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Fecal microbiota transplantation in the treatment of Clostridium difficile infection: state of the art and literature review

Transplante de microbiota fecal no tratamento da infecção por Clostridium difficile: estado da arte e revisão de literatura

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A B S T R A C T

Clostridium difficile infection is a common complication following intestinal dysbiosis caused by abusive antibiotic use. It presents medical importance due to the high rates of recurrence and morbidity. Fecal microbiota transplantation is an effective alternative for the treatment of recurrent and refractory C. difficile infection and consists of introducing the intestinal microbiota from a healthy donor into a patient with this infection. The exact physiological mechanism by which fecal microbiota transplantation alters the intestinal microbiota is not well established, but it is clear that it restores the diversity and structure of the microbiota by promoting increased resistance to colonization by C. difficile. Several routes of transplant administration are being studied and used according to the advantages presented. All forms of application had a high cure rate, and the colonoscopic route was the most used. No relevant complications and adverse events have been documented, and the cost-effectiveness over conventional treatment has proven advantageous. Despite its efficacy, it is not commonly used as initial therapy, and more studies are needed to establish this therapy as the first option in case of refractory and recurrent Clostridium difficileinfection.

Keywords: *Fecal Microbiota Transplantation. Clostridium difficile. Enterocolitis, Pseudomembranous. Anti-BacterialAgents.*

INTRODUCTION

*Clostridium difficile*is an obligate anaerobic gram-positive bacillus that is part of the intestinal microbiota, both in man and in other animals[1]. It was first isolated in 1935 and so named because of the difficulties encountered in achieving its culture. In 1978, it was identified as the main agent causing pseudomembranous colitis, the sigmoid and rectum being the main sites of involvement[2]. The main virulence factors are its exotoxins, enterotoxin A and cytotoxin B. They are responsible for the destruction of the intestinal epithelium and mucosal injury[3].

In recent years, there has been a dramatic change in the epidemiology of the infection caused by *Clostridium difficile*. It is currently considered a global public health problem. At the beginning of the year 2000, an increase in cases of severe *C. difficile* infection was reported, with a high mortality rate. This increase in the mortality rate is mainly due to the involvement of the elderly and the increase in the use of antibiotics of the fluoroquinolones class. The epidemic arose from the appearance of a hypervirulent strain, which is highly resistant to the antibiotics most commonly used in the hospital environment, the NAP1/BI/027[4].

Infection caused by *C. difficile* is the most common form of nosocomial diarrhea associated with the use of antibiotics in elderly, hospitalized patients. Most infected hospitalized patients are asymptomatic carriers and serve as a silent reservoir for continued dissemination in the hospital setting[5]. The transmission of *C. difficile* occurs through the fecal-oral route, person-to-person, through fomites and instruments of hospital furniture. Bacterial spores remain in the environment for extended

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periods and resist most available disinfectants[6].

The main risk factors are age greater than 65 years, use of laxatives, proton pump inhibitors or histamine, chemotherapy, gastrointestinal surgeries, prolonged hospitalization and especially the use of antibiotics. Historically, clindamycin, cephalosporins, penicillins and more recently fluoroquinolones, are the antibiotics most implicated in this infection[7]. However, any antibiotic may predispose to *C. difficile* colonization, including metronidazole and vancomycin, first-line treatment medications for its treatment[8].

The typical clinical picture is of watery diarrhea with several episodes a day (>3 bowel movements/day), abdominal pain that improves after evacuation, low fever and leukocytosis. More severe cases may evolve with toxic megacolon and intestinal perforation, thereby greatly increasing the mortality rate. Complications include hypoalbuminemia, dehydration, and malnutrition[7]. Diagnosis rests on the clinical presentation (presence of diarrhea or ileus) and microbiological detection of *C. difficile* in the feces (detection of toxins A and B by PCR or coproculture)[3]. To choose the correct treatment, it is important to classify the severity of the disease (Table 1)[9].

Table 1. *Classification of Clostridium difficile based on disease severity.*

Category	Clinical signs and laboratory	Associated risk Factors
Mild to Moderate	Diarrhea with signs of systemic infection, leukocytosis <15.000/ml or serum creatinine<1.5x baseline.	Use of antibiotics, prior hospitalization, long hospitalization, use of Proton pump inhibitors, chemotherapy, chronic kidney disease and presence of nasogastric catheter.
Severe	Systemic signs of infection and/or Leukocytosis ≥15.000/ml or serum creatinine ≥1.5x the premorbid level	Age, infection by the BI/NAP1/027 strain
Severe complicated	Systemic signs of infection including hypotension, Ileus or megacolon.	Same as sever, plus recent surgery, history of inflammatory bowel disease and treatment with intravenous immunoglobulin.
Recurrent	Recurrence in up to eight weeks of the end of the full treatment	Age ≥65 years old, concomitant use of antibiotics, presence of significant comorbidity, use of Proton pump inhibitors and initial increase of disease severity.

Source: Adapted from Bagdasarian N, Rao K, Malani p. Diagnosis and Treatment of Clostridium difficile in Adults: A Systematic Review. JAMA. 2015:313(4):398-408[9].

Most studies and guidelines establish the therapeutic regimens based on the clinical picture, severity, risk of recurrence and complications. The two most commonly used drugs are metronidazole and vancomycin. Table 2 illustrates the scheme currently used[10].

Table 2. *Treatment of Infection by Clostridium difficile..*

Episode	Therapy
Initial episode and first recurrence	Mild-moderate infection: metronidazole 500mg PO 3 times daily for 10–14 days or fidaxomicin* 200mg twice daily for 10–14 days Severe infection: vancomycin** 125mg PO 4 times daily for 10–14 days Severe complicated infection: metronidazole 500mg IV 3 times daily and vancomycin** 500mg PO 4 times daily for 10–14 days
Second recurrence	Pulsed and tapered doses of vancomycin 125mg 4 times daily for 14 days 125mg 2 times daily for 7 days 125mg once daily for 7 days 125mg once every 2 days for 8 days (total 4 doses) 125mg once every 3 days for 15 days (total 5 doses)
Third or more recurrences	Vancomycin 125mg PO 4 times daily for 14 days, followed by rifaximin 400mg twice daily or fidaxomicin 200mg twice daily for 14 days Fecal microbiota transplantation

Source: Adapted from Burke KE, Lamont JT. Clostridium difficile infection: the Worldwide disease. Gut Liver. 2014; 8(1):1-6.[10]
** In Brazil, Fidaxomicina is not commercialised. oral formulation, ** in Brazil Vancomycin capsules are not available in. It is recommended to break the ampule and orally administer the antibiotic in its venous presentation. There is no evidence of difference in outcome between the two formulations. PO: orally; IV: intravenous.*

In Brazil, there are few studies on *C. difficile* infection, generally attributed to the difficulty of access to the tests for detecting the bacteria, mainly in the public health system, thus being an underdiagnosed disease in our country[11].

In a recent guideline of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[12], the authors maintained the recommendation for metronidazole as the first-line medication, and vancomycin, as a second option. Fidaxomycin (Fid) was added as a therapeutic option, but with the same degree of recommendation as vancomycin. In the US, Fid is also accepted as atreatment option. This drug is not yet marketed in Brazil[11]. Precarious response to standard oral vancomycin or metronidazole treatment leads to high recurrence rates, around 30%. After two or more episodes of *C. difficile* infection, the estimated recurrence risk with antimicrobial therapy increases to 60%[12].

In search of a more effective and appropriate treatment for recurrent and refractory episodes, the researchers resumed a Chinese practice dating to the fourth century, known as Fecal Microbiota Transplantation (FMT). Although very old, FMT was first reported scientifically in 1958, when it was successfully used in the treatment of four patients with pseudomembranous colitis. Despite its apparent efficacy, FMT began to be widely studied and incorporated into clinical practice only in the last ten years[13].

FMT consists of introducing the intestinal microbiota from a healthy donor into a patient with *C. difficile* infection to restore his/her microbiota[14]. Numerous case reports, retrospective studies and randomized clinical trials have demonstrated the benefits of FMT in patients with severe or recurrent *C. difficile* infection. The cure rates can reach 100% in some works, but with an average rate of 87 to 90% in the more than 500 cases described

in the literature[15].

The donor for this type of treatment is usually a familiar or known one that goes through a thorough investigation for several pathogensbefore selection for the transplant[16]. The routes of administration of FMT may benasojejunal, nasogastric, endoscopic, through enemas or colonoscopy. The choice of route depends on the feasibility of the site, the experience of the physician and the safety offered to the patient[4].

The objective of this work is to characterize and discuss the main forms of FMT application, its indications, existing barriers and efficacy when used as a therapeutic alternative for *Clostridium difficile* infection.

METHODS

For the preparation of this review, we searched for articles in the electronic databases PubMed, Lilacs and in the SciELO portal. The research consisted of the following descriptors: "Enterocolitis, pseudomembranous" "OR" "Clostridium difficile", "AND" "fecal microbiota transplantation". The search was limited to studies in humans older than 19 years and published in English and Portuguese in the last five years.

Two independent researchers reviewed the texts in their entirety and selected the ones that had the most evidence on the subject, excluding those that were not in agreement with the objective and/or that touched on the proposed subject. We also included the bibliographic references of the selected articles.

RESULTS AND DISCUSSION

The imbalance of the intestinal microbiota, called dysbiosis, plays a crucial role in the pathophysiology of *C. difficile* infection. During the last decade, the importance of the intestinal microbiota has gained relevance, it being considered an organ[4]. A longitudinal study analyzed the intestinal microbiota of FMT donors and recipients one week after the procedure and again after one year. All patients submitted to treatment were considered cured of *C. difficile* infection. They also observed the reduction of intestinal microbiota diversity one year after the FMT in comparison to the healthy donor microbiota and its increase in relation to the pre-FMTmicrobiota. They found thatthe microbiota increased soon after the treatment and it remained stable during the first year after transplantation[17].

In relation to the colonizing organisms, only the *Firmicutes* and *Proteobacteria* phyla presented significant changes. Inside the *Firmicutes* are the bacteria of the order *Clostridiales*. This bacterial order is scarce in the microbiota of patients with *C. difficile* infection (12.8%), and high in donors (70%). After the FMT, there was a significant increase of this bacterium (55%) in the receptors. *Clostridium difficile* belongs to this order, but in a healthy microbiota, it should not be present orbe in very low concentration. In patients with acute infection, the nonpathogenic *Clostridiales* species are in reduced concentration, thus facilitating colonization by *C. difficile*[17]. In the same study, they observed the protective effect to the mucosa by butyrate producing bacteria against *C. difficile* colonization. The reduced number of such bacteria in the microbiota of patients with recurrent *C. difficile* infection may be one of the reasons for frequent recurrences.

Another study analyzed the fecal composition of the microbiota and bile acids of 12 patients with recurrent *C. difficile* infection before and after FMT. They observed that the use of antibiotics exterminates part of the microbiota responsible for the metabolization of primary into secondary bile acids in the intestines. Secondary bile acids are responsible for the inhibition of *C. difficile* germination and colonization in the intestinal mucosa and their absence facilitates the infectious process. FMT causes rapid restoration of the primary bile acids metabolizing microbiota, normalizing the amount of secondary bile acids available, thus suggesting the reason for transplant efficacy[18].

In 2010, members of several specialized medical societies formed a working group with the aim of developing a consensus on treatment[15]. As described by the working group, the main indications for treatment with FMT are:

1. Recurrent *C. difficile* infection:

A) Three or more episodes of mild to moderate *C. difficile* infection and failure of a six to eight week cycle with vancomycin, with or without an alternative antibiotic, i.e.,rifaximin, nitazoxanide or fidaxomycin.

B) At least two episodes of *C. difficile* infection resulting in hospitalization and associated with significant morbidity.

2. Moderate *C. difficile* infection not responding to standard therapy (vancomycin or fidaxomicin) for at least one week.

3. Severe *C. difficile* infection (even fulminant) without response to standard therapy after 48 hours

The 2013 *C. difficile* treatment guidelines of the American College of Gastroenterology also recommend FMT as a therapeutic alternative for recurrent cases of *C. difficile* infection that did not respond to a vancomycin treatment regimen[19].

The evidence supporting FMT for treatment of severe and complicated disease (toxic megacolon) is less extensive and has fewer published clinical cases, but case reports suggest that it can be safe and effective even in critically ill patients. Patients with severe *C. difficile* infection are at greater risk of negative outcomes, and deciding between FMT and surgery or other therapeutic modality should prompt caution[15].

An essential aspect of FMT success is the identification of a healthy donor. Several medical societies provide guidelines for donor selection. Most do not stipulate an age limit; however, the vast majority of those selected are between 18 and 60 years old. The donor may be a long-term intimate partner, friend or unrelated volunteer[20]. A single prospective study makes considerations about the characteristics of the donor and the different compositions of its fecal microbiota. It concludes that the human intestinal microbiota undergoes changes with the passage of years, with a decrease in the number of firmicutes and actinobacteria, and an increase in the amount of bacterioides, besides a reduction of global diversity. Despite these changes, no clinically significant changes were found in the results of FMT performed with samples of different ages[20]. Since there are no differences, we can consider the donor eligible at any age provided that he/she had screening performed correctly and does not present contraindications to the donation[20].

The preparation of the material is not yet uniform and different studies aim to find the best option for the patient. In general, the material should be diluted, homogenized (using blender, manual work, or other method) and filtered when necessary (eg, gauze, coffee filter, plain filter) into a form that can be administered. This processed material can be either infused directly into the gastrointestinal tract, or be centrifuged, placed into gelatin capsules and swallowed. Several series of studies have described freezing of fecal microbiota for its use at another time[15].

As there is no clear consensus on how to best prepare the fecal material,the routes of administration are quite varied and include the upper gastrointestinal tract (by endoscopy, nasogastric or nasojejunal catheter or by ingestion of pills)[21-24] and the lower gastrointestinal tract (by colonoscopy in the proximal colon, by enema and rectosigmoidoscopy in the distal colon, or a combined approach)[5,25-34]. Clinical trials were conducted comparing the various forms of FMT application, their results, advantages and disadvantages. The important thing is that all the forms studied were more efficient than the treatment with antibiotics[15]. The enema pathway presented a high rate of resolution of symptoms. However, in most cases it was necessary to repeat the procedure several times until obtaining the clinicalimprovement. Infection severity was a decisive factor for the outcome. More severe cases were more refractory to treatment. No adverse effects were observed, the application is simple and, according to some reports, can be carried out by the patient in the home environment[29].

The nasogastric route is effective and safe for patients with contraindications to the colonoscopic route and it is well accepted, even though patients with advanced age are somewhat disgusted. The biggest concern is the vomiting and aspiration of the infused contents[12]. In the only Brazilian study on FMT, ten patients underwent the treatment with oral enteroscopy with 90% healing rate.

It is believed that the enteroscopic route is also an option to be considered for patients with contraindications to other forms of application. Due to the need for sedation, the physical and moral discomfort of nasogastric infusion of fecal material is avoided[12].

The colonoscopic route is the most used and has the advantage of allowing direct visualization of the affected area, infusion of large volume of fecal material and better retention than the enema. The preparation and the need for sedation are detrimental in highly debilitated patients, in addition to the risk of perforation when the mucosa has abundant inflammation. The risk of perforation can be minimized by the endoscopist's experience and skill[5].

Considering how best to completely restore the microbiota of the entire gastrointestinal tract, a prospective study selected 27 patients with recurrent *C. difficile* infection to receive FMT by combined route (enteroscopy and colonoscopy). All the patients selected had a reduction in the number of bowel movements and dissipation of *C. difficile* toxins in the fecal sample after only one infusion. The mean resolution time was three days. The authors suggest a high resolution rate when the procedure is performed by combined route. One setback of the study was the high cost due to the use of the two techniques, but its high curative potential renders excellent cost-effectiveness[33].

In the analysis of the results the authors concluded that the infusion of feces below the angle of Treitz can reduce the degradation of the microbiota by gastric acid and pancreatic enzymes, and that intrajejunal administration can promote a contact of beneficial bacteria with the surface of the intestinal mucosa till the cecum. The technique allows the infusion of a large volume of fecal material, without rapid elimination through the rectum, besides reducing the risk of aspiration and oral regurgitation[33].

Two studies performed the preparation of FMT frozen capsules, and administered in patients with recurrent *C. difficile* infection with preserved swallowing. Both studies had a curing rate close to 90%. Oral capsules have a resolution rate similar to the other means of administration, but with a longer time to clinical improvement. The advantages of the method are easy storage, low cost, proven efficacy, few adverse effects, easy administration, patient's comfort, non-invasiveness and safety for critically ill patients. The only contraindication is the inability to swallow, increasing the risk of bronchoaspiration[21,23].

Freezing the samples allows donor screening in advance and ease of storage allows donor investigation for possible incubated viral infections. A clinical trial of 232 patients with recurrence or refractoriness to standard treatment divided the sample into two groups, one with 108 patients who received the frozen transplant, and another with 111 patients who received the fresh enema transplant. The results showed no clinical difference between the two forms of preparation, both having a good resolution rate. Considering the advantages of providing frozen/cooled FMT, its use is a considerable option in this scenario[31].

In recent years there have been few published case reports regarding the efficacy of FMT in immunocompromised patients. At the beginning of the century, this population had been excluded from major clinical trials because of the lack of knowledge and fear of the complications of this new form of treatment, especially in relation to possible bacterial translocation in a context of depression of intestinal mucosal defenses[35,36].

The economic impact of *Clostridium difficile* infection in Brazil was not estimated due to the difficulty of establishing the diagnosis and lack of documentation. In the United States, it is estimated that each year *C. difficile* infection costs the government between US$ 1 billion and US 3.6 billions. These high costs are the results of hospitalizations, drug costs, and post-treatment care[37]. Recent studies compared the different forms of treatment of recurrent *Clostridium difficile* infection with FMT. In all studies, FMT was more cost-effective and clinically efficient than treatment with metronidazole, vancomycin, and fidaxomicin (not available in Brazil)[38]. A French study compared the cost-effectiveness of FMT via colonoscopy, duodenal and enema to treatment with vancomycin and fidaxomicin. The authors concluded that FMT in all forms

is more cost-effective than the other treatments and that there is a better cost-effectiveness for the colonoscopic route than for the others. The enema has a characteristic of resolution of the infection and cost very close to the colonoscopic route, and because it is safer for the patients, the authors concluded that it is the recommended route in the work performed[39].

Only one study compared FMT (via colonoscopy) as a form of initial treatment of *Clostridium difficile* infection to the other primary regimens (metronidazole and vancomycin). FMT was more expensive and more effective than metronidazole, and cheaper and more effective than vancomycin. Thus, it practically excluded vancomycin as a therapeutic option for the initial treatment of the infection[40]. No articles were found that assessed the cost of the ingestion of FMT capsules and the feces cryopreservation technique, which could provide data regarding the financial costs of the procedure in relation to already consolidated treatments.

Adverse reactions to FMT are rare. Most describe a feeling of gastrointestinal discomfort that presents resolution in up to 12 hours. There are few reports on the subject, but none directly attributed the complications presented to transplantation. Most of the patients who had adverse effects had previous bowel disease, such as inflammatory bowel disease or diverticulitis[41,42].

Despite the proven efficacy of FMT, there is still little clinical recommendation. One study focused on this issue and found that up to 94% of patients would be willing to accept FMT as a treatment if it was prescribed by their doctor, and that there is a predisposition for patients to accept the colonoscopic method; the odorless pill was the first choice[43]. With this finding and with the objective of elucidating the reason for the low prescription of FMT, another similar study, now turned to the medical class, applied 139 questionnaires on the technique, in which 65% of the physicians answered that they would not indicate FMT. The main justification was to ignore the indication and to believe in the disgust of the patient or the fact that there is no adequate protocol and logistics in the workplace[44].

CONCLUSIONS

Fecal microbiota transplantation (FMT) is a proven technique, with low costs when compared to conventional treatment, and with few adverse effects. Refractory and severe cases are the main indications of FMT. All forms of application had a high cure rate, and the colonoscopic route was the most used.

In view of the severity of *Clostridium difficile* infection, it is not surprising that patients consider FMT as an alternative treatment. Education and patient involvement in the decision-making process are crucial factors for acceptance of the technique. It is perceptible through research that the physician has great influence in the choice of treatment to be performed and, if prescribed, there is a high probability of acceptance. The lack of indication rests on the prejudice towards the procedure.

The lack of regulation and institutional protocols leads to insecurity and is a barrier that needs to be overcome. The adequate use of this technique will only be feasible through the disclosure of its effectiveness, knowledge of the administration routes and acceptance of health professionals.

R E S U M O

A infecção por *Clostridium difficile* é uma complicação comum após a disbiose intestinal ocasionada pelo uso abusivo de antibióticos. Apresenta elevada importância médica devido às altas taxas de recorrência e morbidade. O transplante de microbiota fecal é uma alternativa eficaz para o tratamento da infecção recorrente e refratária pelo *C. difficile* e consiste na introdução da microbiota intestinal de um doador saudável em um paciente portador desta infecção. O mecanismo fisiológico exato pelo qual o transplante de microbiota fecal altera a microbiota intestinal não está tão bem estabelecido, mas é evidente que restaura a diversidade e a estrutura da microbiota promovendo aumento da resistência à colonização pelo *C. difficile*. Diversas vias de administração do transplante estão sendo estudadas e utilizadas de acordo com as vantagens apresentadas. Todas as formas de aplicação apresentaram elevada taxa de cura, sendo a via colonoscópica a mais utilizada. Não foram documentados complicações e efeitos adversos relevantes, e seu custo benefício em relação ao tratamento convencional se mostrou vantajoso. Apesar da sua eficácia é pouco utilizado como terapia inicial, sendo necessários mais estudos para firmar essa terapêutica como primeira opção no caso de infecção por *Clostridium difficile* refratária e recorrente.

Descritores: Transplante de Microbiota Fecal. *Clostridium difficile*. Enterocolite Pseudomembranosa. Antibacterianos.

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