

Applications of Fecal Microbiota Transplantation: Emphasis on *Clostridioides difficile* Infections

Aplicações do transplante de microbiota fecal: Ênfase em infecções por *Clostridioides difficile*

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Abstract

Objective This study aimed to perform a comprehensive review of clinical trials using fecal microbiota transplantation in cases of *Clostridioides difficile* infection.

Methods This manuscript reviews clinical studies published from 2003 to 2020 at the Scientific Electronic Library Online (SciELO Brazil), Latin American and Caribbean Health Sciences Literature (LILACS) and US National Library of Medicine (MedLine/PubMed) databases using the descriptors antibiotic/antimicrobial, *Clostridium difficile*/*Clostridioides difficile*, intestinal microbiota/intestinal microbiome and fecal transplantation.

Results Interventions on microbiota include the use of probiotics, prebiotics, and fecal microbiota transplantation as therapeutic methods. Results show that fecal microbiota transplantation is an excellent alternative for the treatment of recurrent *C. difficile* infections.

Keywords

- ▶ antibiotics
- ▶ *Clostridioides difficile*
- ▶ intestinal microbiota

Resumo

Objetivo Este estudo teve como objetivo realizar uma revisão abrangente dos ensaios clínicos que utilizaram transplante de microbiota fecal associado a casos de infecção por *Clostridioides difficile*.

Métodos Este manuscrito descreve uma revisão de estudos clínicos publicados entre 2003 e 2020 nas bases de dados Scientific Electronic Library Online-Brasil (SciELO-Brasil), Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) e US National Library of Medicine (MedLine/PubMed), utilizando os descritores *antibióticos/antimicrobianos*, *Clostridium difficile*/*Clostridioides difficile*, *microbiota intestinal/microbioma intestinal* e *transplante fecal*.

Resultados Intervenções na microbiota incluem a utilização de probiótico, prebióticos, e o transplante de microbiota fecal como medida terapêutica. Os resultados evidenciam que o transplante de microbiota fecal apresenta-se como uma excelente alternativa para o tratamento de infecções recorrentes por *C. difficile*.

Palavras-chave

- ▶ antibióticos
- ▶ clostridioides difficile
- ▶ microbiota intestinal

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Introduction

For a long time, microorganisms were associated with pathological conditions. In 1888, Ilya Metchnikoff began to discuss the role of the symbiotic relationship between the host and its intestinal “flora”, and how these microorganisms could be modulated for health and longevity.¹ The “flora” referred by Metchnikoff is now known as microbiota, i.e., the population of microscopic and macroscopic organisms that inhabit an organ or region of the human body. The intestines and mouth contain most of the species that make up the human microbiota. The intestinal microbiota plays a fundamental role in homeostasis, since it participates in stages of the metabolism of nutrients and drugs; it also modulates the immune and endocrine systems, acts on lipids metabolism, and prevents pathogenic infections in a symbiotic relationship with the host.^{2–6} In this context, recent studies have shown that the immune system has coevolved with the intestinal microbiota for a collaborative relationship,⁴ and that dysbiosis is associated with several conditions, such as colorectal cancer.⁷

The adult gut has up to 100 trillion bacteria. Bacteroidetes (gram-negative organisms) and firmicutes (gram-positive organisms) are considered the main bacterial phyla in adults, and account for energy homeostasis. Several factors, including diet and lifestyle, modulate the composition of the microbiota. Thus, studies^{8,9} indicate that the excessive intake of calories promotes the proliferation firmicutes bacteria, contributing to weight gain, whereas bifidobacterium, *Clostridium*, and bacteroid are associated with improved metabolism and immune system, endocrine signaling, and brain function, in addition of playing a role in cancer prevention.¹⁰

Several factors change the composition of a person's microbiota, from their gestational period, delivery, and breastfeeding,¹¹ to their lifestyle, including physical exercise¹² and diet.^{13,14} Therefore, antibiotics play a fundamental role due to their actions on the microbial composition and intestinal homeostasis. Studies show that antibiotics are the most commonly prescribed drugs for children,⁶ and that most prescriptions occur in primary care in countries such as Brazil.¹⁵ Excessive or inadequate antibiotic therapy can induce natural selection, and several diarrheal conditions can result from intestinal bacterial asymmetry.¹⁶

Microbiota imbalance, called dysbiosis, comprises a state in which the altered microbiota is deleterious due to qualitative and quantitative changes in species, metabolic activity, and distribution within the gastrointestinal tract.¹⁷ Dysbiosis results in intestinal hyperpermeability, with increased levels of bacterial endotoxins and metabolites, including ammonia, bioactive amines, tumor promoters, bile salts deconjugation, and increased fungal proliferation, eventually leading to intestinal mucosa destruction.^{17,18} Dysbiosis can disrupt normal regulatory immune system process at the intestinal mucosa,¹⁹ resulting in several autoimmune or atopic inflammatory diseases due to the loss of immunological tolerance.²⁰ In addition, its association with conditions such as Parkinson's¹⁸ and Alzheimer's diseases has been shown.²¹

Infection with the gram-positive bacillus *Clostridioides difficile* (CD), previously known as *Clostridium difficile*,²² is

one of the main healthcare-related complications, and it is intrinsically related to antibiotic therapy. This is the main healthcare-associated infection in the United States, accounting for approximately 150 thousand cases per year.²³ CD easily spreads within hospital environments due to spore formation. Elderly patients are at a higher risk, with worse prognosis and a greater recurrence rate. Diagnosis is based on a diarrheal condition with positivity to toxins A and B in feces.²⁴

CD infection rates have increased in recent years due to the indiscriminate use of antibiotic therapy, the greater number of immunosuppressed and elderly people, and the high occupancy rate in hospitals, which favors the spread of spores within the hospital environment. The main risk factor associated with CD infection is previous antibiotic therapy, which was initially restricted to the use of clindamycin. Currently, all antibiotics are related to CD infection. Severe outbreaks have been recorded since 2000 in the United States, Canada, and the United Kingdom, with high mortality rates, ranging from 6.9% to 16.7%. This epidemiological change was attributed to the appearance of a new CD strain in early 2000s.²⁴ It is worth noting that CD spores survive the acidic environment of the stomach, and it is estimated that up to 18% of patients at hospital intensive care units and 20% of institutionalized residents are asymptomatic CD carriers; in contrast, this percentage reaches 10% at the general population.²³

Several interventional procedures to restore the health-associated microbiota are under study, including the use of probiotics²⁵ and prebiotics²⁶ for various conditions, such as Alzheimer's²⁷ and Parkinson's diseases,²⁸ osteoporosis,²⁹ and sarcopenia.³⁰ The need for effective treatments and alternatives to antibiotic therapy to restore the altered intestinal microbiota led to the test of fecal microbiota transplantation (FMT) around the world. FMT was introduced as an alternative treatment for several pathological conditions, including inflammatory bowel diseases, irritable bowel syndrome, and intestinal constipation,^{31,32} in addition to diseases such as cardiometabolic syndromes³³ and cancer.³⁴

In its most widely reported application, FMT is performed in patients with recurrent CD infection. FMT involves the collection of feces from a tested donor, which are mixed with a solution, filtered, and inserted into the recipient's intestine, either by colonoscopy, endoscopy, or enema.³⁵ This procedure requires a selected donor, preferably an adult relative or person close to the patient, who have not been treated with antibiotics within the last three months, and with no history of gastrointestinal diseases, autoimmune conditions, chronic pain syndromes, obesity, malnutrition, or cancer. The donor is submitted to several tests, including serology for hepatitis and HIV, and proto-parasitological tests.³⁶ Prior to the procedure, which is not deemed highly complex, the colon of the patient is prepared with oral laxatives to eliminate all fecal contents.³⁷

FMT outcomes are quite promising, as transplanted fecal bacteria are intended to restore global microbial diversity and stability. FMT has shown a major impact on the recipient's intestinal microbiome, and it is associated with the successful treatment of refractory CD infection.³⁸

Methods

A bibliographic survey was carried out from July 2017 to March 2020, including specialized literature published between 2003 and 2020. Articles, mainly clinical trials, were searched at the electronic databases Scientific Electronic Library Online Brazil (SciELO Brazil), Latin American and Caribbean Literature in Health Sciences (Lilacs) and US National Library of Medicine (MedLine/PubMed). The terminology used was registered at the Health Sciences Descriptors created by the Virtual Health Library and developed from the Medical Subject Headings of the US National Library of Medicine, and common terms in Portuguese, English and Spanish were queried. Searched terms were the following: antibiotics/antimicrobials, *Clostridium difficile*/*Clostridioides difficile*, intestinal microbiota/intestinal microbiome, and fecal transplantation.

Results

The search in the three databases resulted in 23 articles. Fourteen articles were excluded because they were duplicates or bibliographic reviews or publications from studies not performed in human beings. After initial selection, nine

articles were read and used to prepare ► **Table 1**, which shows outcomes from the analysis of papers on FMT in patients with CD infection.

Discussion

For most people, the term “transplantation” implies in organ transplantation, which, according to the Brazilian Ministry of Health Portal,³⁹ is the only hope of life or opportunity for a fresh start for people requiring such procedure. This context of improved quality of life or life maintenance also applies to FMT because, occasionally, intestinal dysbiosis, associated with inflammatory bowel diseases, antibiotic therapy, or other drug treatments, is so severe that it is life-threatening.

Intestinal microbiota imbalance can result in CD colonization, which can be asymptomatic, cause diarrhea, or lead to more severe, life-threatening forms of pseudomembranous colitis. In addition to virulence factors from *Clostridium*, its mere presence affects several operational taxonomic units (OTUs)⁴⁰ contributing to intestinal dysbiosis. In many cases, recurrent CD infections occur in currently or previously hospitalized patients. A recent study⁴¹ identified CD spores on the floor and beds from Canadian hospitals, indicating the risk of infection in admitted patients.

Table 1 Selected studies

Study	Author and year	Study type	Parameters and participants	Results
E1 ⁴⁴	Cheng et al., 2019	Multicenter, retrospective study	Adult patients (94) with a history of organ transplantation and fecal microbiota transplantation to treat <i>Clostridioides difficile</i> infection	Cure: 63.8% within 1 month after the first FMT, and 91.3% when including additional antibiotic therapy.
E2 ⁴⁵	Jiang et al., 2017	Randomized clinical trial	Patients (72) with more than three cases of <i>C. difficile</i> infection	Cure: 100% with fresh FMT, 78% with lyophilized FMT
E3 ⁴⁶	Hota et al., 2017	Randomized clinical trial	Patients (30) with recurrent of <i>C. difficile</i> infection in 120 days after 14 days of oral treatment with vancomycin followed by a single FMT or a 6-week course of oral vancomycin	Infection recurrence: 56.2% at the group treated with oral vancomycin, similar to a single FMT
E4 ⁴⁷	Kelly et al., 2016	Randomized clinical trial	Patients (46) with three or more recurrent <i>C. difficile</i> infection and who have had a complete treatment with vancomycin at the last episode	Cure: 91% with FMT, 62.5% with autologous FMT
E5 ⁴⁸	Ramsauer et al., 2016	Case series	Patients (16) with <i>C. difficile</i> infection received FMT	Cure: 68.75% after one FMT, and 87.5% after a second FMT
E6 ⁴⁹	Lee et al., 2016	Randomized clinical trial	Patients (232) with refractory or recurrent <i>C. difficile</i> infection	Cure: 83.5% with frozen FMT, and with 85.1% fresh FMT
E7 ⁵⁰	Orenstein et al., 2016	Prospective, multicenter, open study	Patients (49) with at least two severe episodes of <i>C. difficile</i> infection leading to hospital admission	Cure: 87.1% with FMT using a microbiota suspension (RBX2660) in two doses
E8 ⁵¹	Ponte et al., 2015	Case series	Patients (6) with recurrent or refractory episodes of <i>C. difficile</i> infection	Primary cure: 83.3%; secondary cure: 100%
E9 ⁵²	Youngster et al., 2014	Case series	Patients (20) with three episodes of mild to moderate <i>C. difficile</i> infection, or at least two episodes of severe <i>C. difficile</i> infection.	Diarrhea resolution: 70% with a single frozen, encapsulated FMT; 90% with 2 doses

Abbreviations: FMT, Fecal microbiota transplantation.

In animals, it has been shown that a previous colonization by a non-toxicogenic CD prevents infection by toxicogenic samples.⁴² In humans, however, the most used treatment consists in antibiotic drugs, although many strains are resistant to several agents, including metronidazole and vancomycin.⁴³ In this scenario, FMT is a feasible, low-invasive therapeutic alternative. The studies shown in ►Table 1 indicate that FMT has been successful with different numbers of doses, and using healthy frozen, fresh, and lyophilized microbiota.

Final Considerations

FMT seems an excellent alternative for the treatment of recurrent CD infections. In addition, the use of fresh microbiota, the performance of the procedure more than once, and the association with antibiotics contribute to better outcomes. Greater dissemination of the subject in different health contexts could generate more studies, which are scarce, especially in Brazil. Thus, future studies can ascertain the effectiveness of this technique in human beings.

Conflict of Interests

The authors have no conflict of interests to declare.

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