

## REVIEW

# Fecal Microbiota Transplantation for Gastrointestinal Diseases

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(Received for publication on May 25, 2014)

(Revised for publication on August 10, 2014)

(Accepted for publication on September 19, 2014)

(Published online in advance on December 15, 2014)

Fecal microbiota transplantation (FMT) is a treatment to restore the normal microbial composition of the gut by introducing fecal microbiota obtained from a healthy donor into a diseased individual. There has been a growing interest in the use of FMT as a treatment of various diseases including *Clostridium difficile* infection (CDI), inflammatory bowel disease, and irritable bowel syndrome. Despite the increasing application of FMT, there are no standard protocols. Many aspects of FMT procedures vary regarding donor selection, preparation of fecal materials, recipient preparation, and route of administration. FMT is most successful in treating recurrent CDI. A randomized controlled trial reported a success rate of approximately 90%. Ulcerative colitis (UC) is a potentially good indication for FMT, although limited evidence is available on the use of FMT for the treatment of UC. Only several small case series have been reported, and the results in terms of efficacy are inconsistent. FMT can also be used to treat diseases other than gastrointestinal disorders in which the gut microbiota is disturbed, e.g., cardiovascular diseases, autoimmune diseases, and metabolic disorders. There remain many unanswered questions with regard to FMT, and more research is required in this field. (doi: 10.2302/kjm.2014-0006-RE; Keio J Med 63 (4) : 69–74, December 2014)

**Keywords:** gut microbiota, transplantation, *Clostridium difficile*, ulcerative colitis, Crohn's disease

## Introduction

The gastrointestinal tract contains more than 100 trillion bacteria of more than 1000 species. The number of bacteria found in one person is 10 times that of all the cells in the human body.<sup>1</sup> The gut microbiota acts like an organ in the human body and affects metabolism, nutrition, and the immune system of the host. This balanced homeostasis between the host and gut microbiota is called symbiosis.<sup>2</sup>

Disturbance of this symbiosis can lead to a variety of diseases including *Clostridium difficile* infection (CDI), inflammatory bowel disease (IBD), irritable bowel syn-

drome (IBS), autoimmune diseases, allergy, cardiovascular diseases, and metabolic disorders. Fecal microbiota transplantation (FMT) is an emerging treatment intended to rebalance the disturbed symbiosis by introducing feces from healthy donors to diseased individuals.

The first therapeutic use of FMT was reported in 1958 for pseudomembranous colitis.<sup>3</sup> Since then, more than 100 case reports of therapeutic FMT have been published for various diseases<sup>4</sup>; however, until recently, there had been no controlled studies of FMT. In 2013, the first randomized controlled clinical trial of FMT for recurrent CDI was published.<sup>5</sup> FMT has finally entered the era of evidence-based medicine.

**Table 1** Summary of fecal microbiota transplantation

Donor selection	Spouses, relatives, friends, or healthy volunteers
Preparation of stools	Fresh, or preserved. Individual, or pooled
Recipient preparation	With or without bowel preparation, proton pump inhibitor, and antibiotics
Route of administration	Nasogastric tube, esophagogastroduodenoscopy, colonoscopy, or rectal enema
Potential indications	Clostridium difficile infection, ulcerative colitis, Crohn's disease, irritable bowel syndrome, diabetes mellitus, autoimmune diseases, cardiovascular diseases, and allergy

There is growing interest in FMT as a treatment for various gastrointestinal diseases as well as metabolic disorders and cardiovascular diseases. We review the current methodology of FMT and its application in gastrointestinal diseases.

### Methodology of FMT

#### Donor selection

Donors are usually selected from relatives, spouses, friends, or healthy volunteers (**Table 1**). Each type of donor has advantages and disadvantages. The risk of transmission of infectious agents may be low if relatives or spouses are donors because they are likely to share some infectious risk factors with the recipient. Healthy volunteers may be able to alter the recipient's gut microbiota most significantly because they do not share a genetic or environmental background with the recipient. On the other hand, healthy volunteers facilitate more flexible donor selections. It is unclear if the donor source affects the efficacy of FMT, but a higher rate of CDI resolution by FMT was reported in unrelated donors (93%) than in related donors (84%).<sup>6</sup>

Donors should be carefully screened because transmission of infectious agents is the greatest risk of FMT. Thus far, there are no standard criteria for donor screening.<sup>4</sup> Donor candidates should be asked about their past/current diseases, travel history, sexual behavior, and defecation habits. A donor candidate with a recent use of antibiotics should be excluded. Family history of autoimmune diseases, cancer, and metabolic diseases may be ascertained. The next screening step includes blood and fecal tests to rule out potentially transmissible diseases that may contaminate the donor feces.

#### Preparation of fecal materials

There is no standardized fecal preparation protocol for FMT (**Table 1**). Feces are usually collected on the day of transplantation from the donor. The feces are dissolved in normal saline or water, homogenized, and filtered to make a liquid slurry.<sup>7</sup> Hamilton *et al.* reported that frozen donor

fecal bacterial preparations were as effective as fresh fecal preparations to treat recurrent CDI.<sup>8</sup> The development of feces-preserving methods will allow the creation of a bank of stools, making FMT easier to perform.

#### Mode of delivery

The routes of administration of fecal materials include nasogastric tube, esophagogastroduodenoscopy, colonoscopy, or rectal enema (**Table 1**). Limited evidence is available as to which route of administration is most effective. In the treatment of CDI, FMT via nasogastric tube is as effective as FMT via colonoscopy.<sup>6,9</sup> The choice of administration route is also likely to depend on the disease type and the anatomical site of the disease. Further studies are needed to determine the best administration route for each indication.

#### Preparation of recipient

When colonoscopy is used to administer fecal materials, the recipient usually takes a bowel preparation to flush out the pre-existing bacteria and allow the donor microbiota to colonize efficiently in the recipient gut. Loperamide may be used to retain the fecal solution in the gut. If fecal solution is administered via a nasogastric tube, a proton pump inhibitor may be given in advance to increase survival of the transplanted bacteria. In some protocols, antibiotics are administered several days prior to transplantation to clear the recipient's gut microbiota.<sup>10</sup> More studies are required to establish the optimal preparation regimen for the recipient.

#### Adverse events

FMT is considered a safe treatment. Adverse events were reported in eight (2.5%) of 317 cases in a systematic review of FMT for CDI. Common adverse events of FMT include transient diarrhea, abdominal cramping, and constipation. Transient inflammatory responses such as elevation of C-reactive protein and fever are more likely to occur in IBD patients, whose mucosal integrity has been impaired.<sup>10</sup>

**Table 2** Protocols of fecal microbiota transplantation used to treat ulcerative colitis

N	Donor	Fecal preparation	Recipient procedure	Ref.
5	Patient's choice	60 g of stool in 250 mL of normal saline	MTZ 500 mg b.i.d. for 5–10 days →PEG administration via NG tube →FMT via NG tube and enema for 3 days with loperamide and PPI	10
6	Patient's choice	200–300 g of stool in 200–300 mL of normal saline	VCM 500 mg b.i.d., MTZ 400 mg b.i.d., and Rifampicin 150 mg b.i.d. for 7–10 days →PEG →FMT via enema for 5 days	21
6	Healthy adults (nonrelated)	100–150 g of stool in 200–350 mL of normal saline	PEG →FMT via colonoscopy →loperamide	22
10	Patient's choice	90 g of stool in 250 mL of normal saline	No pretreatment →FMT via enema for 5 days	23

MTZ, metronidazole; PEG, polyethylene glycol; NG, nasogastric; FMT, fecal microbiota transplantation; PPI, proton pump inhibitor; VCM, vancomycin.

Transmission of infectious agents is the adverse event of greatest concern. Donor feces should be confirmed as negative for common enteric pathogens (e.g., *Yersinia* spp., *Salmonella* spp., *Shigella* spp., *Campylobacter jejuni*, *Clostridium difficile* toxin, enteropathogenic *Escherichia coli*, helminths, ova, and parasites) and common viruses (e.g., hepatitis A, B, and C and HIV-1 and 2). So far, there has been only two reported cases in which an infectious agent was possibly transmitted via FMT.<sup>11</sup>

Limited data suggest that FMT is safe in the long term.<sup>12</sup> However, it is still unclear how the introduction of different microbiota affects the host physiology in the long term.

### Application of FMT in Gastrointestinal Diseases

#### *Clostridium difficile* infection

*Clostridium difficile* is a Gram-positive anaerobic spore-forming bacterium that produces toxins and causes significant diarrhea in antibiotic-treated or immunocompromised patients. Vancomycin or metronidazole is widely used to treat CDI, but 15–30% of patients experience symptomatic recurrence after discontinuation of antibiotics.<sup>13</sup> *Clostridium difficile* overgrows in the colon when the diversity of the gut flora is reduced by administration of antibiotics. FMT, which can restore the diversity of the gut flora to something similar to that of healthy donors, is an ideal treatment for CDI at this point.

Several uncontrolled studies have recently shown the efficacy of FMT for CDI, with success rates of approximately 90%.<sup>8,12,14</sup> The first randomized controlled trial of FMT for CDI was published in 2013. van Nood *et al.* reported marked efficacy of FMT in recurrent CDI.<sup>5</sup> They assigned 43 patients with recurrent CDI to three groups: initial vancomycin administration followed by bowel lavage and infusion of a solution of donor feces through a nasoduodenal tube, a standard vancomycin regimen, or a standard vancomycin regimen with bowel lavage.

In the intention-to-treat analysis, resolution of *Clostridium difficile*-associated diarrhea was observed in 13 of 16 patients (81%) in the infusion group, 4 of 13 patients (31%) in the vancomycin-alone group, and 3 of 13 patients (23%) in the vancomycin with bowel lavage group. Three patients who did not respond to the first infusion received a second infusion from different donors, with resolution in two patients. The study was stopped early because of the significantly higher efficacy of FMT compared with vancomycin. FMT was well tolerated, although the recipients experienced diarrhea (94%) and abdominal cramping (31%) on the day of infusion. Importantly, the recipients of FMT showed increased fecal bacterial diversity after the treatment.

Given these results, FMT has become a promising treatment for recurrent CDI. The latest guidelines for the management of CDI recommend FMT for relapsing CDI.<sup>15</sup> However, FMT has not yet been approved by the U.S. Food and Drug Administration (FDA) for any therapeutic use. An investigational new drug (IND) application is necessary to use FMT in the USA.<sup>16</sup> The American Gastroenterology Association recognizes the importance of FMT and is working with the FDA to streamline the IND process.

#### Inflammatory bowel disease

IBD, including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory disorder of the intestine. The exact causes of IBD are unknown, but there is a hypothesis that alterations in the gut microbiota may evoke an aberrant immune reaction in the gut, resulting in IBD.<sup>17</sup> Although no specific infectious bacteria have been proven to cause IBD, accumulating evidence has demonstrated various alterations of the gut microbiota in IBD, e.g., altered composition, reduced diversity, and a decreased number of bacteria in the gut microbiota.<sup>18,19</sup> In recent hypotheses, those alterations in the gut microbiota

ota, i.e., dysbiosis, elicit chronic intestinal inflammation in genetically susceptible hosts. FMT has been shown to restore the dysbiosis observed in IBD patients.

The first application of FMT in UC was reported in 1989.<sup>20</sup> One of the authors of the paper received FMT for his continuously active UC, resulting in prompt disappearance of clinical symptoms and long-term sustention of this condition without any medications. A recent systematic review identified 18 UC patients without CDI who were treated with FMT.<sup>9</sup> Thirteen of the 18 patients experienced disease resolution; however, selection bias should be considered because all of the cases were from case reports or small case series,<sup>20,21</sup> and there have been no controlled studies of FMT for UC.

Two prospective studies of FMT for adult UC patients were recently published; these included five and six patients, respectively.<sup>10,22</sup> Neither of the studies was a controlled trial; however, both of the studies longitudinally analyzed bacterial composition and changes using 16S rRNA gene-targeted pyrosequencing in FMT recipients. Unexpectedly, none of the combined 11 patients achieved clinical remission after FMT. However, a significant change in the gut microbiota composition was observed in 8 of the 11 patients. One paper reported that the successful colonization of donor microbiota was correlated with clinical improvement in one patient, but the other study did not confirm this finding. Both of the papers reported that the alteration of gut microbiota was temporary in most patients, suggesting the necessity of periodically repeated transplantation to maintain the altered gut microbiota.

A phase I trial of FMT for 10 pediatric UC patients with mild-to-moderate activity has been recently completed; it reported no serious adverse events and a high rate of clinical response (79%) within 1 week.<sup>23</sup> This result stands in contrast to those of the above-mentioned studies. One possible hypothesis to explain this discrepancy is that a certain population of UC patients, but not all, can benefit from FMT. Interestingly, Angelberger *et al.* identified phylotypes that are indicative of disease severity and FMT success, i.e., over-representation of *Enterobacteriaceae* and under-representation of *Lachnospiraceae*.<sup>10</sup> This is an important factor in selecting a subgroup of UC patients that is susceptible to FMT. It should also be noted that FMT protocols are variable among studies, and this fact may have affected the efficacy of FMT (**Table 2**). The optimization of FMT protocols is necessary.

Efficacy data of FMT for CD are limited. To date, only two cases have been reported in the literature. Quera *et al.* applied FMT to a CD patient with recurrent CDI; the patient's clinical symptoms were resolved after FMT despite transient development of bacteremia.<sup>24</sup> Gordon reported a patient with severe Crohn's disease who responded to FMT.<sup>25</sup> Further studies are needed to examine the clinical efficacy of FMT in CD.

Despite limited efficacy data for FMT in IBD, there

is growing interest in the use of FMT for the treatment of IBD. In the ClinicalTrials.gov site (<http://clinicaltrials.gov/>), 10 and seven studies of FMT for UC and CD, respectively, are registered. There remain many unanswered questions regarding the use of FMT for IBD, including patient selection, donor selection, and frequency of administration.

### **Irritable bowel syndrome**

Efficacy data on FMT for IBS are scarce. Borody *et al.* reported their experience on the use of FMT in more than 300 patients with diarrhea-predominant IBS.<sup>26</sup> The details were not reported, but the clinical response rate did not seem to be satisfactory. Given the alteration in the gut microbiota in this disorder,<sup>27</sup> well-designed controlled studies should be carried out with optimized FMT procedures.

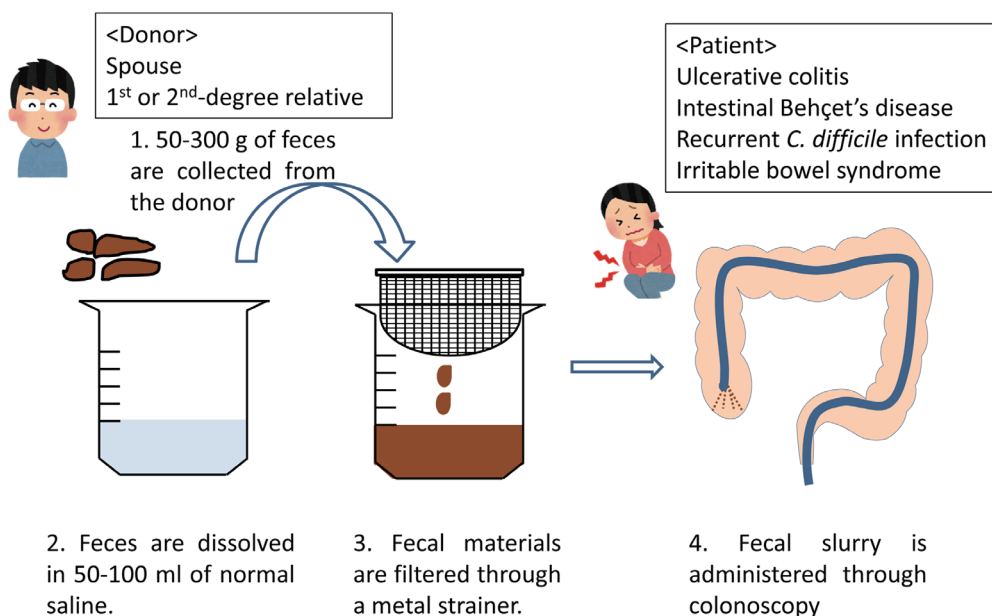
### **Our FMT Study**

We recently launched a clinical study to examine the safety and efficacy of FMT for UC, intestinal Behçet's disease, and CDI (Date of Institutional Review Board approval: February 24, 2014, UMIN registration # 000012814; <http://www.umin.ac.jp/>). This is a single-arm, open-label, non-randomized study. The inclusion criteria are: (1) active UC patients despite treatment with corticosteroids, immunomodulators, tacrolimus, and/or anti-tumor necrosis factor (TNF) agents; (2) recurrent CDI after antibiotic administration; and (3) active intestinal Behçet's disease despite treatment with corticosteroids and/or anti-TNF agents. Patients will select the donor from their spouses or first- or second-degree family members. The donor will be asked about their past and current medical history, drug use, and will be screened for infectious agents. Approximately 50–300 g of feces will be collected, dissolved in 50–100 mL of normal saline, and filtered through a metal strainer to make a liquid slurry (**Fig. 1**). Fecal materials will be administered via colonoscopy after the patient receives the standard bowel preparation for colonoscopy. The components and changes of the gut microbiota will be followed by 16S-rRNA-based sequencing for up to 12 weeks after transplantation. Ten patients with each disease will be enrolled. This study will ensure the availability of FMT in Japanese patients with gastrointestinal disorders.

### **Conclusions**

FMT has emerged as a treatment in conjunction with rapid progress in our understanding of the role of intestinal microbiota in health as well as disease. FMT is considered effective in remedying imbalances of the intestinal microbiota. Consequently, FMT can be applied to





**Fig. 1** Preparation of fecal materials for fecal microbiota transplantation.

a variety of diseases in which the intestinal microbiota is disturbed. This category of disease includes not only gastrointestinal disorders, but other systemic disorders such as metabolic syndrome,<sup>28</sup> diabetes mellitus,<sup>29</sup> non-alcoholic steatohepatitis, autoimmune diseases,<sup>7</sup> and cardiovascular diseases. Although FMT has huge potential in the treatment of various diseases, there remain many unanswered questions on FMT regarding proper indications, optimal protocols, and patient selection, and more research is required.

### Acknowledgments

The authors thank the members of the Keio University FMT team: Keiichiro Saigusa, Kozue Takeshita, and Hirotaka Kiyohara. This study was supported by Grants-in-Aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology; the Health and Labour Sciences Research Grants for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan; and the Keio University Medical Fund.

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