Clostridioides (formerly Clostridium) difficile Infection in Hospitalized Adults: Diagnosis, Prevention and Medical Treatment

Elijah Sadaphal, MD

INTRODUCTION

Clostridioides difficile (*C. difficile*) is a spore-forming, gram-positive anaerobic bacterium that causes antibiotic associated colitis.[1] Frequently after antibiotic therapy, *C. difficile* colonizes the human intestinal tract due to the disruption of normal gut flora.[1] Almost all antibiotics have been associated with the development of a *C. difficile* infection (CDI), but broad spectrum penicillins and cephalosporins, as well as clindamycin and the fluoroquinolones possess a higher risk for CDI induction than other antibiotics.[2] The risk for development of CDI is 8 to 10-fold higher during antimicrobial therapy and the 4 weeks thereafter.[2]

C. difficile infection (CDI) is one of the most common health care-associated infections and is a significant cause of morbidity and mortality, especially among older adult hospitalized patients.[1] There is a 10-fold increased risk for the development of CDI in patients greater than 65 years of age when compared to patients less than 65 years of age.[2] Spores of *C. difficile* are transmitted by the fecal-oral route, and the pathogen is widely present in the environment.[2] Potential reservoirs for *C. difficile* include asymptomatic carriers, infected patients, and contaminated environments because of infected patients.[2]

CDIs are the leading cause of health care-associated infectious diarrhea.[3] *C. difficile* can cause a spectrum of clinical manifestations ranging from an asymptomatic carrier state to mild diarrhea to fulminant disease with toxic megacolon.[1]

Because of the significant morbidity and mortality associated with CDIs, clinicians should be well-informed on how to properly diagnose, prevent and treat *C. difficile*. A successful *C difficile* prevention and treatment program requires early disease recognition, evidence-based treatment and management strategies, and focused antibiotic therapy.[3] Early implementation of medical best practices is imperative for optimal patient outcomes.

DIAGNOSIS

Infection with *C. difficile* should be considered when a patient presents with acute diarrhea, defined by three or more loose stools in 24 hours.[2] Most cases of CDI are linked to healthcare exposure: either hospitalization or residence in a nursing home.[2]

No single test is suitable as a stand-alone to confirm CDI; however, over the past twenty years, diagnostic techniques have changed in line with a greater understanding of the physiopathology of *C. difficile* infection.[4] Diagnosis of an acute CDI is based either on detection of *C. difficile* toxins directly in a stool sample (via an enzyme immunoassay or EIA) or by tests that use amplification of nucleic acid (a nucleic acid amplification test or NAAT).[2]

EIA tests are the most popular because of their longstanding use, low cost and rapid turnaround time (about 1-2 hours).[5] EIA tests detect the presence of *C. difficile* antigens by detecting glutamate dehydrogenase (GDH).[5] Newer generation tests have a sensitivity of 75-85% and a specificity of 95-100%.[5] It is important to note that EIA tests do not distinguish whether a strain of *C. difficile* is toxigenic or not.[5]

Compared to the EIA tests, the NAATs tend to cost more. The NAATs are based on a polymerase chain reaction (PCR), which detects the presence of a toxin encoding gene.[5] This test thus confirms the presence of a *C. difficile* toxin-producing strain, but it does not necessarily mean that the strain is producing toxins at the moment.[5] NAATs have higher sensitivity (80-100%) and specificity (87-99%)

compared to an EIA test.[5] Test results must be taken in consideration of the overall clinical context because patients merely colonized with *C. difficile* do not benefit from treatment.[5]

Proper management of stool specimens is important because the toxin present in a sample is easily degraded at room temperature.[6] Hence, once a stool sample is obtained, it should be stored in a refrigerator (4 °C) and used for testing within the next 24 h.[6] It is not recommended to test stool samples obtained from asymptomatic patients.[2] It is also not recommended to repeat testing for *C. difficile* after successful treatment is completed, as there is a significant proportion of patients who still test positive.[5]

According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) protocols, the best way to optimize diagnosis is to combine two tests.[2] The first test should have a high negative predictive value (the EIA or NAAT).[2] The second test should have a high positive predictive value (the EIA). If the first test is negative, it excludes CDI. If the first test is positive, the second test should be performed. If the second test is positive, it confirms CDI. If the second test is negative, the case needs to be clinically evaluated.[2]

Ancillary radiological studies do not diagnose acute CDI but may reveal complications of fulminant disease. For example, colonoscopy may reveal white to yellow pseudomembranes, typically about 2 cm in diameter, which are irregularly distributed and separated by normal mucosa.[7] Abdominal imaging (X-ray or ultrasound) in patients with CDI reveals distended bowel loops, often with wall thickening.[8] Computed tomography (CT) of the abdomen and pelvis with oral and intravenous contrast is useful in patients with severe CDI, helping to evaluate for the presence of toxic megacolon, bowel perforation, or other findings warranting surgical intervention.[9]

PREVENTION

Formal guidance for prevention of CDI in the acute-care hospital setting was published in 2018 by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.[1] What follows is a brief summary of their recommendations.

Early detection and isolation of patients with CDI is the mainstay of prevention.[1] This requires vigilant screening and rapid testing for any at-risk patient with new onset diarrhea.[1] Patients with suspected or proven CDI should be placed on contact precautions, including assignment to a private room with a dedicated toilet.[1] Disposable gloves and gowns should be put on upon room entry and removed prior to room exit.[1]

Prior to contact with a patient with CDI, health care personnel should perform hand hygiene.[1] Hand hygiene with soap and water is preferred because vigorous mechanical scrubbing and rinsing is more effective than alcohol-based hand rubs for physical removal of *C. difficile* spores.[1] The use of soap and running water also prevents spread of spores.[10] Following contact with a patient with CDI, health care personnel should remove gloves then again perform hand hygiene.[1] Good hand hygiene with soap and water and the use of disposable gloves and gowns are critical to interrupt transmission and prevent CDI.[10] Furthermore, patients with CDI should wash hands with soap and water after using the bathroom, before eating or food preparation, and when hands are visibly soiled.[1]

The spores of *C. difficile* survive in the environment for several months and can be transferred to patients via the hands of healthcare personnel.[10] Additionally, toilets, clinic furnishings, phones, and medical devices (e.g., thermometers, stethoscopes and blood pressure cuffs) may all serve as reservoirs for the *C. difficile* spores.[10] Therefore when possible, disposable medical equipment should be used, since multiuse equipment can serve as reservoirs for transmission.[1] Patient-to-patient transfer of objects (e.g., books or magazines) should also be avoided.[10]

It is critical to pay careful attention to the cleaning of clinical areas where patients with CDI are treated.[1] This includes daily cleaning and cleaning following discharge.[12] Disinfection of clinical areas where

patients with CDI are treated requires use of a sporicidal agent such as bleach or an alternative with a *C. difficile* sporicidal label.[1] Chlorine-based solutions are commonly recommended for environmental cleaning, with 1000 ppm of chlorine concentration being effective, and 5000 ppm being the optimal choice.[11]

Antibiotic stewardship to reduce the unnecessary use of antibiotics plays an important role in both infection control and reducing the incidence of CDI in health care settings.[10] Appropriate testing for specific treatable conditions is important to prevent unnecessary antibiotic prescribing.[10] Antibiotic stewardship programs can significantly aid in the reduction of CDI incidence.[1] Furthermore, targeted restriction of a particular antibiotic agent or class of agents can facilitate control of hospital outbreaks and reduce CDI rates in the community and in health care settings.[1]

TREATMENT

Treatment for patients with acute CDI is dependent on disease severity.[14] Patients with severe or fulminant CDI tend to develop signs of systemic toxicity and warrant admission to an intensive care unit or may require emergent surgery.[14] Cognizant of these considerations, determination of disease severity is left to clinician judgment. Supportive clinical data for non-severe CDI includes a white blood cell (WBC) count of less than 15 000 cells/mL and a serum creatinine of less than 1.5 mg/dL.[1] Severe CDI is associated with a WBC count of greater than 15 000 cells/mL and a serum creatinine greater than 1.5 mg/dL.[1] Fulminant CDI is associated with hypotension, shock or toxic megacolon.[1]

Treatment is warranted for patients with typical manifestations of CDI (3 or more loose stools in 24 hours) with no obvious alternative explanation and a positive diagnostic laboratory assay.[1] Treatment is not indicated in patients who have a positive diagnostic laboratory assay and do not have CDI symptoms.[1]

For treatment for acute CDI (non-fulminant), either vancomycin or fidaxomicin is recommended.[1] The dosage of vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days.[1] Oral vancomycin is bacteriostatic against *C. difficile* and achieves predictably high levels in the colon.[14] Intravenous vancomycin is not effective for *C. difficile* colitis since, during the course of short-term administration, the antibiotic is not excreted appreciably into the colon. Fidaxomicin is bactericidal against *C. difficile* and is not absorbed systemically; it has been associated with a lower recurrence rate than oral vancomycin, but is more costly.[14,15]

It is recommended not to use metronidazole (500 mg orally 3 times a day for 10 days) because this agent had demonstrated a lack of efficacy at achieving a sustained symptomatic cure.[1,14,15] Overall, use of metronidazole has been associated with higher rates of treatment failure.[15] Metronidazole should be avoided in patients who are greater than 85 years of age or who develop CDI in association with inflammatory bowel disease.[1,14,15]

For fulminant CDI, vancomycin is the agent of choice.[1,14,15] The vancomycin dosage is 500 mg orally 4 times per day for 10 days.[15]

The above approach is supported by a meta-analysis including 22 randomized trials of patients with non-severe CDI who were treated with oral vancomycin, oral fidaxomicin, and oral metronidazole.[15] For achieving symptomatic cure, fidaxomicin was modestly more effective than vancomycin (71% vs 61%; relative risk, 1.17; 95% CI, 1.04-1.31).[15] In a randomized trial including more than 600 patients treated with vancomycin or fidaxomicin, initial symptomatic response rates after treatment with fidaxomicin were similar to those after treatment with vancomycin (88% vs 86%).[16] In another randomized trial including 259 patients with non-severe CDI treated with oral vancomycin and 278 patients treated with metronidazole, symptomatic response rates after treatment with metronidazole were inferior to those after treatment with vancomycin (73% vs 81%; P=.02).[17]

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