REVIEW ARTICLE

Clostridioides difficile: An Overview of Current Diagnostic and Infection Prevention Modalities

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Abstract

Clostridioides difficile, previously known as *Clostridium difficile*, has been recognized as an emerging nosocomial pathogen in recent years. Among hospitalized patients, it's a leading cause of increased mortality and morbidity. Earlier *C. difficile* infection (CDI) was not recognized for high morbidity and prolonged hospital stay. But, in last few decades due to uncontrolled usage of antibiotic and immunosuppressive drugs, CDI has increased in frequency and severity. Besides nonmodifiable risk factors, exposure to antibiotics is a single most modifiable risk factor. Various methods for diagnosis of CDI are known these days like toxigenic culture (TC) and cell cytotoxicity neutralization assay (CCNA), available only in reference laboratories. Other methods like enzyme immunoassays (EIA) for toxins A, B, and/or glutamate dehydrogenase (GDH) and nucleic acid amplification tests (NAATs) are routinely used for CDI diagnosis; however, each diagnostic test has some limitations. Early CDI diagnosis is critical for early treatment and effective infection control measures to reduce the morbidity and mortality and preventing outbreak. Poor infection control practices further contribute in spread of CDI and environmental contamination by spores of *C. difficile*. Therefore, a correct and authentic diagnostic modality that can be used to characterize CDI vs colonization and making an effective infection control policy for CDI are urgently needed for prevention of occurrence of CDI.

Keywords: Cell cytotoxicity neutralization assay, *Clostridioides difficile* infection, Enzyme immunoassays, Glutamate dehydrogenase, Nucleic acid amplification test, Toxigenic culture.

Journal of Medical Academics (2019): 10.5005/jp-journals-10070-0043

Introduction

Clostridioides difficile has been recognized as an emerging nosocomial pathogen in recent years. Among hospitalized patients, it's a leading cause of increased mortality and morbidity. The economic impact is throughout the world. In the United States, C. *difficile* infection (CDI) is responsible for approximately 453,000 infections and 29,000 deaths almost every year, with a high economic burden.[1,2] According to a recent report, the prevalence in India is 15–20% in patients taking antibiotic.[3] It has also been reported that 3–5% of healthy adults are asymptomatic carriers reflecting colonization due to the widespread use of antibiotics.[4]

Clostridiodes difficile infection causes a spectrum of diseases, which range from antibiotic associated diarrhea (AAD), which is self-limiting most of the times to life-threatening pseudomembranous colitis and toxic megacolon.[5] Many risk factors are independently associated with development of clinical disease. The risk factors that are of most concern and described in various literature include antibiotic exposure, advanced age, prolonged stay in hospital, severe chronic disease, and usage of antacids.[6]

Clostridioides difficile is an anaerobe, gram-positive bacilli, spore-forming, that presents in the soil and colonize gut of humans and animals. Based on genetic studies of *C. difficile*, more than hundred strains are known. *Clostridioides difficile* possesses two forms: the spore form that is resistant to antibiotics and sensitive to chlorine-containing disinfectants and a vegetative form that is responsible for toxins production and susceptible to antibiotics.[7]

Till 1980s and 1990s, CDI was not recognized for high morbidity and prolonged hospital stay. But, in last few decades due to uncontrolled usage of antibiotic and immunosuppressive drugs, CDI has increased in frequency and severity. Therefore, it's highly needed to reevaluate various diagnostic tests for CDI and formulate effective strategies for prevention of spread of *Clostridioides difficile* in the hospital as well as in the community.[7]

The hands of healthcare staff, contaminated with *C. difficile* spores, and environment contaminated with *C. difficile* spores are mainly responsible for its spread to other patients in a healthcare facility. The exposure to antibiotic agents is the single most significant risk factor for development of CDI. Various antibiotics have been found associated with CDI but fluoroquinolones, carbapenems, clindamycin, and third-/fourth-generation cephalosporins[8,9] have been found strongly associated with this condition. The exposure of these antibiotic drugs increases the risk of CDI because it suppresses the microbiota, thereby providing an opportunity for *C. difficile* to multiply and colonize. Poor infection control practices and uncontrolled antibiotic prescription in India are major causes for increased occurrence of nosocomial spread of CDI. The newly identified hypervirulent strains such as *C. difficile* B1/NAP1/027 is partly responsible for fulminant *C. difficile* colitis. This clone expresses a binary toxin (CDT) and the two other large-molecule toxins, Tcd A and Tcd B.[1,2] This strain is responsible for a

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How to cite this article: Kishore S, Banerjee P, Makkar A. *Clostridioides difficile*: An Overview of Current Diagnostic and Infection Prevention Modalities. J Med Acad 2019;2(2):61–64.

Source of support: Nil

Conflict of interest: None

higher number of urgent colectomies and increased number of case fatalities.[10]

Antibiotics recommended for CDI are metronidazole, vancomycin, and fidaxomicin, but emergence of strains less susceptible and even resistant to these antibiotics indicates a serious problem and left very limited options to treat CDI.[11] Recurrence following antibiotic treatment is another problem. The recurrence rate of CDI varies from 25 to 60% and requires antibiotic treatment. Metronidazole is the drug of choice. However, recurrence is seen in 50% of patients treated with metronidazole. Among treated patients, fecal excretion of *C. difficile* continues even after 2–3 months.[12]

Early detection of *C. difficile* and its capability to produce toxins is immediately required to initiate specific treatment and effective infection control measures to reduce the morbidity, mortality, and preventing outbreak. Many laboratory tests for the diagnosis of CDI are available now. However, the epidemiology of CDI has highly changed, with increasing number CDI and emergence of hypervirulent strains during the last few decades. Therefore, an optimized and accurate diagnostic modality able to differentiate CDI and colonization and effective infection control policies are urgently needed for prevention of occurrence of CDI. In this review, we will discuss both current diagnostic modalities and infection prevention and control measures for CDI.

Current Laboratory Diagnostic Strategies

For prevention of CDI in hospitalized patients, early diagnosis is one of the essential steps. Diarrhea is a key clinical manifestation, and presumptive diagnosis should be made in light of risk factors, increased leukocyte count, and underlying disease or immunodeficiency.[13] The definition of diarrhea is passage of three or more loose stools (corresponding to Bristol stool chart types 5–7) over 24 hours.[14] The laboratory parameters suggested by the European Society of Clinical Microbiologist includes increased leukocyte count (leukocyte count >15 × 10^9/L), reduced blood albumin (<30 g/L), and an increase in the blood creatinine level (≥133 μM or ≥1.5 times the premorbid level) for severe CDI.[13] The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA) have also given guidelines to differentiate mild, moderate, and severe disease on the basis of laboratory test reports. Severe disease such as colitis is associated with a WBC count that is 15,000 cells/mL or higher and a serum creatinine level higher than 1.5 times the premorbid level.[15]

For specific diagnosis of CDI, several methods are recommended including the toxigenic culture, toxin detection in the specimen by the cell cytotoxicity neutralization assay (CCNA), enzyme immunoassays (EIA) for toxins A, B, and/or glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAATs) for detection of toxin genes.[14]

The CCNA is performed by a standard process of preparation of the stool filtrate. Many cell lines are mentioned in scientific research literatures like human diploid fibroblasts, Hep2 cells, MRC-5 lung fibroblasts, Vero cells, and McCoy cells. The fixed volume of the stool filtrate is applied on a monolayer of appropriate cell line. After 24–48 hour of incubation, toxin-induced cytopathic effects (CPEs) are observed by trained laboratory staff. If CPEs are observed, a neutralization assay is performed to ensure that CPE is attributable to CD toxin and not due to nonspecific toxicity.

The CCNA was considered as a gold standard test historically but many factors suggested by experts make it not suitable to be a gold standard. The sensitivities documented in various research articles varied between 65 and 90%. Requirement of expert and well-trained laboratory staff, laborious process, prolonged turnaround time, and a costly infrastructure are some other factors to consider it suboptimal as a gold standard.[7]

The role of cycloserine and cefoxitin is well established as a selective agent in the cycloserine, cefoxitin, and fructose agar (CCFA) culture medium. The CCFA is most commonly used for toxigenic culture of *C. difficile*.[16] The pretreatment of the specimen with "heat shock" or "alcohol shock" further reduces the growth of commensals and contaminants. This selective and differential medium helps in distinguishing suspected colonies. The selected colonies are presumptively tested by Gram stain, biochemical tests (spot indole positive), and hydrolysis of L-proline-naphthylamide ("PRO Disk" positive). Commercial biochemical methods, such as the Remel RapidANA II system can also be used for identification. The matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is also used as a rapid and reliable tool to identify *C. difficile* by some laboratories.[14]

After confirmation of *C. difficile*, the next step is to determine the potentiality of toxin production by the CCNA test using the culture supernatant of broth culture of *C. difficile*. *Clostridiodes difficile* toxins can also be detected by using commercially available toxin EIAs. Toxigenic culture is usually considered a reference method rather than a routine diagnostic test. Because of the laborious process and turnaround time, toxigenic culture is not usually considered a routine diagnostic test but as a reference method. Another disadvantage is to detect the ability of toxin production *in vitro*, which does not always inform *in vivo* production of toxin in the host. Although SHEA/IDSA guidelines support the use of toxigenic culture as the gold standard for comparison of different tests in research work.[15]

Several commercially available toxin-EIAs are available. ProSpecT Toxin A/B (Remel Products, Thermo Fisher Scientific) and *C. difficile* Tox A/B II (TechLab, Inc.) are commonly used for presence of toxins A and B. Other EIAs such as C. Diff Chek-60 and C. Diff QuikChek (TechLab, Inc.) are designed to check GDH. These tests are relatively less laborious, low cost, and a big setup is not required, but their specificity and sensitivity are not proven very good. The specificity of the toxin-EIAs varies widely, and sometimes their positive predictive values (PPVs) are inadequate for a diagnostic test.[17] The disadvantage of GDH-EIA is the cross-reactivity because of production of similar enzymes by other nontoxigenic clostridioides species.[18,19] Therefore, in 2009 EIAs combining GDH-EIA and toxin-EIA were developed to detect toxin A/B simultaneously with GDH presence. These combinations test provided easy, cost-effective, and rapid method for diagnosing CDI with long shelf life under storage guidelines provided by manufacturers. The test result may be available in 30 minutes with specificity reported 98%. A negative outcome with GDH-EIA is considered sufficient to rule out CDI.[14] Samples that are toxin negative but GDH positive should be confirmed by CCNA or a molecular test to confirm CDI.[20]

Nucleic acid amplification tests possess many advantages over EIAs or culture testing. These tests have the following characteristics: highly sensitive and specific, less complexity, easy to report and interpretation, reduced need for repeat testing, and less turnaround time. The commercially available NAATs include a

loop-mediated isothermal amplification (LAMP) assay and a real-time PCR (RT-PCR) assay. It has been noted that the sensitivity of GDH screening tests for *C. difficile* is lower than that using NAATs, and NAATs for *C. difficile* toxin genes are superior to toxin-EIA testing as a standard diagnostic test for CDI.[19] The toxin-encoding genes, TcdB and TcdA, are the targets of most NAATs.[21] Further development of multiplex NAATs ensures the detection of *C. difficile* strains and toxin-encoding genes from stool samples.[22] The FDA approved Film Array Gastrointestinal panel a multiplex nested PCR detects 23 stool pathogens with sensitivity and specificity for detection of *C. difficile* 95% and 99% respectively[23]

Few disadvantages of NAATs are not able to correctly differentiate between CDI and colonization and not obtaining the antibiotic resistance status of the strain. Failure to differentiate between *C. difficile* colonization and disease sometimes leads to overdiagnosis of CDI and such overdiagnosis can lead to unnecessary treatment of CDI, delayed diagnosis of other causes of diarrheal illness, unnecessary intake of antibiotics by the patient for treatment of CDI, and false increase in CDI rates of the hospital.[24,25] As per guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the two-step algorithm approach for diagnosis should be adopted for clinically suspected CDI patients. Samples with a negative result from either NAATs or GDH-EIA tests can be reported as CDI negative, but those having a positive result should be further confirmed by a toxin-EIA. Samples confirmed by this second toxin-EIA test can be reported as CDI positive.[26]

Infection Prevention Consideration

An effective infection control policy should be adopted by the hospitals to reduce the CDI rate. In the present era, prevention of CDI is utmost required for improving quality of health care as well as to reduce the economic burden on the society.

Case Definitions

Passage of three or more loose stools per day or occurrence of toxic megacolon without any other established etiology and one or more of the following positive test or examination: (1) Toxin A and/or B detection from the patient's stool sample yields a positive result by the laboratory assay or toxin-producing strain of *C. difficile* isolated from the stool sample by culture; (2) endoscopic examination shows pseudomembranous colitis; and (3) diagnosis of pseudomembranous colitis is made on histopathological examination.[27]

CDI Surveillance Definitions[27]

- Healthcare facility-associated CDI: passage of three or more loose stools per day or other CDI signs and symptoms after 3 days of admission to a healthcare facility, with 1st day is the admission day.
- Community-onset, healthcare facility-associated CDI: passage of three or more loose stools per day or other CDI signs and symptoms onset outside the healthcare facility in the community or within 3 days of admission in a healthcare facility, with onset of symptoms was less than 4 weeks after the last discharge from a healthcare facility.
- Community-associated CDI: passage of three or more loose stools per day or other CDI signs and symptoms onset outside the healthcare facility in the community or within 3 days of admission to a healthcare facility, with onset of symptoms was more than 12 weeks after the last discharge from a healthcare facility.
- Indeterminate-onset CDI: CDI patient who does not fit any of the above definitions, onset in the community greater than 4 weeks but less than 12 weeks after the last discharge from a healthcare facility.
- Recurrent CDI: recurrent episodes of CDI occur less than or equal to 8 weeks after the onset of a previous episode, with previous episode resolved.

Prevention Strategies

One of the basic step for prevention of hospital acquired infection (HAI) is good hand hygiene practices of healthcare workers (HCWs). An effective hand hygiene policy and its implementation can significantly reduce the spread of CDI. Although the hand hygiene compliance rate is established as an important quality standard by various accreditation bodies, the hand hygiene compliance rate is often ignored in hospitals. As infection is transmitted by spores, present on contaminated hands of HCWs, alcohol-based hand rub is not suitable as spores are not destroyed. Therefore, handwashing with soap and water is recommended by the WHO after touching patients infected or suspected to be infected with *C. difficile*.[28] The WHO's "FIVE MOMENTS OF HAND HYGIENE" must be followed as standard precaution during patient care. A hand hygiene awareness campaign should be conducted for HCWs and visitors by infection control professionals. Hand hygiene role models should be selected and rewarded by infection control professionals for motivation at least annually.

Contact precautions are recommended for patients infected or suspected to be infected with *C. difficile*. The treating doctor and healthcare professional should be immediately informed if the patient is passing three or more loose stools to initiate infection control measures and early sample collection for laboratory testing. Patient placement in a single private room is recommended. In case of unavailability of a single room, these patients should be cohorted. Dedicated bedside commode should be provided to patients and at outside of room a contact precaution signage board should be fixed. The PPE donning and removing steps cards should also be fixed near the PPE box. The PPE must be discarded in an appropriate biomedical waste (BMW) container after attending the patient. In CDI patient rooms, dedicated equipments are more suitable to use as infection control measure but in case of unavailability single-use disposable equipments like thermometer, blood pressure cuff, etc., should be used. The stethoscopes should also be restricted to each CDI isolation room. The CDC recommends contact precautions to be continued for full duration of admission of *C. difficile*-infected patients.[29] Although some infection control professionals continue contact precautions in addition to standard precaution for 48 hours after passage of solid stool or till diarrhea resolves.

Environmental decontamination is another necessary step in this scenario as *C. difficile* spores can remain viable on surfaces for months. Quaternary ammonium compounds are not good as this environmental-decontaminating product lacks sporicidal activity. Therefore, use of 1% sodium hypochlorite solution is advised for routine cleaning of the CDI patient isolation room.[27,28] The environmental cleaning staff must be trained about making proper dilution. The environmental cleaning staff should also be aware about appropriate use of PPE during the cleaning process.

Terminal cleaning after CDI patient discharge or suspected CDI patient death is highly recommended. The high-touch surfaces must be effectively disinfected with 1% sodium hypochlorite solution. The contaminated gloves must be immediately discarded after the cleaning process.

Antimicrobial stewardship helps in reducing CDI. The antibiotics with established association of CDI like cephalosporins, fluoroquinolones, clindamycin, and ampicillin should be given with caution under close monitoring. In recent studies, usage of fluoroquinolones has been linked with acquiring the hypervirulent BI/NAP1/027 strain of *C. difficile*.[27,28] Inappropriate and unnecessary use of antibiotics must be prohibited to reduce the occurrence of CDI. Treating infected patients rather than colonized patients should be encouraged.

In conclusion, a rapid and accurate diagnostic approach for CDI along with good infection control practices are key steps for the prevention and control of CDI. The two-step algorithm test policy should be adopted by the hospitals where CDI patients are admitted to prevent overdiagnosis and overtreatment. To reduce the CDI rate, antimicrobial stewardship and implementation of basic infection prevention measures like proper hand hygiene, justified use of PPE, and environmental disinfection in addition to expanded precaution should be adopted and imposed by the hospital administration and the infection control department, which are commonly overlooked.

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