CLINICAL ENDOSCOPY

Fecal Microbiota Transplantation: An Update on Clinical Practice

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Fecal microbiota transplantation (FMT) is an infusion in the colon, or the delivery through the upper gastrointestinal tract, of stool from a healthy donor to a recipient with a disease believed to be related to an unhealthy gut microbiome. FMT has been successfully used to treat recurrent *Clostridium difficile* infection (rCDI). The short-term success of FMT in rCDI has led to investigations of its application to other gastrointestinal disorders and extra-intestinal diseases with presumed gut dysbiosis. Despite the promising results of FMT in these conditions, several barriers remain, including determining the characteristics of a healthy microbiome, ensuring the safety of the recipient with respect to long-term outcomes, adequate monitoring of the recipient of fecal material, achieving high-quality control, and maintaining reasonable costs. For these reasons, establishing uniform protocols for stool preparation, finding the best modes of FMT administration, maintaining large databases of donors and recipients, and assuring that oral ingestion is equivalent to the more widely accepted colonoscopic infusion are issues that need to be addressed. **Clin Endosc 2019;52:137-143**

Key Words: Fecal microbiota transplantation; *Clostridium difficile* infection; Colonoscopy

INTRODUCTION

Since the first modern descriptions of its use in 1958,[1] fecal microbiota transplantation (FMT) has increasingly gained interest and rapid acceptance during the last 10 years.[2] FMT is defined as the infusion of stool from a healthy individual to a patient with presumed gut dysbiosis.[3,4] FMT can also be delivered through an enteral route either via an endoscope, a nasoenteric tube, or capsules for ingestion. The presumed mechanism of action appears to be the establishment of a new gut microbiota community to restore the normal gut function.[5-7] On the basis of the concept of repopulating the gut with a healthy microbiome, FMT has been successfully used in the treatment of *Clostridium difficile* infection (CDI),

and recommended for other conditions such as inflammatory bowel disease (IBD), autoimmune disorders, certain allergic diseases, and metabolic disorders such as obesity.[8] In recurrent CDI (rCDI), the efficacy and safety of FMT has been proven by several randomized clinical trials (RCTs), and guidelines recommend the use of FMT as a second-line treatment.[9-15] Success rates approaching 92% have been demonstrated in the treatment of rCDI.[10,11]

With the increasing use of FMT owing to its success in treating various diseases, there is growing demand for standardizing the preparation of fecal material, using accepted standards for the delivery, ensuring safety for the recipient, monitoring long-term outcomes, and continuously improving the procedural processes and safety.

INDICATIONS AND CONSIDERATIONS FOR THE RECIPIENT

The use of FMT became rapidly accepted mainly owing to its success in treating rCDI. Data from several RCTs and a large case series revealed the efficacy and safety of FMT.[9-12] A recent systematic review and meta-analysis of 7 RCTs and 30 case series demonstrated the superiority of FMT over

vancomycin therapy, with resolution rates as high as 92%.[16] Moayyedi et al. showed that FMT was superior to placebo or vancomycin therapy.[17] Fischer et al. reported that FMT clinically cured 91% of patients with severe rCDI that failed maximal medical therapy.[18]

The indications for FMT include mild to moderate rCDI after a second recurrence following treatment with a standard antibiotic, moderate rCDI that is not responding to standard therapy after 1 week, and severe CDI that is refractory to standard therapy after 48 h.[3,19] The recent U.S. guidelines recommend FMT in patients with 3 or more recurrences of CDI, although most clinicians prescribe FMT if CDI recurs after 2 courses of antibiotics.[15] The European consensus guidelines suggest that FMT should be considered after the first episode if the disease is severe and refractory to the initial antibiotic therapy.[20] Although there are no strict guideline recommendations stating that CDI should be initially treated with FMT instead of antibiotics, there may be special situations that would justify its application, such as inability to deliver antibiotics to a patient with severe disease, intolerance of the patient to antibiotics, or as a substitute for surgery in highly unstable patients.[21]

It has been suggested that gut dysbiosis underlies the pathogenesis of IBD. Zhang et al.[22] reported that in ulcerative colitis, there is decreased diversity in the patient's microbiota with fewer Firmicutes bacteria and more Proteobacteria. In a recently reported RCT on ulcerative colitis, the response rate to FMT was 55%, with remission in 20% of the patients.[23] Another RCT reported similar response and remission rates of 54% and 27%, respectively.[24] A meta-analysis of 4 RCTs in patients with ulcerative colitis demonstrated a 28% remission rate in patients treated with FMT compared with 8% in those who received placebo.[23] FMT appears to have lower efficacy for IBD than for rCDI, suggesting that other factors are associated with IBD flares besides gut dysbiosis.[25]

Several reports have implied that IBD flares were induced by FMT that was administered for CDI.[2,26,27] A careful follow-up of patients with IBD treated with FMT is warranted because of this concern. An American Gastroenterology Association expert review, however, suggested that earlier FMT in patients with IBD and CDI might be recommendable owing to the relevant complication rate of CDI in these patients.[28] Several RCTs in patients with Crohn's disease are currently under way. To date, there are no standardized practice guidelines for the use of FMT in IBD.

Besides rCDI and IBD, FMT is also being evaluated and considered an experimental treatment for other diseases including irritable bowel syndrome (IBS),[29] nonalcoholic steatohepatitis,[30] hepatic encephalopathy,[31] obesity,[32] and neurological diseases.[33,34]

Although donor screening is well accepted, recipient screening is controversial and without a consensus. Performing viral hepatitis, human immunodeficiency virus, and syphilis tests is recommended before FMT, so that if these diseases were to occur after FMT, clinicians would know that the disease was not transmitted from the donor to the recipient.[21] Kelly et al., in a large case series drawn from multiple centers in the United States, showed that FMT seemed safe in immunocompromised patients, with the exception of neutropenic patients as a standard precaution.[34]

DONOR SELECTION

To minimize the risk of infection or other disease transmission, potential donors undergo rigorous screening including thorough history taking, serological tests, and fecal tests for parasitic, virologic, and bacterial pathogens.[35] Although there are some variations between institutions, there are existing accepted protocols for donor screening (Tables 1, 2).[3,36,37]

Donor stool is provided from 2 sources: patient-directed donors and universal donors through stool banks.[38,39] Patient-directed donors are identified by the recipients, usually

Table 1. Suggested Exclusion Criteria for Potential Stool Donors with a Risk of Infection or Microbiome-Associated Disease

Exclusion criteria[a]
Age <18 yr or >65 yr
BMI >30 kg/m^2
Metabolic syndrome
Moderate to severe undernutrition
History of antibiotics use in the last 6 mo
Diarrhea within the last 3–6 mo
History of *Clostridium difficile* colitis
Immune disorder or use of immunosuppressive medications
History of drug use or other recent risk factor for HIV or viral hepatitis
History of travel to a tropical region in last 3 mo
Any gastrointestinal illness (IBD, IBS, gastrointestinal malignancy, or major surgery) or complaints
History of autoimmune or atopic illness
History of chronic pain syndrome (fibromyalgia, chronic fatigue syndrome)
Neurologic or neurodevelopmental disorders
History of malignancy

HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.
[a]Each institution can adopt different criteria.

family members including spouses, siblings, children, or friends. Patient-directed donors are becoming less frequently used unless the recipient prefers a donor whose diet and other features are known, or if the recipient is concerned about transmissible agents that are perceived to exist in universal donors. The use of patient-directed donor stool incurs treatment delays owing to the time required for sourcing, screening, and testing donors, with resultant increased costs and scheduling problems.[39,40] Additionally, using patient-directed donors may result in the donor feeling coerced and at a risk of revealing confidential information.[41]

Using universal donors for FMT has emerged as the most utilized method in the United States. Healthy volunteers who have a young age and a normal body mass index provide the stool after undergoing thorough history taking, physical examination, and serum and fecal pathogen screening tests.[42]

The use of universal donors has enabled a number of advances in FMT. Decreased microbial diversity is considered a possible cause of rCDI and other diseases of an altered microbiome. Using fecal material from multiple healthy donors could theoretically enhance the therapeutic efficacy of an in-

fusion or ingestion. An RCT on the application of FMT with multiple donors in ulcerative colitis showed clinical remission and endoscopic improvement as well as greater microbial diversity in the recipients.[24] More studies are needed to confirm the value of multidonor FMT.

In addition, Lee et al.[43] conducted a noninferiority RCT of FMT with frozen and thawed stool in comparison with fresh stool for rCDI, to ensure the viability of microbes after freezing. They reported clinical resolution rates of 83.5% and 85.1% in each group, showing that frozen fecal material was as efficacious as fresh stool. Using frozen stool from universal donors reduces recipient costs as well as the time between the decision to perform FMT and the actual infusion.[39,40]

Owing to the cost-effectiveness and convenience of use of fecal material from universal donors, stool banks such as OpenBiome have emerged. OpenBiome uses strict protocols for the recruitment of healthy volunteers: the volunteers are screened, standardized products are generated, and the products are stored after freezing and can be delivered rapidly to 99% of the entire United States.[42] The additional advantages of stool banks are the ability to track registries and perform research on larger data obtained from multiple sites that conduct FMT, with the goal of assuring safety and efficacy.[44] The U.S. Food and Drug Administration (FDA) has approved stool banks such as OpenBiome to provide fecal material for FMT for the treatment of rCDI.[45] For indications other than rCDI, the FDA requires an investigational drug application.[46]

One of the main concerns about the use of stool banks is that multiple recipients could be adversely affected by a currently undetectable infection or transmissible process. Open-Biome has used extremely strict and detailed questionnaires to identify possibly risky donors in advance, and also to rescreen volunteers 60 days after the submission and before the release of the stool. Samples are also stored for future tracking.[42]

PROCESSING OF FECAL MATERIAL

Although there are trivial differences depending on the individual situation, most institutes prepare the stool based on the same protocol. The donor provides fresh stool within 1 month after screening.[3] The potential donors collect their stool into a clean plastic bag and bring it to the microbiology laboratory. A minimum of 50 g of stool is needed.[47] Then, the stool is diluted in normal saline, mixed in a sterile bag by hand stirring, and shaken or blenderized. It is then filtered through moistened 5-layer sterile gauze in a funnel and stored in a restricted safety cabinet to be delivered within 4 h of presentation to the endoscopy suite.

In the case of FMT with a universal donor, the fecal mate-

Table 2. Suggested Laboratory Tests for Potential Donors of Fecal Microbiota Transplantation[a]

Tests	Blood	Stool
Bacteria	Treponema	Enteric pathogen culture: *Salmonella, Shigella, Campylobacter* *Helicobacter pylori* EIA[b] VRE
Viruses	Hepatitis A virus IgM Hepatitis surface antigen Anti-hepatitis C virus HIV 1 and 2	Norovirus EIA or PCR Rotavirus EIA
Parasites	*Entamoeba histolytica* *Strongyloides stercoralis*	Ovum and parasite Microsporidia *Giardia* fecal antigen/EIA *Cryptosporidium* EIA AFB for *Isospora* and *Cyclospora*
Others	Complete blood count Liver function test ESR and CRP	*Clostridium difficile* test Toxin PCR

AFB, acid-fast bacilli; CRP, C-reactive protein; EIA, enzyme immunoassay; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IgM, immunoglobulin M; PCR, polymerase chain reaction; VRE, vancomycin-resistant Enterococcus.
[a]The blood and stool tests should be completed within 1 month of donation, and the tests could be adopted differently depending on each institution and circumstance.
[b]The test for *Helicobacter pylori* is usually needed in the case of upper gastrointestinal delivery.

rial is processed to 250-mL aliquots in a similar standardized method and stored at −80°C until delivered on dry ice to each requesting institute.[42]

Fecal microbiota capsules could be prepared by concentration of the diluted, blended slurry, processed similarly. Then, the fecal solution is pipetted into a capsule holding 650 mL and then sealed into a second capsule. Commercially available acid-resistant, hypromellose capsules (DRcaps™; Capsugel, Cambridge, MA, USA) are usually utilized. A total of 30 capsules are prepared as a single therapeutic dose from each donor stool.[48] Capsules are also stored at −80°C (−112°F) before use, maximally up to 6 months.

PROCEDURE AND PATIENT MANAGEMENT

It seems that FMT for rCDI is most efficacious in patients with mild to moderate disease that responded to antibiotics against *C. difficile* by the fourth day.[11] In the other patients, the concern is that the diarrhea may be from another source. Some clinicians have recommended the earlier use of FMT for patients with severe or severe-complicated disease, as failure of standard therapy could result in higher morbidity and mortality.[49] An accepted method of FMT is to provide antibiotics for at least 3 days before infusion to reduce the amount of *C. difficile*.[20] Antibiotics are generally discontinued at 24–48 h before the FMT.

If the FMT is delivered by colonoscopy, bowel preparation is recommended to improve the visualization of the colon. In patients with a severe ileus, bowel preparation can be replaced by enemas or can be omitted.[38] The standard dose of FMT is specific to each institution or physician; however, about 50–100 g of donor fecal material that has been diluted to 250–500 mL of infusate is most commonly used.[9,12,43,48]

FMT can be administered either directly to the colon or from the upper gastrointestinal tract through capsule ingestion.[38] Delivery to the colon is generally performed using colonoscopy, and less frequently through flexible sigmoidoscopy or an enema. Colonoscopic delivery has an efficacy of 84%–93%[41] and is the modality of choice according to published studies.[47,50,51] If right-sided delivery of FMT is achieved using colonoscopy, the cure rate on a single infusion is 93%.[9] The most serious risk that has been reported with respect to lower gastrointestinal tract administration is perforation.[39,52] Theoretically, bleeding, adverse reaction to sedative drugs, cardiovascular events, transient fevers, or infections could occur, as with any colonoscopy procedure.

For patients with ileus, severe colitis, or objection to colonoscopy, FMT can be provided through the upper gastrointestinal tract via nasoenteric tubes, esophagogastroduodenoscopy, or capsule ingestion.[38] The efficacy rates were reported to

Table 3. Analysis of Administration Modalities for Fecal Microbiota Transplantation

Modality	Strength	Weakness
Nasoenteric tube	1. No necessity for sedation 2. Low cost	1. Discomfort associated with the administration 2. Necessity for radiologic confirmation 3. Risk of vomiting and aspiration
Upper endoscopy	1. Safely performed in patients with a high risk for colonoscopy complications	1. Same weaknesses as those of nasoenteric tube 2. Procedure-related risk 3. Necessity for sedation
Capsule	1. Noninvasive 2. More aesthetic appeal 3. Cost- and time saving 4. Convenience of administration	1. Large burden of the capsule 2. Risk of vomiting and aspiration 3. Cost
Colonoscopy	1. Strong evidence of efficacy for rCDI 2. Useful for differential diagnosis	1. Procedure-related risk 2. Necessity for sedation 3. Necessity for technical expertise 4. Additional cost
Sigmoidoscopy	1. Can be preferred by patients	1. Procedure-related risk 2. Inability to reach the right-sided colon
Retention enema	1. Low cost 2. Well tolerated 3. No need for sedation and can be preferred by patients 4. Can be easily repeated	1. Difficult to retain in some cases 2. Inability to reach the right-sided colon 3. Modality with the lowest efficacy

rCDI, recurrent *Clostridium difficile* infection.

be between 81% and 86%.[41] All forms of upper tract delivery increase the risk of vomiting or aspiration.[53] Capsule delivery is the most recent modality of FMT. Capsules seem to be a reasonable choice for patients who have contraindications to colonoscopy, are geographically distant from an institution that performs colonoscopy, and are opposed to lower gastrointestinal tract access. Capsule delivery reduces the procedure time, colonoscopy cost, need for colon preparation, and risk of colonoscopy complications.[54] Kao et al. demonstrated a comparable efficacy of capsule-delivered FMT to that of colonoscopy-delivered FMT.[55] Although the standard dose per capsule is not yet defined, several studies have shown that a mean 1.6 g of stool per capsule yields a 70% cure rate without adverse events.[48,56] Although no consensus has been achieved, the common impression by a number of authors is that colonoscopic administration has an about 5%–10% higher cure rate in rCDI,[47,50,51] with the additional advantage of assuring that the fecal material reaches the colon because a water jet can be used to spray the material directly onto the mucosa.[21] Table 3 summarizes the strengths and weakness of each modality.

The 2 most common side effects of FMT are bloating and loose stools for the first 24 h, which usually resolve soon thereafter.[35] Most patients generally have formed stool by 1–2 weeks. Stool testing for resolution is not recommended in those with formed stool, but is considered if 3 or more diarrhea stools per day occur after a few weeks.[15,38] The polymerase chain reaction test for *C. difficile* toxin may remain positive for 30 days after a successful treatment, which is another reason not to test asymptomatic FMT recipients.[38] A confusing situation is when abdominal cramping and intermittent frequent bowel movements occur in a patient who might be a carrier of *C. difficile* and who has received an FMT. Such patients most likely have post-infectious IBS. Therefore, the clinician should ideally be able to distinguish post-infectious IBS from rCDI to avoid unnecessarily repeating the FMT.

To date, there is no accepted standard protocol for follow-up. Most physicians and clinic staff contact the patient to assess treatment success and complications about 3–7 days after FMT. Another follow-up contact at 4–8 weeks is recommended.[38]

If the patient develops liquid stool and recurrence of symptoms with a positive stool test for *C. difficile*, the FMT is considered a failure.[13] A recent study suggested that most failures occur within 4 weeks.[49] Allegretti et al.[57] reported that of the failed therapy cases, 25% failed within the first week and the patients are described as primary nonresponders. Another 61% failed between weeks 1 and 4, with the patients referred to as early secondary nonresponders. The rest were considered late secondary nonresponders. On the basis of these data, the authors suggested follow-up of patients approximately 4 weeks after the FMT.[57]

Much of the concern about FMT arises from the fact that the long-term risks are unknown. Screening of donors by means of a thorough history taking may not reveal all future risks. Most FMT protocols endeavor to exclude donors with metabolic syndrome, obesity, neuropsychiatric disorders, and malignancies; however, a disease might emerge in the donor at a later date. This represents both a concern about FMT and a justification for the existence of stool banks, as follow-up of donors and maintenance of records would be more likely in stool banks, allowing the earlier identification of risks.

CONCLUSIONS

FMT is an established treatment for rCDI, and is considered a second-line treatment. It is also being considered for other gastrointestinal diseases such as IBD, IBS, hepatic steatosis, and hepatic encephalopathy. Other disorders that may be related to gut dysbiosis, such as obesity, metabolic syndrome, autoimmune disorders, and neurological diseases, may also be improved by FMT. With stool banks providing universal door fecal material that has been highly screened and catalogued, barriers such as cost and availability can be overcome, allowing research and treatment to be simplified. Additionally, with the advent of capsule FMT, further increases in the use of this treatment may emerge with improved convenience, reduced patient reluctance, and simplified procedural preparation. To maintain patient safety and appropriate use of FMT, standardized protocols for donor screening, stool preparation, methods of delivery, and recipient indications for treatment are expected to emerge.

Conflicts of Interest

The authors have no financial conflicts of interest.

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