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RESEARCH ARTICLE

CLOSTRIDIUM DIFFICILE MOST COMMON HOSPITAL ACQUIRED INFECTION: REVIEW

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ABSTRACT

Clostridioides difficile is the most important cause ofhealthcare-associated diarrhoea. The high incidence andrecurrence rates of C. difficile infection (CDI) is associatedwith high morbidity and mortality. Antibiotics targeting C.difficile bacteria are the first treatment choice. Recurrent CDIinfection is due to antibiotics which disrupt the indigenous gutflora there by creating an environment that is favourable for itsgrowth. Antibiotic-resistant strains of C. difficile, hasincreased the challenge of treating CDI . It has come among thefive emerging resistant threats. The evolution of antibioticresistance in C. difficile involves the acquizition of newresistance mechanisms, which can be shared among variousbacterial species and different C. difficile strains withinclinical and community settings. This review provides a summaryof commonly used diagnostic tests and antibiotic treatmentstrategies for CDI. It aims to enhance our current understandingand pinpoint knowledge gaps in antimicrobial resistancemechanisms in C. difficile, with an emphasis on CDI therapies.This can be associated with the appearance of hypervirulentepidemic isolates of ribotype 027. The aim of this review articleis to characterise C. difficile as a new member of the"superbug" family. Due to its worldwide spread, the lack ofmany treatment options and the high rates of both recurrence andmortality, C. difficile has emerged as a major concern for thehealthcare system

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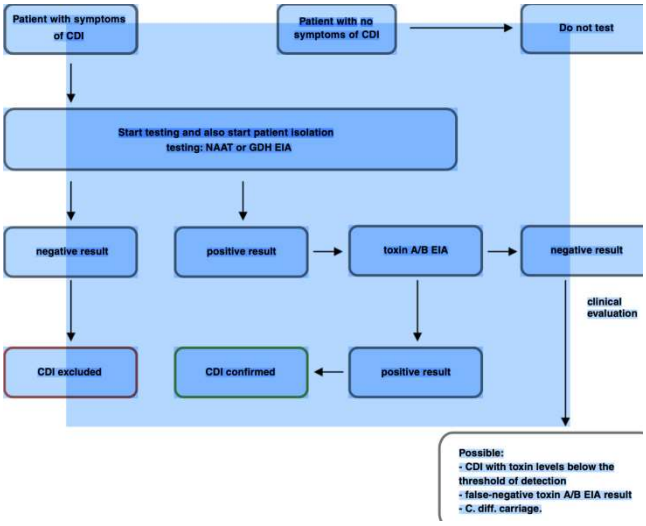
INTRODUCTION

Clostridium difficile infection (CDI) occurs when there is a shift in the colonic microbial flora. This shifts allow toxin-producing strains of the Gram-positive, spore-forming, anaerobic bacillus to over proliferate (1). Antibiotic exposure is the most important risk factor for CDI as its consumption results in a reduction in the population of non-pathogenic anaerobes that normally inhabit the gut providing protective immunity (2). *C. difficile* infections (CDIs) are known to be one of the most common nosocomial (hospital-acquired) infections which is frequently increasing morbidity and mortality in adult hospital patients (3).The clinical features of **C.** difficile infections (CDIs) can vary, ranging from the asymptomatic carriage and mild self-limiting diarrhoea. Sometimes it can cause severe and fatal pseudomembranous colitis. Clinical manifestations of CDI commonly include fever, leuko-cytosis, abdominal pain and profuse watery diarrhea (4). CDI generally occurs from strains that produce two exotoxins, toxin A (*tcdA*) and toxin B (*tcdB*) (5), (6). A third toxin (clostridium binary toxin, CDT) has been identified in approximately 20% of *C. difficile* strains (7),(8),(9). Strains that produce CDT, such as PCR ribotype 027/North American pulse-field type 1, restriction endonuclease analysis type B1 strain (NAP1/B1/027 or RT-027), are often associated with severe disease and are known as hypervirulent strains (10).

LABORATORY DIAGNOSIS: The clinical picture of CDI is very heterogenous, and ranges from the asymptomatic carrier state, mild or moderate diarrhea, to life-threatening fulminant colitis. Although the incubation period is not precisely defined, and some reports suggest 2–3 days, more recent studies demonstrate that the incubation period might be even longer than 3 days and is very individual-dependent.In the most severe clinical presentation of CDI, symptoms are life-threatening, and include significant dehydration, abdominal distension, hypo- albuminemia with peripheral edema, and subsequent circulatory shock. Diagnostic tests include nucleic acid amplification testing (NAAT), enzyme immunoassay (EIA), cell culture cytotoxicity assay, and selective anaerobic cultures. The 2017 Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) guidelines recommend testing patients with unexplained new-onset diarrhea with three or more unformed stools in 24 hours (11).According European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidance, no single test is suitable as a stand-alone test confirming CDI. The best way to optimize

diagnosis of CDI is to combine two tests in algorithm. The first test should be a test with high negative predictive value (it can either be a GDH EIA or NAAT). The second test should be a test with a high positive predictive value (it is toxin A/B EIAs). If the first test is negative, it excludes CDI. If the first test is positive, the second test (toxin A/B EIAs) 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. If GDH EIA is positive, additional testing must be done to confirm the presence of a toxigenic strain. An EIA testing for toxins A and B should also be performed. It should be noted that EIA for toxins A and B have a high false-negative rate due to the large amount of toxin needed for a positive test (12). Radiography of the abdomen and pelvis is usually warranted in patients with severe colitis. Plain abdominal X-rays may show dilated bowels as well as classic signs of bowel edema and inflammation called "target signs" and "thumb printing" (13). For patients with primary infection of CDI, metronidazole should be considered over vancomycin or fidaxomicin for only the mildest cases (14). However, it is important to note that depending solely on molecular tests may result in overdiagnosis, unnecessary treatment and elevated healthcare costs associated with CDI Tox−/PCR+ patients showed a lower bacterial load, less antibiotic exposure and fewer complications compared to Tox+/PCR+ patients. The management of CDI primarily relies on three antibiotics: metronidazole, vancomycin and fidaxomicin, which are routinely employed in its treatment (15). Based on this knowledge, there are studies on intravenous administration of immunoglobulins as well as monoclonal antibodies that may be useful in both the treatment and prevention of CDI recurrences.



TREATMENT: The management of CDI primarily relies on three antibiotics: metronidazole, vancomycin and fidaxomicin, which are routinely employed in its treatment. Belonging to the macrocyclic lactones (macrolide) class of antimicrobial agents, fidaxomicin is unique in its narrow spectrum of anti-bacterial activity (16). Treatment should only be started in patients with CDI symptoms; presence of the *C. difficile* toxin without symptoms of the infection is not an indication for treatment. In 2014, the ESCMID guidelines were published in which two drugs metronidazole and vancomycin were the cornerstone of CDI treatment. Metronidazole was first-line drug in non-severe CDI, while vancomycin was the drug of choice for severe CDI (17). If there is high suspicion of CDI with a negative ELISA assay, it is reasonable to start empiric antibiotic therapy for CDI.

Other antibiotics that show activity against C. difficile include teicoplanin, tigecycline, bacitracin, and nitazoxanide. The role of probiotics in the treatment and prevention of CDI is completely unknown. There are studies on intravenous administra- tion of immunoglobulins as well as monoclonal antibodies that may be useful in both the treatment and prevention of CDI recurrences (18). Bezlotoxumab (a monoclonal antibody that binds to C. difficile toxin B) was approved by the FDA in 2016 for prevention of recurrent CDI in patients with high risk of CDI recurrence (19). The fecal microbiota transplantation (FMT) procedure has been known for over 1000 years. The first report about fecal transplantation in patient with confirmed C. difficile infection was published in 1983 (20). Antibiotic withdrawal together with FMT have the highest rate of prevention of recurrent CDI among all therapeutic options (21).

CONCLUSION

Antibiotic resistance in *C. difficile* is a global concern, marked by a rise in multidrug resistance (MDR) and the emergence of novel, often more virulent, strains worldwide. The evolution of antibiotic resistance in *C. difficile* continues as it acquires new resistance- determining mechanisms. In addition to toxigenic strains, non-toxigenic *C. difficile* strains are gaining significance as a notable reservoir of antibiotic resistance. These strains, prevalent in the natural environment, can colonize both humans and animals, thereby playing a substantial role in disseminating antibiotic resistance. In this regard, continuous surveillance of antibiotic resistance in *C. difficile* isolates from patients is crucial for comprehensing the epidemiology and evolution of *C. difficile*. Moreover, public health surveillance focusing on genomics is essential for understanding and addressing the MDR in *C. difficile*, given its high diversity, mobile resistome and the continual discovery of new resistance mechanisms. Along with monitoring antibiotic resistance over time, practicing antibiotic stewardship and judicious use of antimicrobial agents with minimal impact on beneficial gut bacteria are essential strategies to address the problem. Ongoing research into the resistance mechanisms of *C. difficile*, as well as the development of new antimicrobial agents effective against *C. difficile*, is imperative. Additionally, the pursuit of alternative therapies that boost the host immune response and support gut microbiota and its associated metabolites for CDI should be considered. Ultimately, an effective vaccine would be the most effective way of preventing CDI-associated morbidity and mortality. No FDA-approved *C. difficile* vaccine currently exists; however, clinical trials and research into the development of an effective vaccine against CDI are ongoing.

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