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Review Article

"What's the Deal with Clostridium Difficile?"

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Abstract

Introduction: Clostridioides (Clostridium) Difficile is a serious infection associated with deaths and hospitalizations. According to the Centers for Disease and Control (CDC) Prevention, Clostridioides (Clostridium) Difficile infections (CDI) can be labeled as a threat to healthcare. The introduction of novel agents onto the market have prompted changes in the way we treat CDI, providing clinicians with more robust options, as evidenced by updates to clinical practice guidelines.

Discussion: Exposure to antibiotics (i.e., clindamycin, penicillins, cephalosporins, etc.) are associated with the highest risk in the development of CDI. Presentation can range on a spectrum from asymptomatic carrier to episodic diarrhea to more serious cases such as shock which can lead to death. A proper understanding of risk factors, eliminating unnecessary medications, identifying correct methods in the diagnosis of CDI can help clinicians properly treat patients with the goal to eradicate the infection and prevent recurrence which can lead to a decreased quality of life for the patient.

Conclusions: The approach to the management of CDI in both healthcare institutions and the community involves a coordinated effort between patients, pharmacists and physicians. The recent updates to the guidelines from the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) highlight the value of two novel agents fidaxomicin and bezlotoxumab in treating CDI and its importance in prevention of hospitalizations and recurrence. The economic factors associated with these newer agents and its cost-effectiveness continues to be evaluated through clinical studies.

Keywords: *C. difficile*; IDSA; CDI; bezlotoxumab; SHEA

Introduction

Clostridium difficile (*C. difficile*) is a gram-positive, anaerobic, spore-forming, toxin-producing bacillus. It was originally isolated in the stools of a healthy newborn in 1935 and later renamed to *Clostridioides difficile* in 2016 [1]. Spores are transmitted mainly by fecal-oral route and is widely present in the environment. These spores can survive in the environment for several months and have a multitude of potential reservoirs which include asymptomatic carriers, infected patients, contaminated environments, and animal intestinal tract (canine, feline). On average, 5% of adults and 15-70% of infants are colonized by *C. difficile* and its prevalence is several times higher in hospitalized patients and nursing home residents [1]. While its prevalence is high, its pathogenicity did not become an issue until the introduction of widespread antibiotic use. Even with appropriate interventions such as pharmacotherapy, clinicians today are faced with the issue of treatment failure

and recurrence of the infection which poses a serious problem in the community.

Epidemiology

By the late 1970s, *C. difficile* became the primary cause of antibiotic-associated diarrhea and pseudomembranous colitis (PMC), most of which were attributed to the use of an antimicrobial agent clindamycin.[2] Other antibiotics frequently associated with *C. difficile* infections (CDI) include fluoroquinolones, cephalosporins, and penicillins. By the early 2000s, CDI became more frequent, severe, treatment refractory, and patients were more likely to relapse [2].

According to the Centers for Disease Control and Prevention (CDC), CDI is considered a threat due to increased numbers of hospitalization and rising cases in the community [3].

This increase in severity and frequency of CDI placed a significant financial burden on the US healthcare system. The direct cost of acute care for CDI was estimated to be around $4.8 billion in 2008, while the actual cost was likely higher when considering the indirect costs for the care [2]. The advent of newer and more effective agents on the market such as fidaxomicin and bezlotoxumab have only contributed to the rising costs associated with treating CDI in today's clinical practice.

Pathogenesis

C. difficile infections can be divided into two groups, endogenous and exogenous. Endogenous infections are those transmitted by asymptomatic carriers and exogenous infections are transmitted by infected individuals, contaminated health care workers/environments and from various nosocomial sources.

The infection usually begins with *C. difficile* spores entering a host's gastrointestinal tract. Once in the intestine, the presence of bile acid induces the germinations of spores and the bacteria begin to colonize the host. If during this process, there is an imbalance in the host's gut microbiota, *C. difficile* will start competing for the available resources and may end up being the dominate organism in the GI tract. During this process, the organism will start to produce and secrete two toxins, toxin A (TcdA) and toxin B (TcdB), which are its primary virulence factors. Evidence suggests that TcdA can induce a florid inflammatory response, and TcdB is a potent cytotoxin.

Risk factors

Common patient-specific risk factors for CDI includes antibiotic exposure, older age, hospitalizations, and nursing home residents. Of these, antibiotic exposure is associated with the highest increase in risk of developing CDI. Patients can experience an 8-to-10-fold increase in risk for developing CDI during antibiotic therapy following 4 weeks and a 3-fold increase for the next 2 months [1]. Broad spectrum penicillins, cephalosporins, clindamycin and fluoroquinolones appear to carry the highest risk [4].

Age is another risk factor that can increase the chance of developing CDI. Patients greater than 65 years of age have a 5-10- fold increase in risk when compared with patients less than 65 years of age [5]. These patients not only have an increased of developing CDI but also have a poorer prognosis. This is likely due to a diminished immune response and presence of comorbid conditions which may require additional antibiotic treatment or hospitalization.

Healthcare institutions serve as a vector for *C. difficile*, providing spores numerous opportunities to colonize multiple patients. The longer the hospitalization period, the higher the chances are for *C. difficile* colonization. It should be noted, however, that colonization does not mean symptomatic infections (CDI) but patients are at a higher risk of developing CDI. The high incidence of hospital colonization is likely due to the *C. difficile* spore's ability to survive in harsh environments for several months. Common items such as furnishings (beds, tables), telephones, medical devices (thermometers, stethoscopes) can serve as a reservoir for *C. difficile* spores which can then be transferred to patient. Nursing home residents are also at an increased risk of developing CDI, which is likely due to their age, comorbidities, frequent antibiotic use and frequent hospitalizations. Other risk factors may include inflammatory bowel disease, gastrointestinal surgeries, obesity, chemotherapy, cirrhosis, transplantations, and possibly gastric acid suppression with the use of medications such as proton pump inhibitors [6].

Diagnosis/testing methods

A CDI diagnosis should be suspected in patients that present with symptoms of diarrhea (3 or more loose stools within a 24-hour period) with no alternative explanations, especially in the presence of any relevant risk factors (elderly, hospitalizations, antibiotic use) [7]. Clinicians can evaluate to see if any other causes

such as the use of laxatives to treat constipation can be discontinued.

Over the years, various stool testing methods have been developed as part of a diagnostic algorithm for the detection of CDI which include the following: nucleic acid amplification test (NAAT) which can differentiate between a colonized host versus active infection, Enzyme immunoassay (EIA) for *C. difficile*, which detects *C. difficile* toxins A and B, glucose dehydrogenase (GDH) which detects the presence of antigens, and selective anaerobic cultures [7,8].

Treatment

In *C. difficile* infections, treatment options vary based on disease severity. In their assessment, clinicians must determine whether the patient presents with non-severe disease, severe disease or fulminant disease. Disease severity is based on objective laboratory findings such as elevations in white blood cell count and serum creatinine which can help aid clinicians in their assessment of a patient [9].

According to the 2021 update to the guidelines developed by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America, treatment for a first episode includes the use of one of three agents which include fidaxomicin as the preferred agent, followed by acceptable alternatives such as vancomycin and metronidazole [15].

Fidaxomicin is a macrolide antibiotic which inhibits protein synthesis and results in cell death of *C. difficile*. The dosing of fidaxomicin is 200 mg orally twice daily for 10 days. In their evaluation of fidaxomicin compared to oral vancomycin, Cornely and colleagues found a slightly higher percentage of patients achieving clinical cure rates in the fidaxomicin arm compared to vancomycin as well as a lower rate of recurrence [10].

In their study of economic outcomes with fidaxomicin and 90-day readmission, Gallagher and colleagues found that when used for CDI treatment, fidaxomicin helped prevent readmission and reduced healthcare costs compared to vancomycin [11].

As a novel agent, the high cost of fidaxomicin may prevent patients from access to this first line and effective treatment; however, according to the Centers for Medicare and Medicaid Services (CMS), fidaxomicin is one of several antimicrobial agents that meets the requirement for its new technology add-on-payment (NTAP) program which reimburses healthcare institutions for use of such agents in treating Medicare patients while receiving inpatient care [12].

Vancomycin is a glycopeptide antibiotic that is widely used in clinical practice. In the treatment of *C. Difficile*, vancomycin is a first line agent and the dosing of vancomycin is 125 mg orally twice daily for 10 days. In its oral formulation and administration, vancomycin is associated with minimal systemic absorption. When compared to metronidazole, Zar and colleagues found vancomycin to have a higher overall cure in patients [13]. Vancomycin is available in different formulations such as oral capsules and an oral solution making it a more affordable treatment option.

An alternative for non-severe CDI, if either vancomycin or fidaxomicin are unavailable, is metronidazole 500 mg orally three times daily for 10-14 days. Oral metronidazole is an option for patients experiencing a first episode. In patients who experience fulminant CDI such as hypotension, shock states, ileus or megacolon, metronidazole may be given in its intravenous formulation [7].

In patients experiencing a first recurrence, options include fidaxomicin 200 mg orally twice daily for 10 days or vancomycin 125 mg orally four times daily for 10 days. Vancomycin can also be used in a prolonged tapered regimen. An example is vancomycin 125 mg orally four times daily for 10-14 days, then twice daily for 7 days, followed by once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks. When dosed in a tapered regimen over several weeks, vancomycin is thought to target spores that might potentially cause further recurrences in patients [14].

In 2021, the IDSA/SHEA released a focused update in the treatment of CDI in adult patients. In treating a second recurrence of CDI, the IDSA/SHEA recommends fidaxomicin 200 mg orally given twice daily for 10 days. Another option may include the use of vancomycin in a tapered or pulsed regimen as described above, vancomycin 125 mg followed by rifaximin, and fecal microbiota transplantation [15].

A non-pharmacologic option can include fecal microbiota transplantation (FMT) which involves the process of introducing the stool from a donor to a patient currently experiencing CDI. FMT is only appropriate in patients who have experienced at least 2 recurrences (3 CDI episodes) and who have antibiotic failure [16].

In the 2021 update to the IDSA/SHEA clinical practice guidelines, it now recommends the use of bezlotoxumab 10 mg/kg given intravenously as a single dose during administration of standard of care antibiotics in patients with a history of CDI within the past 6 months [15]. Bezlotoxumab is a human IgG1 monoclonal antibody that binds to and neutralizes *C. difficile* toxin B.

As a novel agent in the treatment of CDI, bezlotoxumab is associated with a high cost to healthcare institutions. Studies are ongoing evaluating the cost effectiveness of this agent in comparison to vancomycin and fidaxomicin.

Bezlotoxumab should be used with caution in patients with congestive heart failure as it was found to be more common in patients during phase III trials [17].

Some adjunct therapies and interventions can include the evaluation of appropriate use of acid suppressive agents such as proton pump inhibitors (PPI); however, current practice guidelines do not have strong evidence to support discontinuing PPI's [2].

Another controversial subject in clinical practice is the use of probiotics as an option due to its effect in providing healthy gastrointestinal flora. Current practice guidelines do not support the use of probiotics due to lack of strong evidence in its favor [7,8].

Conclusion

CDI inflict significant harm in most healthcare systems, resulting in poor patient outcomes due to increased mortality and greater costs due to increased length of hospital stays, therefore, proper diagnosis and treatment are paramount. Although CDI occur primarily in the hospital setting, they are seen in increasing amounts in the community setting as well. However, diagnosis in both hospital and community settings remain a challenge and are often underdiagnosed or misdiagnosed due to lack of clinical suspicion or false positive results from diagnostic testing. Therefore, testing should be a routine part of any patient who experiences any diarrhea in a healthcare setting or unexplainable diarrhea in a community setting.

Two significant guidelines have been updated within the past decade due to the new information regarding *C. difficile* treatment and diagnosis: the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the Infectious Diseases Society of America (IDSA)/the Society for Healthcare Epidemiology of America (SHEA).

ESCMID guidance provided new and expanded definitions for severity compared to old severity guidance provided by IDSA/SHEA which relied solely on serum creatinine levels and leukocytosis. ESCMID expanded upon previous guidance by making it more comprehensive. This more comprehensive approach to stratifying the disease by severity included analysis of imaging, clinical evaluation, colonoscopies and other lab results. ESCMID guidance also identified subgroups who are at increased risk of complications and recurrence. This combination of severity and at-risk subgroups guides treatment in a more specific manner than before. The current guideline places a greater emphasis on the risk of recurrence as a factor to consider when selecting treatment strategies compared to the older guideline which considered disease severity as a more relevant factor.

Compared with the previous guidelines, the updated 2021 ESCMID guidelines highlights a larger role for bezlotoxumab. Metronidazole is no longer recommended for non-severe *C. difficile* infections as long as there is availability of vancomycin or fidaxomicin. The preferred agent for treatment of initial *C. difficile* infection and the first recurrence of *C. difficile* infection is fidaxomicin, while fecal microbiota transplantation or bezlotoxumab is recommended for patients who have a second or further recurrence of *C. difficile* infections in addition to standard of care antibiotics. Additionally, bezlotoxumab in addition to standard of care antibiotics is recommended for the first recurrence of a *C. difficile* infection. Bezlotoxumab is also an option that can be used in addition to vancomycin for patients who have a high risk of recurrence of *C. difficile* infection when fidaxomicin is unavailable [18].

IDSA/SHEA differ slightly from ESCMID guidance. The updated 2021 IDSA/SHEA now prefers fidaxomicin over the standard course of vancomycin in patients who present with an initial *C. difficile* infection and in patients who present with recurrent *C. difficile* infections. A tapered/pulse dose of vancomycin is now an considered to be an acceptable alternative therapy in these patients. For multiple recurrences, a tapered/pulse regimen of vancomycin, vancomycin followed by rifamixin, or fecal microbiota transplantation are options in addition to fidaxomicin. Bezlotoxumab now plays a role in treatment and is recommended for patients with a recurrent CDI episode within the last 6 months as a co-interven-

tion along with standard of care antibiotics, rather than standard of care antibiotics alone. Bezlotoxumab can also provide a benefit in patients with a primary *C. difficile* episode and have other risk factors for CDI occurrence which include age ≥ 65 years, immunocompromised patients, and severe *C. difficile* infection on presentation. Metronidazole remains an alternative agent. Fecal microbiota transplantation is an option for patients who have had appropriate antibiotic treatments for at least 2 recurrences.

Diagnosis and treatment of *C. difficile* infections were relatively simple in the past when data was limited. However, new studies and an improved understanding on the nature of this infection have led to much needed updates regarding proper treatment and diagnosis. New and more efficacious treatment options are now available to practitioners as well as a more sophisticated system of stratifying patients based on severity and at-risk subgroups.

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