

Fecal microbiota transplantation: current clinical efficacy and future prospects

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Abstract: Fecal microbiota transplantation (FMT) has gained mainstream attention with its remarkable efficacy in treating recurrent *Clostridium difficile* infection (RCDI) when there are no other effective therapies. Methods of selecting donors and routes of administration vary among studies, but there are now randomized controlled trials showing efficacy of FMT in treating RCDI. Ongoing trials of FMT for other disease such as inflammatory bowel disease are underway; this therapy should not be used for these conditions unless there is strong evidence for efficacy. Long-term safety data are sorely needed, as well as clarification of regulatory concerns.

Keywords: fecal microbiota transplant, recurrent *Clostridium difficile* infection, *Clostridium difficile* infection, microbiome, inflammatory bowel disease

Introduction

Interest in the microbiome has exploded in recent years, and the National Institutes of Health has launched the human microbiome project to catalog the microbial genes and species associated with the human body. The intestinal microbiome is increasingly recognized as being important in maintaining health and in some diseases such as *Clostridium difficile* infection (CDI). The healthy gut microbiome consists of mostly ten phyla, with a predominance of *Firmicutes* and *Bacteroidetes*.

Fecal microbiota transplantation (FMT) is the term used to describe the delivery of stool from a healthy donor into a patient, either by enema, colonoscopy, or via the upper gastrointestinal (GI) tract (oral capsules, nasogastric, nasoduodenal or nasoenteric tube, or endoscopy). By consensus, the term fecal microbiota transplant replaces other names for the procedure such as stool transplant, fecal bacteriotherapy, and fecal flora reconstitution.¹ FMT is being used to restore normal gut flora as a means of addressing GI and non-GI disease processes. As our understanding of the role of the microbiome and its alteration in disease states extends, we expect to gain a better understanding of therapeutic options through restoration and modulation of existing microbiota.

The disruption of host microbiota has been most clearly illustrated in the setting of CDI, wherein pervasive use of antibiotics has drastically reduced and altered the composition of pre-existing host microbiome, which allows the pathogen to proliferate and produce toxins that cause diarrhea and colonic disease.² While treatment with antibiotics is indicated, this treatment means that the colon microbiota stays abnormal, setting up a cycle of repeat infections that is called recurrent *C. difficile* (RCDI) infection. Studies have demonstrated less diversity in the colonic microbiota in CDI and RCDI patients compared with those in healthy individuals.^{2,3} Rather than eradicating

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the pathogen, as in antibiotic therapy, the goal of FMT is to reestablish a diverse, “normal” microbiome within the colon. Studies demonstrating the ability to introduce different microbiota that resembles the donor’s stool through FMT, with resolution of RCDI and symptomatic improvement, have laid the groundwork for application of these principles to other disease states.^{4,5} Growing evidence suggests that disruption of commensal microbial communities, perhaps through antibiotic overuse or dietary changes, may contribute to other disease states such as metabolic syndrome, autoimmunity, and multiple sclerosis, among others.^{6,7} Currently, FMT is being evaluated in the treatment of a wide range of diseases in addition to CDI, including other GI disease (inflammatory bowel disease [IBD], irritable bowel syndrome [IBS], and chronic constipation), neurological disease (multiple sclerosis, Parkinson’s disease), and hematologic disease (idiopathic thrombocytopenic purpura). Additional studies are being used to explore the role of probiotics in GI, cardiovascular, allergic, oral, gynecological, infectious, rheumatologic, and psychiatric disease.⁸ Of these, most research has focused on the role of FMT in CDI and IBD and IBS. This review gives background on FMT, its role in CDI and potential uses in other conditions, as well as describing methodology, risks, patient perception, and areas of future research.

History of FMT

Although interest in FMT and the microbiome has drastically increased in the last 10 years, the ingestion of stool from healthy individuals as a therapeutic approach is documented far back into history. In the Dong-Jin dynasty in fourth century China, oral intake of human feces was used to treat patients with food poisoning or severe diarrhea.⁹ Later references to therapeutic fecal transplantation occur in the 16th century Ming dynasty and 17th century Italian veterinary medicine. The first appearance of FMT in the United States medical literature was in 1958, when a Colorado surgeon Ben Eiseman and his colleagues successfully used fecal enemas to treat four patients with pseudomembranous enterocolitis.¹⁰ The authors noted that this often-fatal illness was associated with antibiotic use and theorized that suppression of normal bacteria allowed pathogens to proliferate. Despite these initially promising results, there was limited pursuit of this therapy, perhaps in part due to the introduction in 1959 of vancomycin, an antibiotic used in the treatment of CDI. *C. difficile* as the causative agent of most pseudomembranous colitis was not identified until 1976.

The underlying rationale behind FMT to treat patients with microbial “reconventionalization,” or using fecal

microbiota in order to provide colonization resistance, was further investigated with immunosuppressed individuals in the 1970s.^{11,12} Fecal suspensions or microbiota grown in germ-free mice were used in several patients with congenital immune deficiency or undergoing bone marrow transplantation.

Current clinical efficacy of FMT for CDI

CDI now comprises one of the most important causes of health care-associated infections and is responsible for 15%–25% of nosocomial antibiotic-associated diarrhea.^{13,14} Additionally, *C. difficile* has emerged as an increasingly significant cause of community-acquired diarrhea.^{15,16} Although antibiotics (vancomycin, metronidazole, and fidaxomicin) remain the initial treatment strategy for initial presentation, recurrence of CDI occurs in 20% of patients after initial antibiotic treatment.¹⁷ Current guidelines recommend a tapering course of vancomycin after a second recurrence; however, up to 60% of patients do not respond to this treatment strategy or develop further recurrence once the vancomycin is stopped.¹⁸

Antibiotics have long been identified as a major risk factor for CDI. Suppression of the host gut microbiota with antibiotics creates an altered environment for overgrowth of *C. difficile*. CDI patients have decreased overall microbiome diversity and less *Bacteroidetes* and *Firmicutes* than seen in healthy people.^{2,3} Instead, CDI patients have high levels of *Proteobacteria* and *Verrucomicrobia*, which are frequently invasive pathogens.¹⁹ This data support the idea that CDI either results from or is associated with altered intestinal microbiota. FMT repopulates bacteria quickly, restoring dominance of *Bacteroidetes* and *Firmicutes* in the distal gut.⁴ The durability of FMT restoration of microbiome diversity was demonstrated in a study assessing microbiota pre- and post-FMT in CDI patients. Recipient microbiota was similar to donor stool at 2 weeks and 33 days posttransplant, with dominance of *Bacteroides* species.²

Rates of CDI were low and stable for decades until the year 2000, when more virulent strains of *C. difficile* arose with clindamycin and quinolone resistance; they had an increased capacity for toxin production in vitro, and an increased sporulation efficiency.^{20,21} This strain was associated with widespread epidemics of CDI with increased morbidity and mortality. As a result, there were more cases of RCDI and the need for effective therapy; this led to increased use of FMT for those cases in which no other therapy was effective. A case report in which fecal enemas were used to successfully

treat a patient with RCDI was published in 1984²² and was followed by a small series of patients treated with a cultured mixture of facultative aerobes and anaerobes.²³ This mixture was seen as a more aesthetically appealing option than using human stool. However, as RCDI became increasingly common, FMT became an increasingly available option, with the first cases of stool delivered by colonoscopy published in 1998 in the Norwegian literature²⁴ and in 2000 in the United States.²⁵ Over the subsequent years, small case series and case reports were published, allowing for a few hundred cases to be analyzed by meta-analyses showing efficacy of 83%–90% for FMT for RCDI.^{20,21,25–35} The number of practitioners offering FMT has recently grown significantly so that currently it is available throughout most of the United States. The landmark first randomized controlled trial (RCT) published in 2013 demonstrated the efficacy of FMT via the nasoduodenal route in patients with RCDI; the study had to be stopped early because of the effectiveness of FMT compared to standard vancomycin therapy.⁵ Practice guidelines from both the American College of Gastroenterology and the European Society of Clinical Microbiology and Infectious Diseases now recommend FMT for RCDI.^{13,36}

Immunocompromised patients are particularly at risk of CDI, yet application of FMT to this group may be limited due to physician concerns about its safety due to the theoretic potential for bacterial translocation and infection. Concerns for increased risk of adverse events have been raised for patients after solid organ transplant as well as patients on immunosuppressive agents, with decompensated liver cirrhosis, advanced HIV/AIDS, recent bone marrow transplant, or other causes of severe immunodeficiency. However, in a multicenter retrospective series, 89% of immunocompromised patients experienced resolution of symptoms after FMT for CDI, with no deaths due to FMT, although one patient died of pneumonia due to aspiration during the sedation for the colonoscopy.³⁷ There were no infections associated with FMT in these patients. While further evaluation in this relatively high-risk population is warranted, the limited available studies demonstrate that FMT appears to be a safe, efficacious treatment for recurrent, refractory, or severe CDI in immunocompromised patients.

CDI is especially challenging in patients with IBD, given the underlying physiologic complications of disrupted gut mucosa, altered mucosal immunity, and immunosuppressive medications. Patients with IBD develop CDI at higher rates than the general population.^{38,39} FMT appears effective in treating RCDI in these patients, although several studies have reported IBD flares after FMT.

FMT therapy for IBD – an area of investigation

Rationale

IBD is a chronic relapsing inflammatory disorder of the intestine, including ulcerative colitis (UC) and Crohn's disease (CD), which affects approximately 0.5% of adults in the US. Medical therapies focus principally on modulating the inflammatory response, but these immune suppressive therapies have substantial risks including infection and development of neoplasia, especially lymphoma. There is good reason to implicate the intestinal microbiota in the pathophysiology of IBD, suggesting that altered commensal microbiota in a susceptible host may lead to inflammation through a complex interplay of host genetic factors among others. Most animal models of IBD require the presence of bacteria. Moreover, diverting the fecal stream in patients with IBD usually leads to resolution of inflammation distally. Moreover, the microbiota in IBD patients is different than healthy individuals; IBD patients demonstrate multiple perturbations including decreased bacterial diversity and more instability in existing gut flora than in a healthy population.⁴⁰ For example, *Bacteroides* and *Firmicutes* are depleted in IBD. Mouse models demonstrate that some bacteria from these phyla activate T-regulatory cells and could directly contribute to dampening of inflammation.^{40–43} Thus, the rationale behind the use of FMT in IBD is to modulate gut microbiome to improve or alleviate the existing pathologic inflammatory state.

Ulcerative colitis

The first case report of the use of FMT for treatment of IBD was published in *Lancet* in 1989 by Bennet and Brinkman.⁴⁴ Bennet himself suffered from UC that had been refractory to sulfasalazine and steroids, and the case report was a result of self-experimentation with FMT. He transplanted healthy donor stool by large-volume retention enemas. Colonic biopsies taken at 3 months showed resolution of acute inflammation. Bennet reported being symptom free at 3 and 6 months posttransplantation without medication for the first time in many years. A subsequent report by Borody et al⁴⁵ described successful resolution of symptoms, and histological and endoscopic resolution of inflammation in a 45-year-old man with UC and a 31-year-old man with terminal-ileal CD, both of whom had been previously poorly responsive to medications. The durability of each of these responses to FMT was verified at 3–4 months posttransplantation. A 2003 retrospective case series of six patients with endoscopically and histologically confirmed UC who had all failed therapy

with 5-aminosalicylic acid and steroids, including four patients who had also failed azathioprine, demonstrated efficacy of FMT.⁴⁶ These patients were pretreated with antibiotics and whole-gut lavage and received FMT by multiple retention enemas over 5 days. Impressively, all patients achieved a relatively durable response, with disease remission lasting 1–13 years.

Not all patients have been positive. In 2013, Angelberger et al⁴⁷ conducted a prospective study using FMT in five adult patients with moderate to severe UC, who had all previously failed immunosuppressive therapies. None of the five patients achieved clinical remission and only one showed clinical improvement during the 12 week follow-up. Additionally, there was some indication of harm, as all patients had transient fever and elevation of C-reactive protein. Another study in six patients with refractory UC treated with single colonoscopic FMT demonstrated transient clinical improvement in all patients, yet none of the patients achieved clinical remission.⁴⁸ Two RCTs of FMT for UC have just been published; both were stopped early due to futility.^{49,50} However, in one study, the final follow-up of the enrolled patients showed efficacy in the primary endpoint of remission in treated patients (9/38, 24%) compared to controls (2/37, 5%).⁴⁹ Clearly larger studies are needed.⁵¹

Crohn's disease

There are few studies of FMT in patients with CD. A very early case of a patient with refractory CD demonstrated clinical improvement, although the patient relapsed 18 months later.⁴⁵ A 2014 case report described a patient with Crohn's colitis who had failed immunosuppressive therapy and subsequently achieved clinical, endoscopic, and histologic remission after a single fecal infusion.⁵² The study went on to analyze fecal microbial changes pre- and post-FMT. Interestingly, the authors noted that although a clinical improvement was associated with a change in the fecal microbiome, the change did not persist once FMT was discontinued, suggesting that unlike patients with RCDI, patients with IBD may require continual or repeated FMT as maintenance therapy.

Conclusion

Criticism of FMT studies in IBD focuses on the lack of controlled experiments, heterogeneity in disease genotype and phenotype, variable patient and sample preparation, the potential for harm, and the unclear causal relationship of whether the dysbiosis seen in IBD is related to the underlying cause of disease or instead is a downstream result of the

inflammatory mucosal environment.⁵³ However, one of two RCTs of FMT for UC did show benefit. In conclusion, studies suggest that FMT may have a role in therapy of UC,⁴⁹ but more RCTs are needed before this therapy can be adopted. Data for CD are very limited, and RCTs are also needed here. It will be important to correlate therapy with disease location, ie, colon versus small intestine versus both locations.

FMT in irritable bowel syndrome, chronic constipation, and metabolic syndrome: areas under study

The number of reports of FMT for indications other than CDI and IBD is limited, although there are scattered case reports of its successful application in constipation, and irritable bowel syndrome.^{45,54,55} While case reports suggest that FMT may provide symptomatic improvement in refractory IBS, there are no RCTs. A double-blind RCT on the use of FMT for diabetes and obesity in 18 male subjects demonstrated improved fasting triglycerides and insulin resistance.⁵⁶ Additional interest has been raised about potential relevance of FMT in metabolic syndrome, autoimmunity, and autism, all of which have been associated with some degree of altered microbiome or "dysbiosis."^{57,58} However, further investigation is needed to determine the directionality of cause and effect between each of these diseases and the microbial changes that are seen as well as efficacy and long-term safety before using FMT for these conditions.

Risks and long-term safety of FMT

Overall, there are few reported risks associated with FMT, and no serious events in the clinical trials reported to date. In one long-term follow-up study, 77 patients treated at five medical centers using colonoscopic FMT were surveyed.⁵⁹ Long-term follow-up (>3 months up to several years) showed 91% of patients achieved primary cure (resolution of diarrhea within 90 days) and 98% were secondarily cured after additional FMT, probiotics, or antibiotics. In this study, three patients developed new immune conditions (rheumatoid arthritis, Sjogrens syndrome, and idiopathic thrombocytopenic purpura),^{53,60} but it is not known if they were related to the FMT.¹⁰ A long-term patient registry would be helpful to track complications and outcomes.⁵³ Transient fevers, bloating, and constipation have been reported. There are risks associated with the procedure to administer the FMT by either colonoscopy, sigmoidoscopy, or the upper route when aspiration could occur. We do not know the possible long-term sequelae of changing the microbiota, or even if it remains changed longer than several months.⁶¹

Public perception of FMT

Despite the apparent barrier of FMT's lack of "palatability," patient acceptance does not appear to be a major factor precluding FMT. In a survey of 77 patients who recently had colonoscopic FMT for RCDI, 53% of patients stated they would have FMT as their preferred first treatment in case of future CDI recurrence.⁵⁹ A separate survey of 192 patients' (70% women) attitudes toward FMT for the treatment of RCDI demonstrated that although most patients express that they find aspects of this treatment unappealing, the majority still find it to be an acceptable treatment and would prefer FMT to repeated courses of antibiotic therapy.⁶¹ In a separate study, physicians were surveyed about their experience with FMT. Among the most common reasons for not offering or referring RCDI patients for FMT was the belief that patients would find it too unappealing (24%), and only 8% of physicians predicted that most patients would prefer FMT as a treatment if given the choice.⁶² This discordance between physician beliefs about FMT and patient interest in FMT as a therapy suggests that inaccurate preconception of patient attitudes may function as a greater barrier to utilization of FMT than a true lack of "palatability." Limited availability of FMT has led to websites offering instruction on self-administered methods. We cannot condone FMT without medical supervision.

FMT – methodology

Stool donor selection and screening has been variable, and stool donors can be spouses, close relatives, or a healthy unrelated donor. Studies have shown slightly better resolution of symptoms in FMT recipients who receive transplanted stool from intimately or genetically related donors (93.3%) compared to healthy unrelated donors (84%).³⁴ Intimate contacts share risk factor exposure with recipients. Maternal first-degree relatives share the most microbial species in the intestinal microbiota, so the recipient may be more tolerant from an adaptive immune response. There is no consensus on donor screening of stool and blood, but one group suggested criteria including serologic testing (HIV, hepatitis A IgM, hepatitis B antigen/antibody/core antibody, hepatitis C antibody, and serum RPR) and stool tests for enteric pathogens and parasites including *C difficile*, *Giardia*, *Cryptosporidium*, *Cyclospora*, *Isospora*, and *Helicobacter pylori* if administration is via upper GI.¹ Prescreened frozen stool has been shown to be efficacious.⁶³ Stool banks are now available that provide prescreened frozen donor stool. Recipients should get serologic testing (HIV, hepatitis A IgM, hepatitis B antigen/antibody/core antibody, hepatitis C antibody, and serum RPR) to establish baseline values pre-FMT.

There is significant heterogeneity in published procedures for donor stool preparation and transplantation, depending on the route of transplant and volume infused. Methods include enema, colonoscopy, nasogastric, and nasoduodenal routes. In general, donor stool is collected and then mixed with a nonbacteriostatic saline solution into a fecal suspension, which can be strained or blended to remove particulate matter. The fecal suspension is drawn up into syringes. If the recipient undergoes colonoscopy, the material in the syringes is infused into the colon and/or the terminal ileum. There is some evidence to suggest that a larger volume of infused stool promotes more effective treatment for RCDI. When patients were given >500 mL of stool, 97% had resolution, whereas only 80% improved with <200 mL of stool.³⁴ No stool weights are consistently reported, making these results difficult to interpret. Additional research is needed to determine the ideal approach.

Patient preparation, stool processing, and transplant delivery method are likely to affect engraftment of transplanted flora. All patient preparations to date have used pretreatment with antibiotics prior to transplantation and some have also used polyethylene glycol. However, animal studies suggest that antibiotic pretreatment may further decrease already narrowed diversity of the native microbiome. Studies need to address whether antibiotics and polyethylene glycol preparations aid or detract from engraftment of FMT.

Studies also demonstrate considerable variability in stool processing prior to transplantation, further complicating comparison of trials. No study has evaluated whether organisms maintain better viability and diversity under anaerobic conditions, despite the fact that most species in the microbiota are strict anaerobes. To aid in transport, studies have demonstrated that stool can be frozen at -80°C with equally viable engraftment as fresh stool.

Future directions

There are many unanswered questions about FMT. We know that it works, but we really do not know why; is it specific bacteria or groups of bacteria? What is the role of metabolites and of bile salts? The idea that we can identify specific microbes is supported by studies of a synthetic microbiota approach that selected a mixture of bacteria that showed efficacy in the treatment of RCDI.⁶⁴ This approach is appealing because it may eliminate the risk of transmissible disease. The use of pills containing bacteria or spores is currently being tested in clinical trials.^{65,66} This will certainly be the starting point for the extensive use and wide industrialization of FMT.

The specific diseases evaluated for FMT interventions are widely variable in host genetic factors and microbial conditions prior to transplant. For example, CDI patients have often been recently exposed to a substantial antibiotic load before FMT. The condition of the gut microbiome in the aftermath of heavy antibiotic use is significantly more disrupted than the pretreatment flora in other conditions. Careful consideration of pretreatment conditions and a better understanding of disease-specific microbial states must inform protocol development.

Finally, public policy will become an increasingly important consideration regarding appropriate regulation of FMT. Currently, the US Food and Drug Administration treats stool samples as a drug and biologic.⁶⁷ As FMT becomes increasingly common, a push toward industrialization of FMT will raise additional regulatory questions and increase the need for standardization. Specific areas for future research include protocol development (donor selection and screening, preparation, delivery mechanisms), efficacy, health policy, safety and regulation, long-term follow-up as well as the effects of sex, age, ethnicity, and geographic location. Well-designed RCTs to reach an informed consensus regarding suitable indications, safety, donor screening, and administration route are urgently needed prior to more wide-spread use of FMT.

Disclosure

The authors report no conflicts of interests in this work.

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