Acta Scientific Microbiology (ISSN: 2581-3226)

Volume 7 Issue 1 January 2024

Review Article

Antibiotic and Immunological Alternatives for the Management of *Clostridioides difficile* Infection

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DOI: 10.31080/ASMI.2024.07.1334

Received: December 08, 2023

Published: December 29, 2023

Abstract

Clostridioides difficile is one of the most important healthcare-associated pathogens in both developed and developing countries. Infections caused by this bacterium generate a high cost on health care systems. Traditionally, the management of this infection is given through therapy with antimicrobials such as metronidazole and vancomycin. However, with the increase in resistance to antibiotics and the emergence of hypervirulent and epidemic strains such as NAP1/027, the search for other therapeutic options is essential. The objective of this review is to study the first-line treatment that has been used for this bacterium, as well as to learn about new antibiotic molecules and active and passive immunization strategies that have emerged in recent years as alternative treatments, some of which are still are under investigation.

Keywords: *Clostridioides difficile*; Ridinilazole; Raja 42; Bezlotoxumab; Vaccines

Abbreviations

CDI: *Clostridioides difficile* Infection; FMT: Fecal Microbiota Transplantation

Introduction

Clostridioides difficile is a Gram-positive, spore-forming, strictly anaerobic bacteria, and is considered as one of the most important pathogens in the health care-associated environment of industrialized and developing countries. *C. difficile* infection (CDI) is developed after the ingestion of a toxigenic strain spores through contact with a symptomatic patient or with spores present in the environment [1]. If a patient has a disruption of the intestinal microbiota, mainly due to treatment with antibiotics, the spores can germinate in the large intestine. Besides the intake of antibiotics, other predisposing factors for CID are advanced age, chemotherapy and the presence of chronic diseases [2,3].

Once the infection is established, *C. difficile* manages to develop the disease through the production of two toxins: TcdA and TcdB. Some strains can have a third toxin known as binary toxin (CDT) [4]. The most common clinical presentation is antibiotic-associated diarrhea, but complications such as pseudomembranous colitis, toxic megacolon and fulminant disease can also occur [5]. An early detection and treatment of CDI would help prevent the transmission of the bacteria, and reduce costs to the health systems. The objective of this review is to study the first line of treatment established for CDI and learn about the different alternatives that have emerged in recent years, some of which are still under investigation.

Materials and Methods

A review of published literature (in english and spanish) regarding the pathophysiology, management and treatment of *C. difficile* infections was performed using databases such as PubMed (NCBI), PLOS, Redalyc, Google Scholar and Science Direct. For this purpose, keywords and DeCS terms such as "*Clostridioides difficile*", "CDI treatment", "anti-bacterial agents", "anti-bodies, monoclonal" and "vaccines" were used. The articles found were classified according to the year of publication, and only research and review articles in which the content was completely available were included. Finally, only articles published between 2007 and 2023 and those included in digital journals with a Digital Object Identifier System (DOI), were taken into account.

Results and Discussion

Treatments according to international guidelines against *C. difficile* infection

Treatment of CDI can be classified into non-severe, severe, and fulminant disease according to different guidelines. The guideline published by the American College of Gastroenterology (ACG), for a non-severe episode, recommends the use of oral vancomycin (125 mg) four times a day for 10 days. An alternative option is the use of oral fidaxomicin (200 mg) twice a day for 10 days. In the case of low-risk patients, oral metronidazole (500 mg) three times a day for 10 days can be used. For severe episodes, it is recommended the

use of oral vancomycin and oral fidaxomicin in the same way as for a non-severe case. According to several studies, the use of metronidazole is not recommended since it has been shown to have lower performance than vancomycin for the treatment of severe CDI [6,7]. For example, in a retrospective study, patients with severe infection who received vancomycin only after treatment failure with metronidazole had longer hospital stays, a higher percentage of kidney damage, and a lower curing rate than those who received vancomycin from the time of diagnosis [8].

On the other hand, those patients who are diagnosed with fulminant disease should receive adequate volume replacement therapy and the administration of 500 mg of oral vancomycin every six hours daily for the first 48-72 hours. This can be combined with 800 mg of intravenous metronidazole every 8 hours. Additionally, if the patient has ileus (transient arrest of intestinal peristalsis) the use of vancomycin enemas (500 mg every six hours) can be beneficial [6].

According to different guidelines and studies, an alternative treatment is the fecal microbiota transplantation (FMT), which is recommended for recurrent or antibiotic-refractory CDI [6,9]. This procedure consists of the transfer of fecal microbiota from a screened healthy donor to a recipient. Its objective is to establish a stable and complex microbiota to reverse the phenomenon of dysbiosis (Figure 1) [10]. The effect of FMT on CDI varies according to the method of application and the number of FMT administrations, where endoscopy and repeat FMT are the most effective combination [9].

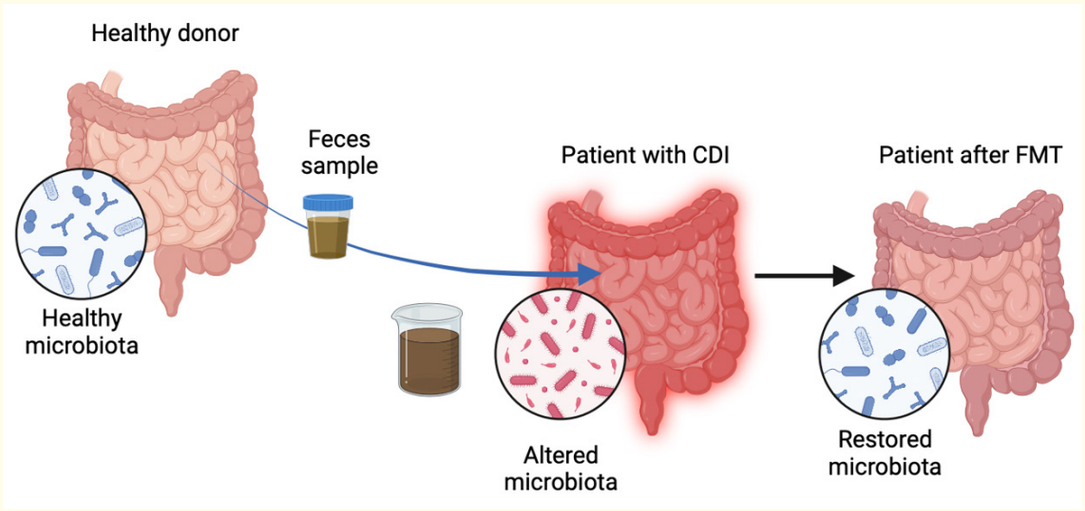

Figure 1: Diagram of fecal microbiota transplantation (FMT) used for the treatment of recurrent or antibiotic-refractory CDI. Source: Own elaboration from reference 6 and 9. Created with BioRender.com.

New antibiotic molecules against *C. difficile* under study

The main approach for treating CDI has been the use of antibiotics. In recent years, a molecule called ridinilazole has been tested. This is an orally administered antibiotic, with a narrower spectrum of action and minimal systemic absorption [11]. The mechanism of action is not known with certainty, but it has been demonstrated that it interferes with bacterial growth by altering the expression of a group of genes involved in cell division. Confocal and fluorescence microscopy studies have also shown that ridinilazole restricts septum formation. The activity against *C. difficile* reduces by up to 91% and 74% the production of toxin A and toxin B, respectively, and consequently, the inflammatory response of the host [12]. Ridinilazole has also shown to preserve secondary bile acids in the intestine, which play a role in inhibiting toxin-producing vegetative cells [13].

An additional advantage of ridinilazole is that, after oral administration, it causes high concentrations of the antibiotic in feces because the absorption in the gastrointestinal lumen is minimal. In *in vitro* and *in vivo* studies, (in both human and murine models), the molecule has demonstrated being effective against different strains of *C. difficile* with variable resistance phenotypes [14,15]. In one of these studies, a range of 0.015-0.5 mg/L was obtained when calculating the minimum inhibitory concentration (MIC) for this antibiotic, a lower value than those recorded for metronidazole (0.125-2 mg/L) or vancomycin (0.5- 8 mg/L), and comparable to the value obtained for fidaxomicin (0.004-0.125 mg/L) [16].

In addition to the powerful activity against *C. difficile*, it has been proven that ridinilazole has minimal interference with the intestinal microbiota. For example, when tested *in vitro* against 350 bacteria commonly found as intestinal microbiota, limited activity was obtained against Gram-negative and Gram-positive anaerobes different than *Clostridium* spp. such as *Bacteroides fragilis*, *Peptostreptococcus anaerobius*, and *Prevotella* spp. [17]. Furthermore, in

phase II studies, samples from patients treated with ridinilazole and vancomycin were analyzed. In the first case, a very limited impact on the intestinal microbiota was demonstrated. However, for vancomycin, an approximately 3-log decrease count was observed in *Bacteroides* spp., *Prevotella*, spp. and *Clostridim leptum* per gram of feces [15].

Phase I studies, designed to elucidate the pharmacokinetics and safety of ridinilazole, have been completed. The survey was done with healthy volunteers who took single and multiple doses of the antibiotic. All doses were well tolerated, and adverse effects associated with the drug were mild, being diarrhea and abdominal pain the most common. Safety and efficacy were evaluated in Phase II studies comparing ridinilazole with vancomycin. Patients who received the antibiotic under evaluation showed a greater and more sustained clinical response than those who received vancomycin. Disease recurrence was observed in 14.3% of patients on ridinilazole versus 34.8% of patients given vancomycin [15].

As for phase III studies, a global, randomized, double-blind study with 759 patients has already been published, in which a 10-day treatment with 200 mg of ridinilazole and 125 mg of vancomycin was evaluated for CDI. The objective was to determine the clinical response and the rate of recurrence of the infection in the 30 days following the end of the treatment. Among the results, ridinilazole achieved a numerically higher sustained clinical response rate than vancomycin (73.0% vs. 70.7%, p=0.4672) and a lower recurrence rate (8.1% vs. 17.3%, p=0.0002). Ridinilazole also preserved the diversity of the intestinal microbiota at a higher level [18].

In addition to ridinilazole, other compounds have been tested as potential antimicrobials against *C. difficile*. Certain isatin-benzothiazole analogs have been synthesized for use as potential chemotherapeutic drugs. One of them, known as Raja 42, has shown to be effective against Gram-negative and Gram-positive bacteria such as *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Helicobacter pylori*. For this reason, its effectiveness against clinical isolates of *C. difficile* was tested. Of the 60 isolates studied, 49 were classified as susceptible. Among these 49, there were some resistant to metronidazole and vancomycin, which raises the possibility that Raja 42 could be designed as an alternative drug for the treatment of patients with *C. difficile* strains resistant to these antimicrobials. Additionally, when estimating the therapeutic index of this compound, it was observed that its toxicity could be lower than the one from vancomycin; however, this must be experimentally proven [19]. With these findings, it is necessary for compound Raja 42 to enter further safety and efficacy studies.

Active and passive immunization strategies against *C. difficile*

On the other hand, there are alternative immunological approaches that have also been investigated for the management of CDI. Bezlotoxumab, for example, is a monoclonal antibody that is administered intravenously, and it is directed against *C. difficile* toxin B in a way that neutralizes its effect. It is currently used as a complement to the antibiotic therapy to reduce recurrence of CDI. Its use as monotherapy for the treatment of the disease is not indicated [20]. In different clinical trials, there was no effect on the clinical cure of the patients, but bezlotoxumab was able to reduce the percentage of recurrent CDI from 27% in the placebo group to 17% in the group that received the monoclonal antibody. This benefit has been limited to patients with risk factors for recurrent CDI such as age over 65 years, immunosuppression, severe disease, among others. In the case of infection with epidemic and virulent strains, despite the fact of being a risk factor, the effect has not reached a statistically significant difference [21,22].

Another approach that has been studied for the prevention of CDI is active immunization through vaccination. The presence of anti-toxin antibodies has been associated with protection against the disease and its recurrences. Pfizer has designed one of the vaccines being tested (PF-06425090). It is based on a genetic and chemical inactivation of *C. difficile* toxins A and B. For this potential vaccine, Phase I and Phase II studies are now ready. They have demonstrated a powerful neutralizing and immune response to the toxin in all groups tested, and adequate safety and tolerance. The adverse reactions observed, both local and systemic, were mild to moderate. Phase III studies are currently underway. The commercial company Valneva has also designed a vaccine (VLA84) which consists of a fusion protein that has portions of TcdA and TcdB. Phase I and II studies are complete and both show good levels of tolerance and safety. In addition, good immunogenicity of VLA84 has been observed since it induces an immune response in young adults and adults comparable to the response exerted by TcdaA and TcdB. Phase III studies have also been completed [11,23]. Despite these advances, none of these vaccines have yet been approved for clinical use.

Even though there is a good IgG antibody response exerted by these vaccines (when administered intramuscularly), *C. difficile* colonization and dissemination is not prevented. For this reason, an approach based on surface antigens of the bacterium is under investigation. Recently, a test with an oral vaccine (CDVAX) containing inactivated *Bacillus subtilis* spores expressing two recombinant *C. difficile* antigens on their surface: a spore colonization factor and a toxoid antigen, was initiated. The adverse effects and immune response on both, systemic and mucous membranes, of this potential vaccine were recently evaluated in a phase I study. However, the results are not yet known, and more research is needed on effectiveness for prevention of CDI [24].

Conclusion

CDI is a public health problem that exerts a very high cost on health systems in both industrialized and developing countries.

Therefore, the development of timely and effective diagnostic, prevention and treatment strategies is important to reduce its impact. The traditional approach to the treatment of CDI has been the use of antibiotics such as metronidazole and vancomycin. The development of new molecules such as ridinilazole and Raja 42 has shown to be effective *in vitro* against *C. difficile* and, in the case of ridinilazole, it has minimal effects on the rest of the intestinal microbiota. With these results, they are potential antimicrobials that would help in the battle of *C. difficile* strains that already show high resistance to certain antibiotics, as is the case of the hypervirulent and epidemic strain NAP1/027.

Immunological approaches to the management of CDI include the use of monoclonal antibodies directed against TcdB, such as bezlotoxumab. This has demonstrated efficacy in preventing recurrences when combined with antibiotic therapy. However, its use as monotherapy for the treatment of CDI is not indicated. Vaccines, on the other hand, are a strategy intended for the prevention of CDI. Currently, most of vaccines that have been designed are pending clinical trials at any stage, but have demonstrated good immunogenicity and safety; nevertheless, efficacy in the prevention of the disease remains to be proven. These therapeutic options deserve more attention and research, as they could be a way to minimize the use of antibiotics and to battle the high resistance that some strains have developed.

Conflict of Interest

The author declares no competing interests.

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