

Clostridium difficile: Current Status and Treatment Perspectives

Beatriz Suay García and
María Teresa Pérez-Gracia

Área de Microbiología, Departamento de Farmacia, Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad CEU Cardenal Herrera, Avenida Seminario s/n 46113, Moncada, Valencia, España.

Corresponding author:
María Teresa Pérez-Gracia

✉ teresa@uchceu.es

Área de Microbiología, Departamento de Farmacia, Instituto de Ciencias Biomédicas, Facultad de Ciencias de la Salud, Universidad CEU Cardenal Herrera, Avenida Seminario s/n 46113, Moncada, Valencia, España

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Abstract

Clostridium difficile is considered one of the most important pathogens in both, hospital and community settings. This pathogen is responsible for most antibiotic-associated colitis in hospitals and a major cause of morbidity and mortality within the elderly. *Clostridium difficile* infection (CDI) usually appears as a result of antibiotic therapy, which disrupts the normal gut flora. *Clostridium difficile* infection presents itself in two very distinct ways, it can be either asymptomatic, with the infected person acting as a carrier, or symptomatic, where patients may experience a broad range of symptoms depending on their severity. Symptoms range from mild diarrhea to severe complications such as pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis and death.

Conventional treatment of CDI consists on antibiotic treatment with vancomycin or metronidazole. However, the number of recurrences after using these treatments is growing exponentially. New molecules such as fidamoxin have been included in treatment guidelines but still; the cases of recurrent CDI continue to grow. As a result, a novel therapy has emerged: fecal microbiota transplants (FMT). It is a procedure in which fecal matter, or stool, is collected from a tested donor, mixed with a saline or other solution, strained, and placed in a patient by colonoscopy, endoscopy, sigmoidoscopy or enema. With its efficacy being proven constantly study after study, it is only a matter of time for health organizations worldwide to include it in the guidelines for rCDI treatment.

Keywords: *Clostridium difficile*; CDI; RCDI; Fecal transplant; FMT

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Introduction

Clostridium difficile is considered one of the most important pathogens in both, hospital and community settings. This pathogen is responsible for most antibiotic-associated colitis in hospitals and a major cause of morbidity and mortality within the elderly. *C. difficile* infection (CDI) is increasing at such a rate that the Centers for Disease Control and Prevention (CDC) have assigned it as an urgent threat due its association with antibiotic use and high morbidity and mortality [1]. In 2010, CDI incidence was estimated at 500,000 cases [2], with treatment costs being around 1 billion dollars in the US alone [3].

CDI usually appears as a result of antibiotic therapy, which, by disrupting the normal gut flora, causes dysbiosis (a change of the normal gut bacterial population), thereby enabling colonization

of the intestinal tract by *C. difficile* [4]. Symptoms range from mild diarrhea to severe complications such as pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis and death [5]. *Clostridium difficile* has the ability to form spores, which introduces further challenges to reduce transmission seeing as these spores can persist in the environment for long periods and require chlorine or peroxide based sporicidal agents or ultraviolet devices for environmental decontamination [6]. It is this characteristic which makes *C. difficile* distinct from other infectious agents common to the healthcare settings. The most common transmission routes for CDI are fecal-oral route and direct contact with contaminated surfaces [7]. Person-to-person transmission, environmental contamination and carriage of *C. difficile* on the hands of healthcare workers have been extensively described [8] but it is the admission of asymptomatic CDI patients

what plays an important role in sustaining *C. difficile* transmission within a ward [9] seeing as their lack of symptoms may result in less strict controls and, therefore, a wider spread of spores within emergency rooms and hospitals in general. CDI treatment is based on antibiotics such as vancomycin and metronidazole [10]. However, about 20% of patients suffer recurrent cases of CDI after the initial treatment and 40-50% after treatment for a second episode [11]. Seeing as conventional treatments fail in up to 50% of the cases, newer treatments such as the fecal microbiota transplantation (FMT) are being used experimentally with positive results [12]. The main purpose of this article is to review the current status of CDI and the latest findings regarding its treatment options.

Clinical presentations

Clostridium difficile infection presents itself in two very distinct ways, it can be either asymptomatic, with the infected person acting as a carrier, or symptomatic, where patients may experience a broad range of symptoms depending on their severity. Asymptomatic CDI is the condition where *C. difficile* is detected in the absence of symptoms of infection. It is thought that these patients are protected from progression of the infection because they can mount a humoral immune response to the clostridial toxins [13]. It is precisely their lack of symptoms what makes them the perfect infection reservoir seeing as they could be spreading toxins without knowing, which would present a risk for other patients and hospital workers [14].

On the other hand, symptomatic CDI has been defined as the presence of diarrheal symptoms along with a stool result positive for *C. difficile* toxins, detection of toxigenic *C. difficile*, or colonoscopic findings demonstrating pseudomembranous colitis [15]. The issue for symptomatic CDI is not the development of clinical manifestations, but the possible appearance of recurrences after receiving the first antibiotic treatment. A study by [16] shows that, out of 1527 patients, 25% developed a first recurrent CDI (rCDI) and 9% went on to suffer two or more rCDIs [16]. Recurrent CDI can turn into a chronic, recalcitrant disease, which can continue for years, leading to a persistent use of antibiotics, repeated hospitalizations, and, in some cases, death [17].

Treatment options

As CDI infection becomes increasingly common, the number of patients who experience failed treatments or recurrences is also growing. Conventional CDI treatment consists in a 10-14 day course of antibiotics such as metronidazole and vancomycin. However, studies suggest that metronidazole is losing efficacy, which leaves vancomycin as the first-line antimicrobial therapy [18]. This led to further research with antimicrobials, which resulted in the approval of fidaxomicin by the US Food and Drug Administration (FDA), the first macrolide antibiotic to be approved in more than 20 years for the treatment of CDI. Early studies showed that recurrence rates of CDI were lower with fidaxomicin than vancomycin [19].

The issue with antibiotic treatment is that it represents a double-edged sword seeing as antibiotics suppress pathogen as well as

protective microbiota, causing adverse effects on the intestinal flora. Vancomycin, being a broad-spectrum antimicrobial agent with activity against most Gram-positive organisms, may ultimately increase susceptibility to rCDI by maintaining a persistently altered state of bowel flora. These cases, where antibiotic treatment is responsible for multiple rCDI, are what have encouraged the development of alternative treatments; with the fecal microbiota transplant (FMT) being the most successful up to now. Early research studies suggested the idea of using probiotics as adjuvants when antibiotic treatment leads to rCDI. In fact, a study by [20] showed that using *Saccharomyces boulardii* as an adjunct to antibiotics decreased the frequency of relapses in those with rCDI when compared to a placebo group (34.6% vs. 64.7% placebo) [20]. This idea triggered more interest in the development on probiotic-based treatments, which ultimately lead to FMT. The rationale behind FMT is simple, by reintroducing normal flora via donor feces, the imbalance in colonic flora, which has been disrupted by antibiotics, is restored, and therefore reestablishing normal bowel functions. It is a procedure in which fecal matter, or stool, is collected from a tested donor, mixed with a saline or other solution, strained, and placed in a patient by colonoscopy, endoscopy, sigmoidoscopy or enema [21]. Another administration option currently under study is the use of encapsulated frozen stool samples [22].

The first FMT dates back to 1958, where fecal enemas were administered to four patients with pseudomembranous enterocolitis, three of which were in critical state, and in all patients symptoms resolved within hours [23]. It was not until 1983 when FMT was used for the first time to treat a confirmed case of CDI [24]. The 65-year-old woman had a "prompt and complete normalization of bowel functions" after receiving the treatment. The year 2013 marked the beginning of controlled trials in which FMT was used to treat rCDI. The first randomized controlled trial proved the efficacy of FMT with a nasoduodenal administration in rCDI patients [25].

Since that first study, approximately 200 patients suffering rCDI with FMT treatment have been reported, resulting in a success rate of 96% [26]. This is proven by studies such as that of [27], where patients with at least 2 rCDI episodes received enema administered FMT, with an overall efficacy of 87.1% and no adverse events related to the treatment. In fact, results are so promising that practice guidelines such as those from the American College of Gastroenterology [28] and the European Society of Clinical Microbiology and Infectious Diseases [29] have already included FMT as a recommended treatment for rCDI.

Conclusion

In conclusion, CDI continues to be a serious threat to the public health, especially in hospital environments. The increasing appearance of recurring CDI after conventional treatments such as vancomycin or metronidazole has opened the path for novel treatments. Of these treatments, the fecal microbiota transplant appears to be the most promising, judging by the results of its early applications. Further research is necessary in order to develop optimal administration routes and treatment protocols.

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