

Human microbiome: From the bathroom to the bedside

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Abstract

The human gut contains trillions of bacteria, the major phylae of which include *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria*. Fecal microbial transplantation (FMT) has been known of for many

years but only recently has been subjected to rigorous examination. We review the evidence regarding FMT for recurrent *Clostridium difficile* infection which has resulted in it being an approved treatment. In addition there is some evidence for its use in both irritable bowel syndrome and inflammatory bowel disease. Further research is needed in order to define the indications for FMT and the most appropriate method of administration.

Key words: Fecal microbial transplant; *Clostridium difficile*; Side-effects; Indications; Metabolic disorders

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Core tip: Fecal microbial transplantation is approved for the treatment of recurrent *Clostridium difficile* infection by either nasojejunal administration or colonoscopy. In addition there is some evidence for its use in both irritable bowel syndrome and inflammatory bowel disease. There are, however, reports of side effects including weight gain, diverticulitis and development of autoimmune disease. Treatment for non-approved conditions should be performed in the framework of clinical research trials in order to better define the indications.

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INTRODUCTION

The human microbiome is defined as the collection of organisms and their genomes inhabiting locations both in and on humans. Our understanding of the gastrointestinal microbiome (GIMb) has been assisted by the Human Microbiome Project^[1] and the Metagenomics

of the Human Intestinal Tract investigational groups.

Trillions of bacteria are present in the human gastrointestinal tract and encompass from 2000 to 4000 different species of bacteria, both aerobic and anaerobic. The major phyla include *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria*.

The human GIMb is in many ways an additional organ of the body. It has ontogeny, anatomy and physiology and its function may be disturbed in certain pathological conditions. It is possible in some instances to restore normal GIMb function by fecal microbiota transplantation (FMT).

Although the concept of fecal transplantation has become more widely practiced in recent years, it has a long history. More than 2000 years ago Ge Hong used FMT to treat food poisoning and severe diarrhea^[2]. Fabricius of Acquapendente in the 16th century described the transplantation of enteric bacteria. The first report of the use of FMT in recent times in more traditional medicine was that of Eiseman *et al*^[3] in the form of a fecal enema obtained from a healthy donor in 4 cases of pseudomembranous colitis.

It is the purpose of this paper to review the current state of fecal transplantation.

FMT FOR CLOSTRIDIUM DIFFICILE INFECTION

Clostridium difficile infection (CDI) is a gram positive anaerobic bacillus that produces spores. It is present in the bowel of 4%-13% of asymptomatic people^[4-6]. CDI is an increasingly recognized cause of infectious hospital-acquired diarrhea in the developed world^[7]. In healthy people it has been thought that it lacks the potential to produce toxins which can result in diarrhea. However, there is an increasing recognition of *C. difficile* in children, healthy adults and pregnant women^[8-10]. Treatment consists of antibiotic therapy with metronidazole, vancomycin or fidaxomicin^[11]. About 25% of those suffering from CDI have a recurrence after the first course of treatment^[12]. For those patients with a recurrent episode of infection, there is a 40% chance of experiencing another recurrence and for those who have had more than 2 episodes there is a 60% chance of a further episode^[12].

In view of the need for a more effective treatment for recurrent CDI, the use of FMT has been examined. In modern clinical research, there is usually an hypothesis that is examined in laboratory animals and then tried in placebo-controlled double blind clinical trials. However, for FMT as treatment for recurrent CDI this order has been reversed. The success of FMT for recurrent CDI has been demonstrated in case series^[13-15] and one randomized controlled trial^[16].

Hamilton *et al*^[13] have reported their experience with 43 consecutive patients treated with FMT for recurrent CDI at the University of Minnesota from 2009. The FMT was performed by colonoscopy. Fourteen of these

patients had inflammatory bowel disease (IBD). There was a mean of 5.9 relapses and the mean success rate was 86%.

Mattila *et al*^[14] reported a retrospective review of 70 patients from 5 medical centers in Finland from 2007-2010. The FMT was performed by colonoscopy. Thirty six (51%) of the patients had the 027 ribotype strain that is more virulent and associated with a higher rate of relapse. All of the 34 patients with the non-027 strain had a resolution within 12 wk compared to 32 of 36 patients (89%) with the 027 ribotype. The four nonresponders had serious comorbidity. Four of the patients who responded experienced a relapse after a year. Two were cured by repeat FMT and 2 by repeat antibiotic treatment.

Brandt *et al*^[15] reported the multi-center United States experience of FMT for recurrent CDI. There were a total of 94 patients of whom there was follow-up data in 77. The primary cure rate was 91%. The secondary cure rate for the 7 patients that did not respond or relapsed was 98%. The mean follow-up period was 17 mo and was up to 68 mo.

There has recently been published a randomized controlled open-label trial of patients with at least one episode of recurrent CDI from Holland and Finland. The numbers of patients involved was small-13 in each of three groups. The groups were randomized to receive initial vancomycin for 4 d and then either bowel lavage, bowel lavage and donor feces through a nasoduodenal tube or just vancomycin alone. The study was stopped prematurely after an interim analysis revealed a resolution of CDI of 81% in the group receiving feces by nasoduodenal infusion as compared to 31% receiving vancomycin alone and 23% receiving vancomycin with bowel lavage^[16] (Figure 1). These were much smaller numbers than initially planned for. Thus this study is consistent with previous case reports.

In view of the limited data from randomized controlled trials a systematic review of FMT involving 317 patients from 27 case series and reports has been published^[17]. Two thirds of these were case series. There was resolution of the disease in 92% of cases, 89% after a single treatment. The lowest rate of resolution was by infusion *via* gastroscopy or nasojejunal tube. This is especially relevant regarding the above mentioned randomized trial^[16], since the number of cases was very small due to the early termination of the trial mandated by the review committee. Although there is great heterogeneity between the various case reports and case series making up this systematic review, there was found to be a higher relapse rate in patients who received both bowel lavage and antibiotics before FMT (4/33, 12.1% vs 5/150, 3.3%).

In the light of this data FMT is now recognized as treatment for a third recurrence of CDI^[18].

The rationale for use of FMT has been shown in a mouse model of mice treated with clindamycin and then infected with *Clostridium difficile* that had been

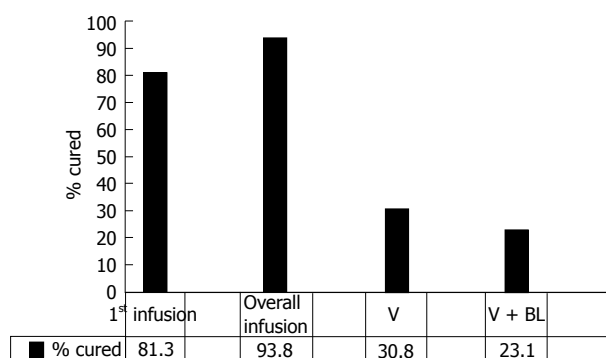


Figure 1 Rates of cure after treatment of recurrent *C. difficile* infection by nasojejunal infusion of donor feces. The data show first infusion, overall infusion after retreatment for a treatment failure, vancomycin (V) treatment, and vancomycin treatment and bowel lavage (V + BL) (16).

isolated from patients with CDI. The mice developed chronic disease and responded to the administration of homogenized feces from healthy mice^[19]. Thus the data that is available support the use of FMT for the treatment of recurrent CDI.

FMT - HOW TO DO IT

The first issue to be addressed is the donor of the feces. Initially the donors of the feces were "healthy donors" with no other details provided^[3]. In some case the stools of medical residents were used. Until 2011, a partner or family member was the most frequent source of donor. It was assumed that any infectious diseases would already have been transmitted between the donor and recipient. This has not been examined by evidence-based medicine. More recently the NIH in the United States has required that donor stool be examined for *C. difficile* toxin, enteric bacterial pathogens (including *Listeria monocytogenes*, *Vibrio cholera* and *Vibrio parahaemolyticus*), parasites including *Giardia* (*via* antigen test), *Cryptosporidium* (antigen test), *Isospora* (acid-fast stain) and Rotavirus. In addition the donor blood needs to be screened for hepatitis A (IgM), B (HBsAg, anti-HBc-IgG and IgM, and anti-HBsAg) and C (HCV antibody) viruses, HIV type 1 and 2 and syphilis. In addition *H. pylori* should be tested for. The Israel Ministry of Health protocol is shown in Table 1. The tests for the donor may not be entirely covered by the medical insurance organizations since they may not be indicated for the routine medical care of the stool donor.

There is a growing trend for DIY stool transplants with instructions being available on the Internet- for example www.thepowerofpoop.com. There are cases when patients refer themselves to centers performing FMT after self-administration of unscreened donor stool from a family member has failed^[20]. The only systematic review of FMT suggested that stool from a related donor (spouse or intimate partner) resulted in a higher rate of cure (93.3%) as compared to an unrelated donor (84%).

The FMT program at the University of Minnesota

has reported their experience with frozen/thawed or fresh fecal preparations from universal donors^[13] with cure rates of 90% for frozen material and 92% for fresh material. This is higher than those reported with patient selected donors (70%), although only small numbers of patients were included in each group- 10 individual donors and 33 standard donors. A recent report of increase in weight after fecal transplantation from a related obese donor provides a note of caution^[21]. For these reasons we believe that the use of individual donors should not be the first choice for obtaining feces for transplantation.

The donor needs to provide the stool sample into a clean plastic container. The amount is variable although 50 g in 250 mL of diluent is a common method. Different fluids have been used as the suspending fluid, including milk, water and saline. The resolution rates with saline and milk are 86.2% and 88.6%, with recurrence rates of 3.0% and 3.2%^[17]. The use of water resulted in a resolution rate of 98.5% and recurrence of 7.8%. Three hundred milliliter is the usual dose for colonic FMT and 60 cc for upper GI tract FMT.

The patients who will receive the FMT need to have a large volume colonic lavage prior to the procedure. This is thought to cleanse the spores of *C. difficile* that are responsible for the recurrence of the infection. There are different variations and some reports include loperamide if receiving a fecal enema^[22], and proton pump inhibitor (to reduce the bactericidal effect of gastric acid) if the infusion of stools is *via* a nasogastric or nasojejunal route^[23,24].

Some groups maintain the patient on vancomycin orally until the time of the FMT^[16,25]. This practice is thought to reduce the vegetative forms of *C. difficile* since vancomycin has no action on the spores. However, the systematic analysis of Gough *et al.*^[17] found a higher relapse rate with the combination of bowel lavage and antibiotics. Our group policy is to discontinue antibiotics two days prior to FMT.

Recently, there has been a report of the use of capsules containing frozen stool. Twenty patients with recurrent CDI were treated with 15 FMT capsules daily for 2 d. The resolution rate was 70%. The 6 failures were retreated and 4 of these had resolution, resulting in an overall response rate of 90%. A total of 30% of the patients experienced mild abdominal complaints that resolved within 72 h. This is a preliminary study that needs to be repeated and expanded but is promising and if successful will probably replace the current methods of administration of the donor stools.

SAFETY AND COMPLICATIONS

Two studies have provided information regarding long-term follow up after FMT. A study from Finland of 70 patients had no data on complications^[14], although the authors state "none of our patients had any serious adverse effects that could be related to fecal transplantation". A multi-center North American study

Table 1 The Israel Ministry of Health protocol for donor screening for fecal microbial transplantation

<p>Patient eligibility for FMT</p> <p>1 Questionnaire to exclude potentially transmissible diseases</p> <p>(1) Practices protected sexual intercourse (or in a monogamous relationship with a healthy partner)</p> <p>(2) Has not had tattooing in the previous six months</p> <p>(3) Does not have any known infectious diseases</p> <p>(4) No drug abuse</p> <p>(5) Has not travelled to the Far-East, India, Africa, Central or South America within the previous six months</p> <p>(6) Has no known autoimmune disease</p> <p>(7) There is no history of any gastrointestinal disease, including inflammatory bowel disease, celiac disease or irritable bowel disease</p> <p>(8) Has not had any previous bowel resection</p> <p>(9) There is no history of infectious diarrhea in the previous 12 mo</p> <p>(10) Has not received antibiotic therapy in the previous 2 mo</p> <p>2 Laboratory tests</p> <p>(1) Negative stool culture</p> <p>(2) Negative stool microscopy, including Giardia, Cryptosporidium and <i>Isopora belli</i></p> <p>(3) Negative <i>Clostridium difficile</i> toxin</p> <p>(4) Negative serological testing for HIV, HBV, HCV, HAV, VDRL, CMV</p> <p>(5) Negative test for <i>Helicobacter pylori</i> (either C¹³ urea breath testing, stool antigen or serum antibodies)</p>

FMT: Fecal microbial transplantation. HCV: Hepatitis C virus; HBV: Hepatitis B virus; CMV: Cucumber mosaic virus; VDRL: Venereal disease research laboratory; HIV: Human immunodeficiency virus.

reported data from more than 3 mo follow up in 77 of the 94 eligible patients. Ninety-seven percent of the patients stated that they would choose FMT again as treatment for a recurrent CDI and 53% would prefer it as a first option. Twenty-seven percent of the patients developed abdominal pain following FMT but it was minor and resolved within 10 d. Four patients developed an autoimmune disease-peripheral neuropathy, rheumatoid arthritis, Sjogrens and thrombocytopenia^[15]. We have recently treated a patient with severe CDI who required 2 consecutive FMTs and developed thrombocytopenia after each transplantation. Recently, there has been a report of diverticulitis following FMT for CDI^[26].

The field of FMT is rapidly developing and as experience accumulates there are more reports of possible side effects or complications. Thus it is important to carry out these procedures in centers with approved protocols and to discourage patient or non-physician supervised self-administration.

CDI is common in patients who are immunosuppressed. Recently a retrospective study from 16 medical centers in the United States reported their experience in FMT in 80 immunosuppressed patients with severe or recurrent or refractory CDI^[27]. The majority of the patients were immunosuppressed due to solid organ transplantation or treatment for IBD. The cure rate was 79% for the first time and 89% overall. There was a 15% incidence of serious adverse events within 12 wk. Five of the 36 IBD patients had post-FMT disease flare. Thus it appears that successful FMT is possible in immunosuppressed patients, although with a slightly reduced success rate and a higher rate of adverse

events.

OTHER USES FOR FMT

IBD

FMT appears to be an established treatment for CDI and attention has focused also on IBD. Gastrointestinal microbiome dysbiosis has an important role in the pathogenesis of IBD^[28]. In addition a recent study employing the molecular biology technique of terminal restriction fragment length polymorphism (T-RFLP) to profile the bacterial species in fecal samples has enabled the calculation of a discriminant score which was shown to be a biomarker for disease activity in UC^[29]. The first FMT for ulcerative colitis (UC) was reported in 1989^[30] and described the reversal of the UC that Bennet (one of the authors of the paper) had suffered from for 7 years by FMT administered as fecal enemas. Case series have suggested some role for FMT in UC^[31-33]. However, a recent report^[34] of a prospective study of FMT in 5 adult patients with moderate to severe UC who had failed various immunosuppressive therapies adds a note of caution. None of the patients were receiving concomitant immunosuppressive therapy. None of the patients entered clinical remission after 12 wk of follow-up and only one had some clinical improvement. Additionally all of the 5 patients had fever and an elevation of CRP after the FMT and a worsening of the diarrhea the day after the procedure. In the patient who experienced some response there was an alteration of the fecal flora after FMT. Another recent trial of FMT for UC did not demonstrate a significant effect^[35] in 6 patients but there was a change in the gut microbiota. The alteration of gut microbiota was temporary and it may be necessary to undergo repeated transplantation in order to maintain the altered gut microbiota. A phase 1 trial of FMT for 9 pediatric UC patients with mild-to-moderate activity reported no serious adverse effects and found that 7 of these (79%) had responded within a week^[36]. It may be that certain population subgroups suffering from UC will derive benefit from FMT. A recent systematic review and meta-analysis of FMT therapy for IBD showed a clinical remission of 22% for UC^[37].

Crohn's disease (CD) has also been treated by FMT. The data are limited to case reports and small case series^[32,38]. The recent systematic review and meta-analysis of FMT as therapy for IBD found higher pooled estimate of clinical remission for CD, 60.5% as compared to UC 22%^[37]. There have been 2 previous systematic reviews of FMT for IBD^[39,40]. The success rate of FMT for adult IBD patients was 77.8%^[39] but outcomes were measured by "success rates" only. There were also other methodological problems^[37]. The other review^[40] noted endoscopic and histologic remission of 63% in 24 patients but this too has been criticized for methodological flaws^[37]. A note of caution is necessary following the report of bacteremia after FMT in a patient

with Crohns and CDI^[41].

Thus the jury is out regarding the utility of FMT for IBD and further work is required in order to define the effect of different methods of delivery, changes on the microbiome and the interaction between phases of the illness (induction or maintenance) and the impact of additional therapies.

Irritable bowel disease

There is evidence linking dysbiosis to irritable bowel disease (IBS)^[42,43] and thus there is a question regarding the possibility of FMT for treatment. There have been reports of a favorable outcome after FMT in diarrhea - predominant IBS^[32]. A recent report of single-center experience of 13 patients with IBS of whom 9 had diarrhea-predominant, 3 constipation-predominant and one mixed-type^[44], found resolution or improvement in symptoms in 70% of the patients overall. Presumably, the small sample size prevented the reporting of the response rate in each group separately. This subject has recently been reviewed^[45]. There is a need for further research to define the role of FMT in the treatment of this common condition.

FMT and metabolic disorders

It is now apparent that there is an interaction between the microbiome of the intestinal tract and the metabolism of the human host and that there is a link to obesity^[46]. Although there are reports of changes in the ratio of *Firmicutes/Bacteroides* with human obesity^[47] other groups have not found such changes^[48,49]. There are reports in mice of the induction of a phenotype of the metabolic syndrome *via* fecal transplants^[50]. This complex subject has been reviewed^[46,51,52]. Furthermore in mice the intestinal microbiota plays a role in the development of non-alcoholic fatty liver disease^[53]. Recently stools from twins discordant for obesity has been shown to promote or impair the development of obesity in adult male germ-free mice^[54].

In humans there is a single study reporting that FMT using stool from lean donors improves insulin sensitivity in obese male individuals concomitant with an increase in butyrate-producing intestinal bacteria^[55].

We are currently conducting a randomized controlled trial of FMT in obese individuals undergoing screening colonoscopy in order to determine if there is a clinical effect on obesity in humans (clinical trials.gov NCT02336789).

Other conditions

Immune thrombocytopenia (ITP) was reported to be reversed in a patient treated with FMT for UC - but only published in an abstract form^[55]. Other fields include autoimmune disease, allergic disorders, and neuropsychiatric disorders. This exciting field has recently been reviewed^[56].

In summary, fecal microbial transplantation is now prime time treatment for refractory *Cl. difficile* infection. In addition, it may be of use for treating other disorders

of the gastrointestinal tract including irritable bowel syndrome and IBD. Further research is needed to define the optimal method of administration of the stools as well as the indications for treatment in other conditions. In addition there needs to be vigilance for the development of side-effects related to this technique. For this reason it is important that treatments for other indications be conducted in the framework of research protocols.

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