REVIEW ARTICLE

An overview of fecal microbiota transplantation: techniques, indications, and outcomes CME

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Fecal microbiota transplantation has emerged as a highly effective treatment for recurrent *Clostridium difficile* infection with very early experience to suggest that it also may play a role in treating other GI and non-GI diseases. Donor screening guidelines are now available along with recommendations regarding routes of administration, diluents, stool weights, and volumes of stool to be used. This review aims to provide an overview of fecal microbiota transplantation, to summarize the data on its efficacy, and to provide the reader with an understanding of how to perform this novel treatment.

Fecal microbiota transplantation (FMT) refers to infusion of a fecal suspension from a healthy individual into the GI tract of another person to cure a specific disease. FMT is by no means a new therapeutic modality; however, it did not receive public attention until recently, after several studies were published that showed stool is a biologically active, complex mixture of living organisms with great therapeutic potential for *Clostridium difficile* infection (CDI)[1-3] and perhaps other GI[4-7] and non-GI[8,9] disorders. The revelations about the human microbiome that are being published by the Human Microbiome Project consortium are bringing the strength of science to clinical observation, thereby enhancing our understanding of just how much of our daily function, health, and even disease states are dependent on the microorganisms living in an intimate relationship with each cell in our body.[10]

Transplantation of stool for the treatment of GI disease was first reported in 4th century China by Ge Hong, who described the use of human fecal suspension by mouth for patients who had food poisoning or severe diarrhea.[11] In the 16th century, Li Shizhen described oral administration of fermented fecal solution, fresh fecal suspension, dry feces, or infant feces for the treatment of severe diarrhea, fever, pain, vomiting, and constipation.[11] In order to make FMT more palatable, herb doctors at the time referred to the fecal suspension as "yellow soup."[11] In the 17th century, FMT was used in veterinary medicine, both orally and rectally, and was later termed "transfaunation."[4] The first use of FMT in humans was for the treatment of pseudomembranous colitis caused by *Micrococcus pyogenes* (*Staphylococcus*); it was given as fecal enemas and was reported in 1958 in a 4-patient case series by Eiseman et al.[12] The first use of FMT for CDI was also by enema and reported in 1983 by Schwan et al.[13] Until 1989, fecal retention enema was the most common technique for FMT;[14] however, alternative methods have been used subsequently, including fecal infusion via nasogastric tube (1991),[15] gastroscopy and colonoscopy (1998, 2000),[16,17] and self-administered enemas (2010).[18] To date, more than 400 cases of FMT have been reported worldwide including approximately 75% by colonoscopy or retention enema and 25% by nasogastric or nasoenteric tube or by gastroduodenoscopy.[19,20]

The incidence of CDI has increased to epidemic proportion over the past 10 to 15 years. In the United States, from 1996 to 2003, CDI increased from 98,000 to 178,000 cases and 31 to 61/100,000 hospital discharges,[21] whereas the unadjusted case-fatality rate rose from 1.2% in 2000 to 2.3% in 2004.[22] It is now estimated that 500,000 to 3 million cases of CDI occur annually in U.S. hospitals and long-term care facilities, with an estimated hospital excess cost of care of approximately $3.2 billion.[23]

Currently, first-line treatment for CDI includes cessation of the culprit antibiotic, if possible, and treatment with metronidazole, vancomycin, or fidaxomicin, depending on disease severity.[24,25] Most patients with CDI initially respond to this treatment, but recurrence rates are 15%

Abbreviations: CDI, Clostridium difficile *infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; RCDI, recurrent* Clostridium difficile *infection.*

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to 35%.[26] Patients who have 1 recurrence have up to a 45% chance of a second recurrence, and after a second recurrence, up to 65% of patients will have a third.[27] Recurrences are usually treated with additional courses of metronidazole, oral vancomycin, or prolonged oral vancomycin in various pulsed-tapered regimens, occasionally "chased" by other antibiotics such as rifaximin.

The high recurrence rates of CDI prompted the need for alternative therapies, to which we believe FMT offers a rational and relatively simple approach. It is now accepted that disruption of the normal balance of colonic microbiota as a consequence of antibiotic use or other stresses results in CDI. Patients with recurrent CDI (RCDI) have decreased phylogenetic richness and a reduction of *Bacteroidetes* and *Firmicutes* phyla in their stool compared with patients who have just 1 episode of CDI.[3] Chang et al[3] showed in just 3 control subjects, 4 patients with 1 episode of CDI, and 4 patients with RCDI that stools of those with RCDI had roughly one third the number of phylotypes of control subjects, and one fourth to almost one half the number of phylotypes present in patients with an index episode of CDI. Furthermore, stools of control subjects had means of about 36% Bacteroidetes (~38%, 60%, 10%) and 58% Firmicutes (~54%, 38%, 82%) compared with 57% Bacteroidetes (~48%, 38%, 72%, 68%) and 40% Firmicutes (~48%, 58%, 22%, 30%) in patients with an index episode of CDI. In patients with RCDI, there was a perturbed microbiome that consisted of 100% Firmicutes in 1 patient, ~63% Proteobacteria (with ~37% Firmicutes) in another, and ~72% Verrucomicrobia (with ~10% Firmicutes and ~18% Bacteroidetes) in a third. FMT is thought to provide its therapeutic benefit by re-establishing a balanced microbiota with its "colonization resistance."[28] Studies using terminal restriction fragment length polymorphism analyses and gene sequencing techniques have shown that the bacteria of the recipient's stool closely resemble that of the donor about 2 weeks after FMT and is dominated by *Bacteroidetes*[1,2]; this alteration persists for more than 30 days after transplantation.[1,2] Stable engraftment of intestinal bacteria after FMT also was demonstrated in a study using previously frozen fecal bacteria from a healthy donor.[29] Post-FMT samples in this study displayed an increased abundance of Bacteroidetes and Firmicutes to resemble donor stool, whereas *Proteobacteria* and *Actinobacteria* were less abundant (<5%) after FMT compared with pre-FMT stool samples.[29] Quantitative differences in groups of intestinal bacteria were reported in a study of patients with RCDI who underwent FMT via a nasoduodenal tube.[30] Specifically, increased numbers of Bacteroidetes and of *Clostridium* clusters IV and XIVa (by a factor of 2-4 for both groups) and decreased numbers of *Proteobacteria* (by a factor of up to 100) were noted after FMT.[30]

Although FMT is best known for its use in RCDI, it also has been used successfully for inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), idiopathic constipation, and a variety of non-GI diseases. Although there is no doubt that FMT results in impressive cure rates for the treatment of RCDI and may also be beneficial for other diseases, its optimal route of administration remains uncertain. FMT is most commonly performed via colonoscopy; however, donor feces also have been administered via a nasogastric or nasoenteric tube, gastroduodenoscopy, and enema. Few studies have attempted to answer the questions of which route is most efficacious and safe; however, to date, there have been no serious adverse effects directly attributable to FMT, and all have remarkable cure rates.

FMT: A SUCCESS STORY

Gastrointestinal diseases

Current literature on FMT for RCDI predominantly comprises single-center case series and case reports,[6,18,31-40] a meta-analysis,[41] 2 systematic reviews,[13,14] and 1 recently published randomized, controlled trial.[30] In all, about 92% of patients were cured of their RCDI, with a range of 81% to 100%.[6,18,20,31-40,42] The only multicenter long-term follow-up study of patients who underwent colonoscopic FMT for RCDI reported an astounding overall ultimate cure rate of 98%.[43] Patients in this study had symptoms for an average of 11 months before FMT, and most (74%) reported resolution of diarrhea within 3 days.[43] Immediate symptom resolution and long disease-free intervals after FMT for RCDI also have been reported in other studies,[4,10,31,32] including the index report in 1958,[12] and may result from of the durable effect of FMT to repopulate the colon with normal commensal organisms.[1,2] A systematic review of FMT, including all methods of administration and comprising 317 patients from 8 countries and 27 case series and reports, found an overall cure rate for RCDI of 92%.[20] In another systematic review of FMT, comprising 124 patients with RCDI, 83% of patients reported improvement in symptoms immediately after 1 FMT.[42] FMT has even been proposed as first-line treatment for patients with CDI rather than antibiotics because of its rapid effect, minimal risk, relatively low cost, ability to avoid exposure to antibiotics, and re-establishment of a "balanced" colonic microbiota.[44]

FMT also has been successfully used to treat a variety of other GI disorders including IBD,[5,45-48] IBS,[10,49-52] and constipation,[51] and there is a growing literature on an altered intestinal microbiome in these and other disorders[54-56] (Table 1). In a case series of 55 patients with diarrhea, constipation, abdominal pain, or IBD treated with FMT, cure was reported in 20 (36%), decreased symptoms in 9 (16%), and no response in 26 (47%) patients.[5] A systematic review, comprising 17 studies and 41 patients with ulcerative colitis or Crohn's disease who underwent FMT found a reduction or complete resolution of symptoms in 76%, cessation of all