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Review article

Fecal Microbial Transplantation: A Review

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Abstract

Gut microbiota is defined as healthy when there are groups of microorganisms that enhance the host's metabolism, confer resistance to infections, inflammatory processes, the development of malignancies or autoimmunity, promote endocrine functions and support neurological function through the so-called gut-brain axis. Fecal microbial transplantation is the transfer of fecal matter from a healthy donor into the gastrointestinal tract of another person, usually a patient with a specific pathology, to manipulate the composition of the recipient's microbiota and contribute to the treatment of his or her condition. The concept of fecal microbial transplantation breaks with the traditional thought of bacteria as harmful elements and draws attention to what is probably the most undervalued of the human body's excreta: feces. Its high efficiency has been demonstrated and the procedure is recognized by the many patients it has helped, which can already be counted in thousands. The objective of this literature review was to describe the basics of fecal microbial transplantation for the treatment of *Clostridioides difficile* infections.

Keywords

Dysbiosis; Fecal microbiota; Fecal microbial transplantation; Bacteriotherapy; Infectionn; Clostridium difficile.

INTRODUCTION

The most abundant and best studied microbiota in the human body resides in the intestinal tract. Its impact extends beyond the limits of the mucosal surfaces since it plays an essential role in systemic functions, such as the development of the immune system (1). Before the discovery of penicillin in the 1940s, infectious diseases were the leading cause of death in humans, and they remain so in much of the world. In fact, there has been a significant increase in antimicrobial resistance, which has raised great concern since this poses an obstacle to the treatment of infectious agents, but it also generates great interest in the development of new therapeutic strategies (2).

One of these strategies is fecal microbiota transplantation (FMT), which is defined as the transplantation of a fecal preparation, properly screened, and taken from a healthy donor, which is inoculated into the gastrointestinal tract of an ill individual. Since this is not a therapeutic concept, FMT has raised great interest in recent years as it

has become the treatment of choice for infections caused by *Clostridioides difficile* (formerly called *Clostridium difficile*) (3). Thus, FMT is no longer considered an alternative medical practice, gaining acceptance as a valuable therapy, even though it is still little known about it worldwide. Its popularity has increased because of its ease of use, feasibility and effectiveness (4).

METHODOLOGY

For conducting this literature review, a search was performed using the following DeCS (Health Sciences Descriptors) and MeSH (Medical Subject Headings) terms and keywords: dysbiosis, fecal microbiota, fecal microbiota transplantation, bacteriotherapy, infection, *Clostridium difficile*.

The search was limited to studies conducted on humans, written in English, French and Spanish, and published from 2013 to date. The search was conducted in the Science Direct, Redalyc, PubMed and NCBI databases. In addition, manual searches for gray literature were made in databases and Google Scholar. The most relevant publications were chosen according to the authors' criteria.

GUT MICROBIOTA

Gut microbiota consists of numerous bacteria, viruses and fungi that live in the intestinal content (feces), as well as in the mucus that covers the intestinal mucosa. These two habitats constitute two separate ecological communities of commensal microorganisms that play different roles in the interaction between them and the host organism. To date, more than 1000 genera of intestinal bacteria have been identified (5).

Intestinal microbiota is composed of four phyla of bacteria: *Bacteroidetes*, *Firmicutes* and, to a lesser extent, Proteobacteria and Actinobacteria (6). The exploration of this ecological community, which coexists with the human body, has been possible due to the introduction of molecular DNA research techniques and 16S rRNA gene sequencing (rRNA) (7). This occurs because classical microbiological methods used to identify strains of bacteria or fungi, such as microbiological culture, are ineffective in the case of human microbiota, as some bacterial strains in the gut cannot be grown under laboratory conditions.

The number of bacterial cells in the human digestive tract of a healthy individual reaches 100 trillion, 10 times more than the number of cells in the human body (5). Therefore, gut microbiota plays a key role in human health and is increasingly recognized as a measure to treat several diseases when (8) dysbiosis occurs. Moreover, compared to the microbiota in healthy controls, it has a lower abundance of bifidobacteria and a higher abundance of gram-negative bacteria (9). The latter have multiple functions involving the mucosal immune system and resistance to colonization against, for example, *Clostridioides difficile* (10).

FMT AND CLOSTRIDIOIDES DIFFICILE INFECTION (CDI)

Microbiota is considered a tissue. Regarding FMT, it is used to implant the fecal microbiota preparation of a healthy donor into the gastrointestinal tract of an ill person or a recipient (11) in order to recover microbial composition (12). This process also improves dysbiosis by increasing overall diversity and restoring the functionality of the microbiota (3).

In this scenario, FMT is increasingly being used to treat CDI since *C. difficile* is a gram-positive, anaerobic, spore-forming bacillus associated with endogenous (colonization) or exogenous (healthcare-associated infections/consumption or indication of broad-spectrum antibiotics) infections. Pathogenesis is mainly attributed to toxin A (an enterotoxin), toxin B (a cytotoxin) and binary toxin (13).

CDI mainly causes pseudomembranous ulcers and dysbiosis due to an overgrowth of this bacterium in the gastrointestinal tract, which is induced by antibiotics such as metronidazole, vancomycin and, more recently, fidaxomycin or rifaximin (14,15). These therapies trigger adverse events including damage and death of the human gastrointestinal microbiota. Consequently, FMT is considered an alternative therapy to correct the underlying imbalance in this pathogenesis and provide sick patients with microbiota with a high degree of structural and functional homeostasis, obtained from a suitable donor (12).

In this sense, *C. difficile* is the main cause of diarrhea associated with antibiotics, particularly in hospitalized patients in the Western world, and is associated with high morbidity and mortality, as well as with the use of health resources. Clinical isolates of toxigenic *C. difficile* are genetically diverse and some hypervirulent ribotypes, such as 027, have been associated with outbreaks in health care facilities (16). The clinical manifestations of CDI vary from self-limited diarrhea and severe diarrhea, to pseudomembranous colitis, severe ileus, toxic megacolon, peritonitis, and even shock or organ failure (13).

A significant number of patients do not respond to the initial treatment or suffer a recurrence (2-38%) in the first 8 weeks (17). Recurrent CDI is defined as an episode that occurs within the first 8 weeks after the onset of a previous CDI and whose symptoms have resolved (18).

It is important to know the composition of the microbiota of patients before and after performing the transplant to be able to identify the changes produced by it (19). FMT is a very low-cost antibacterial therapy and is the most promising for the treatment of patients with recurrent CDI or

who are refractory to antibiotic treatment. As a matter of fact, the superiority of FMT has been shown in multiple case series. Recently, as reported in experimental prospective randomized clinical trials, the infection has been effectively treated in more than 90% of these patients (20).

HISTORICAL APPROACH TO FMT

Strangely enough, FMT is not a new therapeutic concept. There are some very old data that refer to it more or less directly. For example, in the fourth century, during the Dong Jin dynasty in China, physician Ge Hong successfully described the oral administration of a suspension prepared using human feces in patients with food poisoning or severe diarrhea (21). Later, Li Shizhen used various stool preparations, which he called the 'yellow soup', to treat all kinds of digestive ailments such as diarrhea, vomiting, pain, fever or constipation. Another report of the oral administration of feces to relieve certain intestinal ailments in livestock was described in the seventeenth century by Fabrizio d'Aquapendente (20, 22).

CDI was first described in 1978. Since then, it has been identified as the leading cause of hospital-acquired diarrhea and the main identifiable source of diarrhea associated with the indiscriminate use of antibiotics (23). During World War II, Bedouins in the North African desert instructed soldiers to eat dromedary feces to treat dysentery and other diseases caused by *C. difficile*.

However, the successful use of FMT in modern medicine was first reported by Eiseman et al. in 1958. These researchers administered fecal microbiota in enemas to patients with pseudomembranous colitis (22), with the aim of displacing pathogenic microbes from their intestine by restoring a healthy microbiota. In doing so, they sought to generate efficient results for treating CDI (24). This approach to the disease, which conceptually challenged the then prevailing view of microbiota as a harmful element, fell into oblivion by the scientific community for more than half a century.

However, in the last decade, FMT has been positioned as one of the therapies with greater theoretical and practical interest in the field of gastroenterology, autoimmune processes, and metabolic diseases (17). In modern medicine, the first successful FMT was reported in 1958 by Eiseman et al., who treated 4 patients with pseudomembranous colitis caused by *C. difficile*, formerly known as *Clostridium difficile*.

Since then, resolution rates of 70 to 90% of recurrent CDI cases after FMT have been consistently reported in both observational studies and randomized trials (25). Likewise, in 2013, Van Nood et al. published the results of their first randomized, controlled, open-label clinical trial, which examined the therapeutic advantages of FMT compared to vancomycin treatment (26).

FMT PROCEDURE

Donor selection and screening has not been standardized, so the criteria described in the multiple studies on this matter vary. The types of donors selected can be classified in terms of their relationship with the recipient into 4 groups: blood relatives (54%), individuals with intimate contact with the patient (husband, wife, or partner) (8%), healthy volunteers with no relationship with the recipient (25%) and unspecified donors (12%) (22). Although FMT is deemed as a safe and reliable procedure that has not caused any adverse effects to date, from a theoretical perspective, there may be risks associated with its performance, such as the transmission of infectious agents that could trigger the development of diseases in the recipients (13).

Therefore, to avoid such adverse effects, it is recommended to perform a series of tests on the donor including a complete blood count and a viral profile (immunoglobulin M [IgM] anti hepatitis A virus [HAV], Hepatitis B surface antigen (HBsAg), immunoglobulin G (IgG), IgM anti-hepatitis C virus (HCV), IgM anti-hepatitis B virus (HBV), IgG anti-HCV, human immunodeficiency virus (HIV) (HIV-1 and HIV-2), human T-lymphotropic virus (HTLV), and syphilis (rapid plasma reagin [RPR] and fluorescent treponemal antibody absorption test [FTA-ABS]).

It is also necessary to carry out a polymerase chain reaction (PCR) test in the feces to identify enteropathogenic microorganisms and *C. difficile* toxins, as well as a serial stool analysis (*Giardia* sp., *Cryptosporidium* sp., *Cyclospora* sp. and *Isospora* sp.) (27), and to administer questionnaires to detect risk behaviors (17).

The donor is selected considering factors such as sexual behavior, blood transfusions, travel history, history of major surgeries on the digestive system (excluding appendectomy) (23), active cancer or history of cancer in the last 10 years, inflammatory bowel disease or functional dyspepsia (23), and other aspects that may increase the risk of suffering from a communicable disease (17).

In relation to the preparation of the receptor, the conditioning of their colon seems to reduce the density of bacteria such as *C. difficile* and even of their inactive spores. Therefore, although its direct relationship with the efficacy of FMT has not been proven, the use of laxative preparations the day before the procedure is recommended in patients whose clinical condition allows it, regardless of the route chosen for performing the procedure (22).

Once the broad selection and review of (potential) donors is concluded, the stool is received. Then, it should

be processed as soon as possible (within the first 6 hours) to maintain the viability of the donor microbiota. A cryoprotectant is then added to the fecal preparation to allow for proper storage at -80 °C. In addition, an aliquot portion of each donation should be stored for possible analysis in case of any serious adverse event (28).

The donor stool preparation can be kept at room temperature for up to 3 h or refrigerated at 4 °C for 6 h (29). This shows that storage with the best viability is obtained when supplying glycerol, because it favors the viability of fecal microbiota. Escherichia coli isolates have been found to be viable (and in similar proportion to fresh samples) after 1 year of frozen storage in infant and calf feces in the presence of 10% glycerol solution at -70 °C (30).

Meanwhile, the preferred route of administration for FMT remains a topic of discussion. Currently, different procedures have been established for performing FMT, and the routes used have been the upper and lower digestive tract. This choice varies according to the patient's clinical condition (31).

The use of the upper digestive tract by the nasogastric or nasoduodenal route is possible, easy, less costly and involves less risk of intestinal perforation compared to colonoscopy. However, it has the disadvantage that it can encourage bacterial overgrowth in the small intestine. In addition, it may not reach the most affected distal sites and may produce unpleasant symptoms for the patient, such as reflux or abdominal distension (32, 33).

On the other hand, FMT can be done through the upper route using ingested capsules (34). In this regard, a recent study showed high cure rates in patients treated with FMT using oral capsules, a method that may reduce patient discomfort. However, this practice requires the ingestion of large quantities of capsules, which are not readily available (30).

Finally, administration through the lower digestive tract is done by colonoscopy (the route of choice) or by enemas. Colonoscopy allows direct visualization of the mucosa, although it can be associated with an increased risk of perforation, especially in patients with toxic megacolon (32, 35).

EFFECTIVENESS AND DISADVANTAGES OF FMT

The high effectiveness of FMT, with a positive response >80 % in the scenario of recurrent CDI, as reported in systematic reviews, has raised the interest in this therapy among patients, doctors, and researchers, as well as in the pharmaceutical industry. Thus, FMT is no longer considered an exceptional resource in recurrent CDI cases and is increasingly practiced on a common basis (36).

Nevertheless, the disadvantages of this therapy can be classified according to their appearance in the short- and long-term. Short-term disadvantages are related to the occurrence of abdominal pain, bloating, flatulence, diarrhea, and fever, while long-term consequences include signs such as perforation, bleeding, and cardiorespiratory depression (37). Cases of infectious agent transmission and bacteremia have also been reported.

Furthermore, long-term effects are related to the modulation of certain diseases such as obesity, diabetes mellitus, atherosclerosis, fatty liver, inflammatory bowel disease, irritable bowel syndrome, asthma, and autism (31, 34).

The most relevant literature and systematic reviews on FMT are described below, together with representative findings regarding its effectiveness and adverse events (**Table 1**) (17, 34, 38-41):

Accordingly, FMT may be effective and a safe strategy in the treatment of recurrent and refractory CDI. Indeed, it has been documented that the resolution rate of CDI is directly proportional to the volume of stool transplanted. In turn, the recurrence of the symptoms is associated with the weight of the stool used in the transplant (17). Efficacy is similar in controlled and uncontrolled studies. Also, more adverse events associated with FMT have been reported for the treatment of inflammatory bowel disease than for the treatment of CDI. Furthermore, there are no true placebo-controlled trials addressing the efficacy of FMT.

OTHER FMT USES

Currently, FMT is turning into a highly effective treatment option for CDI cases and other dysbiosis, as well as for liver encephalopathy, irritable bowel syndrome, and inflammatory bowel disease, all metabolic disorders that greatly affect patients (42). It is said that FMT can even play an important role in the treatment of obesity (43), psoriasis, cancer, and Parkinson's disease (44).

Within this context, multiple clinical trials assessing the use of FMT in the treatment of inflammatory bowel disease, hepatic encephalopathy, primary sclerosing cholangitis, acute pancreatitis, constipation, steatorrhea, eradication of multi-resistant bacteria in fecal carriers, HIV, and epilepsy are underway (32).

Meanwhile, gastrointestinal disorders such as dysbiosis have been observed in patients with autism spectrum disorder, which are associated with infection by the *Clostridium* genus, including strains of *C. difficile.* However, this is not the only strain that can be associated with behavioral disorders in autistic children. Other microorganisms such as *Candida* spp. have also been described. Thus, it is considered that FMT regenerates intestinal microbiota by producing abundant diversity of bacterial microorganisms (45).

Table 1. Effectiveness vs. adverse events of FMT

Year	Country	Type of study	Results
2015 (38)	China	Systematic review that included 18 studies with 611 patients.	A primary cure rate of 91.2% was reported. There were 6 deaths by CDI. In total, 38 deaths were reported in 7 studies, of which 6 were associated with recurrent CDI or severe CDI caused by the *C. difficile* strain 027. Another 3 deaths were associated with unrelated infectious diseases, such as pneumonia and peritonitis. About 69 cases of gastrointestinal symptoms were reported in 11 studies, being the most common flatulence, abdominal pain, cramps and diarrhea. Almost all symptoms were of short duration, moderate and treatable. Other adverse effects included self-limiting fever and emerging diseases such as sepsis, pneumonia, and peritonitis (all infectious). Age over 65 years was identified as a risk factor for further complications.
2016 (39)	England	Systematic review that included 109 studies with 1555 patients.	Mild, self-limiting adverse events of gastrointestinal nature were found, including flatulence, diarrhea, abdominal pain and distention, constipation, and nausea. In some cases of serious complications, a credible association was not established due to the lack of controlled data. Serious complications included 3 deaths caused by bacteremia, respiratory failure and feculent vomiting.
2017 (40)	England	37 studies were included: 7 randomized controlled trials and 30 case series, with a total of 1 973 patients.	Symptom resolution was 92% in all studies. FMT was more effective than vancomycin therapy for CDI. Mild diarrhea, transient spasm, long-term constipation, and flatulence were the most frequent mild adverse events. 50 deaths were reported. However, almost all were due to critical illness in elderly patients. One death occurred as a result of aspiration at the time of sedation during a colonoscopy to administer the FMT. In addition, 2 patients with recurrent diarrhea died after FMT from ileus and colonic perforation. It should be noted that a series of FMT cases in 80 immunocompromised patients, with a 3-month follow-up, did not report any serious adverse effects.
2018 (34)	United States	6 studies were included in this review: 5 case series and 1 randomized controlled trial, for a total of 341 patients	Only 3 major adverse events were reported and there were no deaths directly related to FMT. In total, 285 patients responded positively to the first treatment and did not present any recurrence during the specified follow-up, while 42 underwent a second treatment, with resolution of symptoms in 28 of them. It was reported that at least 5 patients underwent a third treatment, with resolution in 3 of them. Only 1 patient received 4 treatments, with no long-term resolution of symptoms. With regard to efficacy, encapsulated FMT has been shown to be safe and cost-effective for the treatment and prevention of recurrent CDI.
2018 (41)	United States	44 studies were included, none of them were randomized designs. A total of 303 immunocompromised patients using immunosuppressive drugs were studied. They included patients of all ages, with HIV, primary or inherited immunodeficiency syndromes, and cancer under chemotherapy or organ transplantation (including bone marrow transplantation).	76% of the patients received FMT through a colonoscopy. Of the 234 individuals with reported follow-up results, 207 (87%) reported resolution after the first treatment, with 93% effectiveness, indicating success after multiple treatments. 2 deaths, 2 colectomies, 5 treatment-related infections, and 10 subsequent hospitalizations were reported. It was concluded that in immunocompromised patients FMT appears to have comparable efficacy and safety data to immunocompetent patients. However, due to the heterogeneity of the immunosuppression subtype, no strong conclusion can be drawn about any specific or combined immunocompromised state with respect to the response to FMT. Further randomized trials are needed.
2018 (17)	Chile	Observational study of patients with recurrent CDI conducted between 2013 and 2017.	FMT was performed on 8 patients with recurrent CDI; 6 of them were women. The average age was 48. The effectiveness of FMT was 100% and all patients had a clinical response with bowel movements formed within one week. No patient presented a new episode of diarrhea within 6 months after FMT was carried out.

FMT: fecal microbiota transplantation; CDI: *Clostridioides difficile* infection; *C. difficile*: *Clostridioides difficile*. Taken from references 17, 34, 38-41.

On the other hand, in a small, phase I, open-label clinical trial was conducted in 18 children aged 6-17 years who were administered combined antibiotic treatment for 2 weeks, underwent a colon cleanse and then FMT with a high initial dose, followed by lower daily maintenance doses for 7-8 weeks, a significant change in the abundance of *Bifido bacterium* spp., *Prevotella* spp. and *Desulfovibrio* spp. was found in the control of microbiota composition. An improvement in gastrointestinal symptoms was also observed, as well as in language behavior (25%), social interaction, repetitive behavior, hyperactivity, and irritability, changes that were maintained for 8 weeks (46).

Recent studies associate intestinal microbiota with the physiopathology of obesity. The use of FMT in patients with obesity and type 2 diabetes mellitus is based on the composition of the intestinal microbiota since it varies significantly between obese and thin subjects. Moreover, it has been reported that those receiving FMT have a significant increase in insulin sensitivity after the procedure (2). Research findings in patients with metabolic syndrome or type 2 diabetes are encouraging in light of the expanding pandemic of obesity and require further exploration. Additional studies are also needed to determine the effects of microbiota alterations on tumor growth and therapies against some types of cancer (47).

CONCLUSIONS

While there are several techniques for performing FMT according to various protocols, the procedure itself is considered safe. In addition, there is a need to standardize and randomize controlled trials to qualify and quantify the risks of FMT. This therapeutic procedure, economically accessible, simple, and validated with scientific evidence, opens the possibility of further research on other human diseases, both digestive and extradigestive, which represent high health costs, readmissions, prolonged hospital stays, and high morbidity and mortality rates.

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Conflict of interest

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