to determine resolution of infection should not be done. Resolution of CDI is determined based on clinical factors alone. Therefore, if a patient is treated for CDI and their diarrhea resolves, then there is no indication to test again for *C. difficile* to prove the patient is cured [4].

Patients with asymptomatic carriage do not need any further diagnostic testing as long as they remain asymptomatic [9].

Impact of *C. difficile* Testing on the Elderly and Long-Term Care Patient Populations

The elderly, especially in long-term care facilities (LTCFs), are at higher risk of developing infection as increasing age often leads to alterations of the gastrointestinal tract, changes in cellular and humoral immunity, and impaired immunoglobulin production. This allows for more frequent invasion of pathogens causing severe disease. While the majority of true *C. difficile* infections occur in adults 65 and older, a high proportion of LCTF patients are already colonized at the time of admission to the facility [8]. Thus, it becomes even more important to distinguish asymptomatic carriage from clinically significant disease in order to avoid unnecessary administration of antibiotics and breeding of resistance.

The diagnosis of CDI becomes more complicated in the elderly population, as they often do not mount as robust of an immune response to infection and thus do not have the typical systemic signs and symptoms of infection as aforementioned. It has been shown that fever is absent in 20–30% of the elderly as there is impaired thermoregulation with increasing age [5]. Interestingly, a non-specific decline in functional status noted by increasing confusion, falls, or anorexia is often a good surrogate marker for

infection [7]. There is no doubt that having watery bowel movements is an important diagnostic component for CDI and is universal among all ages. Even in the absence of systemic signs and symptoms of infection, there should be a lower threshold to test for CDI in the elderly population, especially if they have a sudden decline in functional status.

References

1. Asempa TE, Nicolau DP. *Clostridium difficile* infection in the elderly: an update on management. Clin Interv Aging. 2017;12:1799.
2. EID Authors. Etymologia: *Clostridium difficile*. Emerg Infect Dis. 2010;16(4):674.
3. Hall IV, O'toole E. Intestinal Flora in new-born infants with description of a new pathogenic anaerobe, *Bacillus difficilis*. Am J Dis Child. 1935;49(2):390–402.
4. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V. Clinical practice guidelines for *Clostridium difficile i*nfection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66(7):e1–48.
5. Norman DC. Fever in the elderly. Clin Infect Dis. 2000;31(1):148–51.
6. Planche T, Wilcox MH. Diagnostic pitfalls in *Clostridium difficile* infection. Infect Dis Clin. 2015;29(1):63–82.
7. Rao K, Micic D, Chenoweth E, Deng L, Galecki AT, Ring C, Young VB, Aronoff DM, Malani PN. Poor functional status as a risk factor for severe *Clostridium difficile* infection in hospitalized older adults. J Am Geriatr Soc. 2013;61(10):1738–42.
8. Simor AE, Bradley SF, Strausbaugh LJ, Crossley K, Nicolle LE, SHEA Long-Term–Care Committee. *Clostridium difficile* in long-term–care facilities for the elderly. Infect Control Hosp Epidemiol. 2002;23(11):696–703.
9. Stone ND, Ashraf MS, Calder J, Crnich CJ, Crossley K, Drinka PJ, Gould CV, Juthani-Mehta M, Lautenbach E, Loeb M, MacCannell T. Surveillance definitions of infections in long-term care facilities: revisiting the McGeer criteria. Infect Control Hosp Epidemiol. 2012;33(10):965–77.