FMT: What’s Next?
A Narrative Review of Fecal Microbiota Transplantation in Clostridioides difficile Infection and Inflammatory Bowel Disease

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ABSTRACT
Fecal microbiota transplantation (FMT) is an increasingly employed treatment option for Clostridioides difficile infection (CDI), with growing data supporting its safety and effectiveness in patients with concurrent inflammatory bowel disease (IBD). Given that alterations in the gut microbiome are associated with both ulcerative colitis (UC) and Crohn’s disease (CD), the use of FMT for the treatment of IBD itself is another area of active investigation. In this narrative review, we highlight the evidence for use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone, and provide insight into the future of microbiome therapeutics.

KEYWORDS: fecal microbiota transplantation; Clostridioides difficile infection; inflammatory bowel disease

INTRODUCTION
The normal gastrointestinal microbiome contains a delicate and diverse balance of bacteria and other microorganisms which are increasingly recognized to play a major role in health and disease. Fecal microbiota transplantation (FMT) is a powerful therapeutic option in conditions caused by an imbalance in the microbiota, or dysbiosis, such as Clostridioides difficile infection (CDI). FMT aims to restore gut homeostasis through the reintroduction of the community of organisms contained in the fecal material of healthy donors.

The use of FMT in Western medicine was first described in 1958 for the treatment of pseudomembranous enterocolitis.1 It remained rarely utilized until the early 2000s, when the rates of multiply recurrent CDI, refractory to standard antibiotic therapies, sharply increased.2 After a number of cohort studies and randomized-controlled trials (RCTs) demonstrating high efficacy,3,7 FMT is now considered a standard treatment option for CDI. The American College of Gastroenterology (ACG) 2021 guidelines on the treatment of CDI recommended the consideration of FMT for patients after a second or further episode of recurrent CDI and for patients with acute, severe and/or fulminant CDI that is refractory to antibiotic therapy, especially when patients are poor surgical candidates.8

In addition to being effective for the treatment of CDI in patients with IBD, FMT may also be effective in the treatment of IBD itself, as several RCTs have shown promising results.8,12 However, FMT for this indication is still considered investigational and only permissible within clinical trials being performed under an investigational new drug application (IND).13

The process of FMT includes donor selection, serological and stool screening for transmissible infections, anaerobic or aerobic preparation and processing of fecal material, and homogenization of stool to a form which can be administered to the recipient [Figure 1].11,14 Delivery of FMT through colonoscopy or capsules appears to be most effective15,16 though enema delivery may be considered in some circumstances.8

In this narrative review, we discuss the evidence surrounding use of FMT in the treatment of CDI in patients with IBD, as well as for IBD alone. Additionally, we provide insight into future investigations around microbiota therapeutics for these indications.

Figure 1. Preparation of donor stool in saline.
Fecal Microbiota Transplantation for Clostridioides Difficile Infection in Patients with Inflammatory Bowel Disease

In patients with IBD, many variables can predispose to C. difficile colonization and infection, including increased exposure to antimicrobials, immunosuppression, and altered [reduced, less diverse] fecal microbiota. Patients with IBD tend to suffer from more severe CDI owing to an increased prevalence of virulent and refractory C. difficile strains in this population. Patients with IBD who contract CDI are at increased risk of IBD flare, hospitalization, C. difficile carriage, recurrence, and death.

The most recent evidence on the use of FMT in patients with IBD is gathered in a meta-analysis from Tariq et al, who reviewed 25 observational studies addressing the use of FMT for recurrent C. difficile infections in both the adult and pediatric IBD populations. Of the 25 studies included in this meta-analysis, one was a prospective study, the remainder were retrospective. In their analysis, single (i.e., one-dose) FMT was associated with a pooled CDI cure rate of 78% in both the adult and pediatric populations. The definition of cure rate varied by study, ranging from clinical resolution to clinical remission to endoscopic resolution. In studies reporting single and multiple FMTs combined, the pooled cure rate was 88% in the adult population and 77% in the pediatric population, a difference that was significant in the adult population.

Based on early case reports, there was concern that altering the microbiome of the recipient through FMT could lead to worsened IBD symptoms or negatively impact the trajectory of the underlying disease process. In their meta-analysis, Tariq et al found that after FMT, a pooled 26.8% of adult patients experienced an IBD flare, which was defined in most studies as escalation of therapy and/or worsening symptoms. Conversely, the authors of seven studies in this meta-analysis noted that a pooled 33.8% patients had an improvement in IBD symptoms after FMT. This improvement may reflect the notion that FMT may treat underlying IBD symptoms – a concept addressed in later sections of this review.

A systematic review analyzing side effects of FMT for the treatment of CDI [without underlying IBD] found that amongst 1089 patients, most common adverse events included abdominal discomfort, fever, and nausea. Serious adverse events (SAEs) included severe infection (2.5%) and death (3.5%), though the authors of this review acknowledged that many of the studies suffered from small sample sizes. Tariq et al noted that the most common adverse events (AEs) after FMT were fever and diarrhea, with isolated reports of abdominal pain, small bowel obstruction, cytomegalovirus colitis, pancreatitis, and upper respiratory tract infection. The pooled rate in the adult population of undergoing colectomy after FMT was reported as 7.3%, with authors citing worsening IBD symptoms and increased colon cancer risk in the setting of primary sclerosing cholangitis as the indications for colectomy. Eight deaths were reported in this meta-analysis, one of which was due to aspiration during anesthesia, and seven of which were unrelated to FMT. Tariq et al found variables that may be associated with failure of FMT included severity of CDI, low serum albumin, proton pump inhibitor use, and hypertension. There was insufficient data to carry out a meta-analysis on this subject.

The prospective study by Allegretti et al referenced in the meta-analysis is the largest to date on the subject of CDI and IBD outcomes. In this study, the authors enrolled 50 patients with IBD [15 with Crohn’s disease (CD) and 35 with ulcerative colitis (UC)] and a history of two or more confirmed episodes of CDI within the past year. All patients in the study underwent single FMT delivered via colonoscopy. The primary outcome assessed was FMT failure by week 8 [diarrhea and positive C. difficile stool testing]. If FMT failure occurred, patients underwent a second FMT; C. difficile colonization [no diarrhea but polymerase chain reaction positive for C. difficile] was a secondary outcome. The authors found that 89.8% of patients achieved cure after a single FMT. All four of the patients who initially failed FMT underwent a subsequent FMT, resulting in clinical cure by the eighth week. 91.8% of the patients enrolled were found to have decolonized C. difficile by one-week post-FMT. The authors found that two SAEs occurred, both of which were determined to be unrelated to the treatment, and FMT was otherwise well tolerated. A secondary analysis of the patients in this prospective study found that 62% of those enrolled with UC experienced an improvement in clinical severity and disease activity rating scores, 29.4% experienced no change, and 4% had a flare. 73.3% of patients with CD experienced improvement, and 26.6% had no change in disease activity. None of the patients with CD experienced a disease flare.

The most recent ACG guidelines note that in patients with IBD who develop recurrent CDI, FMT should be considered, though the quality of evidence is considered very low. Early evidence on the role of FMT in the treatment of CDI in those with concurrent IBD is promising.

Fecal Microbiota Transplantation for the Treatment of Ulcerative Colitis

Recently there has been more research into the role of FMT in the primary treatment of IBD. This research is based on knowledge that the pathophysiology of IBD involves altered intestinal microbiota.

A meta-analysis of four RCTs investigating the role of FMT in the treatment of UC found a pooled rate for clinical remission of 42.1% in the treatment group and 22.6% in the placebo group, with most assessing clinical remission a
few weeks to months after delivery of FMT. In one of these RCTs, 42% of patients studied had achieved clinical and endoscopic remission 12 months post-FMT.11

There is no clear consensus on dosing of FMT in the IBD population. Paramsothy et al conducted their RCT using intensive dosing (40 infusions of stool blended in saline initially delivered directly to the terminal ileum or cecum via colonoscopy and later self-administered via enema over 8 weeks).10 Others used lower intensity FMT in their RCTs (6 doses of stool blended in water delivered by once weekly retention enemas over 6 weeks12 or 3 doses of stool blended in saline and glycerol initially delivered directly to the right colon via colonoscopy and later administered via enema over 1 week13). It does, however, seem clear that lower dosing employed for the treatment of CDI may not suffice for the primary treatment of IBD, which may require multiple doses for effect.

In an RCT analyzing the safety and tolerability of FMT in the UC population, the side effects most associated with FMT delivered via frozen oral capsule were nausea, fever, and a flare of disease requiring steroid taper.25 Delayed side effects have been seen. In another RCT testing the effect of FMT on UC, low-dose FMT delivered colonscopically and via enema was associated with at least one AE in 51% of participants at 12 months, including worsening colitis requiring colectomy in 13% of patients.11 Notably, 12-month data were considered observational by the authors, as 97% of the control group had crossed over to the treatment group. Two other RCTs on the matter found no significant difference in AEs between treatment and control groups at the 8-week mark.10,12

Pouchitis is inflammation of the ileal pouch, a condition affecting patients with UC who have undergone proctocolectomy. FMT in the management of pouchitis has also been investigated. In a systematic review of four studies (one RCT, one prospective trial, and two cohort studies) by Kayal et al,26 rates of clinical response and remission varied, and FMT in pouchitis was found to be generally safe but ineffective. The authors note that it was difficult to analyze these studies in aggregate given the differing characteristics of the four studies.

**FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF CROHN’S DISEASE**

Evidence for the use of FMT in the treatment of CD is less robust, though early results were promising. A recent systematic review by Fehily et al analyzed 2 RCTs and 13 cohort studies on this topic, finding that FMT may be an effective treatment option for CD; however, large RCTs are lacking.

In one of the RCTs analyzed in this systematic review, the authors investigated the use of FMT in the treatment of CD over 24 weeks, with the primary outcome of colonization of donor fecal microbiota and with clinical parameters as secondary outcomes. In this RCT, a significant difference was found between the FMT and placebo groups in the reduction in CD severity index at the 6-week time point after FMT.9 Of the 17 patients analyzed, 44% of patients in the placebo group had clinical remission (defined as a score of <5 on the Harvey-Bradshaw Index, a calculator assessing CD severity) at 10 weeks, which dropped to 33.3% at 24 weeks. In the FMT group, 87.5% and 50.0% of patients experienced clinical remission at 10 weeks and 24 weeks, respectively. These, however, were not statistically significant differences. AEs were reported in both treatment and placebo groups, including disease flare; however, the authors did not consider these phenomena to be related to FMT itself.9

**PATIENT PERCEPTIONS ON FECAL MICROBIOTA TRANSPLANTATION**

Patient perceptions of FMT may vary, but most patients are amenable to the procedure after counseling and education. Authors of a 2017 study conducted surveys of FMT perceptions amongst 267 patients in gastroenterology waiting rooms.27 The authors found that those with a university degree were likelier to agree to FMT as compared to those without (p=0.04), suggesting that health literacy may play a role in the acceptance of FMT, and 77% of those surveyed were willing to undergo the procedure if indicated, with respondents’ greatest concerns being lack of hygiene (22%) and risk of disease transmission (30%).

Sentiments on hygiene were echoed in a survey of 95 patients medically managed for UC who were surveyed regarding preferences and concerns surrounding FMT in the management of their IBD.28 In this study, 46% of patients surveyed were willing to undergo the procedure, with 41% citing infection, 24% citing cleanliness, and 18% citing potential to worsen UC as their main concerns regarding FMT.

Patients who have undergone FMT appear to be satisfied with the procedure. In a survey of 54 patients who underwent FMT for recurrent CDI, 96% were willing to recommend FMT to others, and 94% were satisfied with the outcome.29

As the concept of FMT has made its way into the public domain, do-it-yourself [DIY] FMT has emerged – a phenomenon in which the public accesses and administers FMT for various conditions. In a 2019 survey of 84 people who had administered FMT to themselves or others, 43% had performed more than 10 FMTs, with 87% of those surveyed using techniques garnered through the internet.30 92% of these patients surveyed had acquired the DIY stool from a donor known to them. Conditions DIY FMT was used to treat included IBD (35%), IBS (29%), and CDI (26%). Notably, 86% of those with CDI felt that FMT improved their condition, and 90% of those with IBD reported improvement. Some of the reasons cited in this survey for implementing DIY FMT included lack of efficacy of other treatments (64%) or lack of access to physicians offering FMT (33%).
CONCLUSION AND FUTURE DIRECTIONS

FMT is now well-established as an effective intervention in the fight against CDI. In patients with recurrent CDI in the setting of underlying IBD, there is mounting evidence for its high effectiveness and safety. The evidence for FMT as a therapeutic for IBD itself is in its infancy, though with notable potential (Table 1). As FMT continues to gain acceptance, improving access to FMT for both patients and physicians will be necessary.

Table 1. Relative Approximation of the Strength of Evidence for the use of FMT

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<tr>
<th>Condition Treated with FMT</th>
<th>Strength</th>
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<tr>
<td>CDI</td>
<td>+++</td>
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<tr>
<td>CDI in patients with IBD</td>
<td>++</td>
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<tr>
<td>Ulcerative Colitis</td>
<td>++</td>
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<td>Crohn's Disease</td>
<td>+</td>
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Directions for future studies include determining optimal strength, dose, processing conditions, and duration of FMT in the treatment of IBD. Further research is necessary to determine whether the effects of FMT on the treatment of IBD are sustained, or if recurrent FMT is necessary. Future studies will ideally risk stratify patients and provide predictions for which patients with IBD will benefit most from treatment with FMT.

Additionally, the role of individualizing FMT, perhaps by manipulating microbiota, needs further investigation. Live biotherapeutic products (consortia of bacteria or other microorganisms) are an exciting new frontier in the management of CDI and possibly other conditions. This is a topic under active investigation, and may represent a future where the standard of care for IBD extends beyond conventional immunosuppressant therapies.

References


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