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

TABLE 1. Disorders associated with an altered intestinal microbiome

GI
Cholelithiasis
Colorectal cancer
Hepatic encephalopathy
Idiopathic constipation*
IBS*
IBD*
Familial Mediterranean fever
Gastric carcinoma and lymphoma
Recurrent *Clostridium difficile* infection*
Non-GI
Arthritis
Asthma
Atopy
Autism*
Autoimmune disorders
Chronic fatigue syndrome*
Diabetes mellitus and insulin resistance*
Eczema
Fatty liver
Fibromyalgia*
Hay fever
Hypercholesterolemia
Idiopathic thrombocytopenic purpura*
Ischemic heart disease
Metabolic syndrome*
Mood disorders
Multiple sclerosis*
Myoclonus dystonia*
Obesity
Oxalic acid kidney stones
Parkinson's disease*

IBS, Irritable bowel syndrome; *IBD*, inflammatory bowel disease.
*Some reports on improvement or cure with fecal microbiota transplantation.

IBD medications in 76%, and "prolonged remission" of active disease in 63%.[47] Additionally, the majority of patients (86%) who were refractory to IBD medications subsequently responded to them after FMT.[57] In those with IBD and CDI, FMT resulted in the cure of CDI in 100% and marked reduction or resolution of diarrhea in 92%.[47] A recent review that summarizes the data of 3 publications comprising 9 patients with refractory IBD (8 patients with ulcerative colitis and 1 with Crohn's disease) treated with fecal enemas, reported remission of disease in all 9 patients for a period ranging from 3 months to 13 years.[48] In another series, 45 patients with chronic constipation were treated with colonoscopic FMT and subsequent fecal enema infusions, 89% of whom (40 of 45 patients) reported relief of defecation, bloating, and abdominal pain immediately after the procedure.[58] Rigorous studies are needed in these areas to determine the optimal route of administration, frequency, and long-term efficacy of FMT.

Non-GI diseases

Therapeutic use of FMT is not confined to GI diseases, and there is a growing scatter of studies on the intestinal microbiota or FMT in a wide range of other disorders (Table 1) including Parkinson's disease,[9] chronic fatigue syndrome,[55] multiple sclerosis,[59] myoclonus dystonia,[60] obesity,[61] insulin resistance and the metabolic syndrome,[8] and childhood regressive autism,[62] among others. The beneficial effect of FMT on non-GI disorders was an unanticipated observation that was initially made in 1 patient with ulcerative colitis and idiopathic thrombocytopenic purpura who had remission of both diseases after FMT[63] and in 3 patients with multiple sclerosis who underwent FMT for chronic constipation, in whom normal defecation was achieved and improvement was noted in motor symptoms and urinary function resulting in a regained ability to walk and the removal of indwelling catheters.[59] Of 34 patients with chronic fatigue syndrome, 14 (41%) reported persistent relief and 12 (35%) showed little or late relief of their chronic fatigue symptoms on interview 11 to 28 months after FMT.[64] In autism, the link with the intestinal microbiota is supported by observations that disease onset often follows antimicrobial therapy, associated GI abnormalities are not uncommon, certain *Clostridium* spp are present at 10-fold higher numbers in stool samples from autistic children, and autistic symptoms have sometimes been reduced by oral vancomycin treatment.[10] Although at first glance it appears as if there is no connection with neuropsychiatric disease and intestinal flora, studies now have expanded the original concept of the brain-gut axis and recognize the brain-gut-microbiota axis.[53] Moreover, the increasing recognition of the role that microbiota play in affecting mood and thought is actively being studied.[65,66]

FMT: METHODOLOGY

Although FMT has been practiced intermittently since the 4th century, a standardized protocol rooted in evidence-based practice is still being sought.

TABLE 2. Donor and recipient screening for FMT

History
Has the donor received antibiotics within the past 3 months?
Has the donor been incarcerated, gotten any tattoos or body piercings within the past 3 months?
Has the donor engaged in high-risk sexual behaviors within the past 3 months?
Does the donor have a history of chronic diarrhea, constipation, IBD, IBS, colorectal polyps or cancer, immunocompromise, morbid obesity, metabolic syndrome, atopy, or chronic fatigue syndrome?
Does the recipient have any food allergies? If so, the donor must not ingest these items for several days before FMT.
Donor stool testing
Clostridium difficile toxin
Stool culture
Stool ova and parasites
Giardia stool antigen
Helicobacter pylori stool antigen
Cryptosporidium antigen test
Isospora (acid fast stain)
Rotavirus
Donor serologic testing
Hepatitis A IgM
Hepatitis B surface antigen
Hepatitis B core IgG and IgM
Antibodies to hepatitis B surface antigen
Hepatitis C antibody
HIV types 1 and 2 antibody
Syphilis

FMT, Fecal microbiota transplantation; *IBD*, inflammatory bowel disease; *IBS*, irritable bowel syndrome.

How should donors and recipients be screened?

FMT carries a potential for transmission of infectious agents, and, therefore, rigorous screening tests are recommended to reduce such risk (Table 2).[67] Donor stool should be screened for *C difficile* toxin, enteric bacterial pathogens and parasites such as *Giardia* (*Giardia* antigen test); in some cases, testing for *Cryptosporidium* (*Cryptosporidium* antigen test), *Isospora* (acid fast stain), and Rotavirus may be important. Donor blood is screened for hepatitis A (IgM), B (hepatitis B surface antigen, anti–hepatitis B core [IgG and IgM], and anti–hepatitis B surface antigen) and C (HCV antibody) viruses, HIV types 1 and 2, and syphilis. Screening for *Helicobacter pylori* is also prudent regardless whether FMT is performed via the upper or lower route. Recipients are tested for HIV types 1 and 2; hepatitis A, B, and C; and syphilis. Because of the ready availability of stool, patients who desire FMT may accept offers of unscreened stool from well-meaning friends and relatives, but this practice of using unscreened stool is to be avoided, except perhaps for emergent FMT, when timing may be more critical than long-term safety outcome.

Donors should be excluded if they have received antibiotics within the past 3 months because the perturbing effect of antibiotics on the intestinal microflora can persist for 3 months or more. High-risk sexual behaviors, a body piercing or tattoo in the previous 3 months, or recent incarceration also exclude one from being a donor.[67] A history of chronic diarrhea, constipation, IBD, IBS, colorectal polyps or cancer, immunocompromise, morbid obesity, metabolic syndrome, atopy, and chronic fatigue syndrome are additional donor exclusions because they conceivably may be transmittable by inoculation with intestinal microbiota.[67] Exclusion of donors with a history of major GI surgery (eg, gastric bypass) or systemic autoimmunity (eg, multiple sclerosis, connective tissue disease) also should be considered,[68] and perhaps, as other diseases and conditions become clearly associated with specific changes in the intestinal microbiota, they too might constitute reason to be exclusionary. If the recipient has any known food or medication allergy, the donor must not ingest the allergen for several days before donation.

Is one donor preferable to another?

One systematic review provided data that suggest use of stool from a related donor (family member, spouse or intimate partner) yields a higher rate (87.2% and 90.5%, respectively) of CDI resolution than use of stool from an unrelated donor (84%).[58] More recent experience with frozen/thawed or fresh fecal preparations obtained from standard or "universal" donors, however, gave excellent results (90%-92% resolution, 9% recurrence) exceeding those (70% resolution, 30% recurrence) obtained with patient-selected donors and casting doubt on the need to use related or intimate contacts for donation samples.[69] The long-term multicenter follow-up study cited previously also showed that CDI cure rates were not influenced by the relationship between the FMT recipient and donor.[43] It is appropriate to offer FMT from a pool of volunteers to patients who do not have a related donor because the use of stool from an unrelated standard (volunteer) donor has resulted in impressive cure rates.

How is FMT performed?

Administration of donor feces can be performed via a nasogastric or nasoenteric tube, gastroduodenoscopy,

colonoscopy, flexible sigmoidoscopy, or enema. If stool is to be mixed by hand rather than by blender, it is easier to place it in suspension if the donor takes a gentle laxative such as milk of magnesia before bedtime the night before the procedure. Stool is passed into a clean plastic container and should not be frozen, but may be refrigerated before use. Recipients should take a large-volume bowel lavage before the procedure, regardless of whether FMT is performed by upper or lower tract route to reduce the resident population of clostridial organisms, although this concept has never been formally tested. It was shown in 1 small study, however, that bowel lavage results in altered mucosal-adherent microbiota,[57] although it has not been studied whether this alteration changes the efficacy of FMT. In cases of RCDI, we instruct patients to stop vancomycin and other antibiotics 2 to 3 days before the procedure if possible, although this also has not been compared with continuing antibiotics up until or even after the procedure. The recipient takes 2 loperamide tablets about an hour before the procedure to promote retention of administered stool for at least 4, and preferably 6, hours after FMT.

It is recommended that stool preparation should be performed under a hood because stool is rated as a level 2 biohazard,[70] although this recommendation is not practical and may not be necessary considering the detailed screening tests that have been performed on donor stool. A specimen of stool weighing 50 to 60 g is added to 250 to 300 mL of diluent, which typically is a nonbacteriostatic saline solution, although milk and even tap or bottled water has been used without apparent ill effect. Despite the theoretical likelihood that the hypotonicity of a water diluent may lyse bacteria, apparently so many bacteria survive that the diluent does not have an efficiency-altering effect. The mixture is then suspended either by hand stirring and shaking or by the use of a blender. Some practitioners have requested that patients bring their own blender with them to the procedure. Obviously if a blender is to be used for several patients, its parts would have to be sterilized before the next procedure. After suspension with the diluent, the mixture is filtered through a coffee filter or gauze pad or strained through a kitchen-type steel strainer to remove larger particulate matter that may obstruct the nasoenteric tube or endoscope channel. Coffee filters tend to clog easily; therefore, gauze pads and steel strainers are more functional. The suspension is then drawn up into 60-mL catheter-tip syringes.

To perform FMT by colonoscopy, the instrument is inserted to the cecum, or occasionally into the ileum, where the fecal suspension is infused over 2 to 3 minutes. In patients in whom the procedure is difficult or deemed too dangerous for full-depth insertion, FMT may be delivered into the ascending or transverse colon or even the descending colon or sigmoid. On reaching the desired location, the accessory channel cap of the colonoscope is removed and connected to a 10- to 12-inch length of suction tubing. Then 1 syringe full of stool suspension after another is infused until the desired amount has been given. Biopsy specimens can be safely obtained during the colonoscopy; however, after infusion of the donor stool, the endoscope should come out swiftly, aspirating air only from the distal left colon, sigmoid, and rectum for patient comfort.

Administration of donor feces into the upper GI tract via a nasogastric or nasoenteric tube or endoscope can be performed with minor procedural modifications. Nasoenteric tube insertion should be followed by radiologic imaging to confirm correct positioning, after which the filtered stool is infused. Smaller stool volumes and slower infusion rates should be used when FMT is performed via the upper tract in order to reduce the risk of aspiration and minimize nausea and vomiting. With upper endoscopy, on reaching the distal duodenum, 50 to 75 mL of fecal suspension is infused, also via a 60-mL catheter-tip syringes. In the recently published randomized, controlled trial of Van Nood et al,[30] 500 mL of stool suspension was slowly infused into the duodenum via a nasoenteric tube over 20 to 30 minutes without adverse effect. There are 2 methods of FMT administration by enema: use of a squeeze enema bottle or a traditional enema bag, both of which the patient can self-administer. Donor stool is prepared as previously described, and with the first method, approximately 50 to 60 mL are loaded into a squeeze-type enema bottle that can be given once or even twice daily; the more frequent use is for patients whose rectum cannot accommodate a larger volume of infusate. Regardless of method, the enema nozzle is inserted into the rectum with the patient lying in the left lateral position. With traditional enema bags, gravity determines the rate of flow, and the bag should not be at a height more than 18 inches above the patient's hips. If the patient is lying on the bathroom floor, the bag can be hung on the doorknob, but never from a shower head, which will cause too great an infusion pressure and may cause colon perforation. A volume of 300 mL can easily be infused by enema bag technique but must be slowly instilled. With enema bottles, the bottle is gradually squeezed to infuse the contents slowly. The fecal infusion is retained for a minimum of 4 hours in order to achieve maximal therapeutic benefit. Ideally, fecal enemas should be administered before bedtime in order to promote maximal retention.

Which route of administration is best?

The advantages and disadvantages of the various routes of administration of FMT have been described, and each may be appropriate under a particular set of individual patient circumstances. Administration of donor feces via the nasogastric or nasoenteric route is quick, convenient, inexpensive, and technically simple, while circumventing the need for endoscopy.[71] Almost the entire length of the GI tract is exposed to donor feces when the upper

route (nasogastric, nasoenteric, or upper endoscopic) is used, and the effect of such exposure compared with only colonic exposure is unstudied. Compared with the lower route, smaller volumes of infusate or slower infusion rates are usually used[20] to decrease the likelihood of vomiting and aspiration.[42,71] The risk of aspiration may be reduced in patients who undergo FMT via duodenoscopy or a nasoenteric tube compared with nasogastric administration,[71] especially if smaller volumes of stool are instilled slowly. Small intestinal bacterial overgrowth is a theoretical risk in those undergoing FMT via the upper tract,[42,71] but clinically, this has not seemed to be a problem; a small intestinal motility disorder or anatomic configuration that might promote stasis such as jejunal diverticulosis, blind loop, or stricture formation would, in our opinion, preclude FMT via the upper tract.

Fecal enemas are easy to administer, are inexpensive, and can be infused in the comfort of a patient's home. Some patients have reported an aversion to handling stool, which obviously might interfere with the acceptability of fecal enemas.[72]

Although there is no consensus, the colonoscopic approach to FMT is favored over fecal enema and upper tract FMT for CDI, not only because of patient acceptance, but also because enemas only reach the splenic flexure,[17] and with colonoscopy, the entire colon can be infused with stool, and the extent and severity of disease can be elucidated, at the same time that treatment is being given.[19] A recent multicenter long-term follow-up study on colonoscopic FMT for RCDI comprising 77 patients reported that colonoscopic FMT was well received by study participants and was highly successful, with an overall primary cure rate of 91% and a secondary cure rate of 98%.[43] Colonoscopic FMT has even been proposed as first-line therapy for the treatment of CDI,[44] although this has yet to be validated. In patients with severe colitis and significant colonic distention, colonoscopy may be technically challenging and potentially dangerous. In such patients, flexible sigmoidoscopy or gentle retention enema may be preferable,[42] and a nasogastric or nasoenteric tube or upper tract endoscopy may be attractive modes of FMT administration if ileus is not present.

To date, only 2 publications have directly compared outcomes based on the route of administration of donor feces. The first is a recently published systematic review that compared FMT via gastroscopy, nasoenteric tube, colonoscopy, and enema.[20] In this review, FMT by gastroscopy or a nasoenteric tube was found to be less effective than by enema and colonoscopy (resolution rate, 76.4% vs >85%).[20] Excellent resolution rates (>85%) were reported with both enema and colonoscopy[20]; however, enema therapy may necessitate repeated infusions[4,19,73,74] as opposed to colonoscopy in which single infusions are more commonly given.[18,31,75,76] The second is a review that compared colonoscopic FMT with nasogastric tube FMT in 12 studies of patients with RCDI and found superior cure rates in the colonoscopy group (93.2%) compared with the nasogastric tube group (85.3%); the difference, however, was not statistically significant.[71] Two significant differences were noted in pre-FMT management between these groups: most patients in the nasogastric group received a proton pump inhibitor before FMT compared with none of the patients in the colonoscopic group[71]; also in addition, most patients in the nasogastric group received antibiotic treatment without bowel lavage as opposed to patients in the colonoscopic group for whom bowel lavage was standard protocol.[71]

The only randomized, controlled trial to date assigned patients with RCDI to receive an abbreviated course of vancomycin (500 mg orally 4 times daily for 4 days) followed by bowel lavage and FMT via a nasoduodenal tube, "standard" vancomycin regimen (500 mg orally 4 times per day for 14 days), or "standard" vancomycin regimen with bowel lavage.[30] The study was prematurely stopped when it was deemed unethical to continue because of the remarkably superior cure rate in patients undergoing FMT.[30] Thirteen of 16 patients (81%) in the FMT group had resolution of RCDI after the first infusion.[30] Two of the 3 remaining patients were cured after a second infusion with feces from a different donor (overall cure rate of 94%).[30] Resolution of RCDI only occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage.[30] Further investigation is required to determine whether bowel lavage contributes to or detracts from the efficacy of FMT.

Which diluent should be used?

Donated stool is mixed with diluent to a consistency that can be injected through the biopsy channel of a nasoenteric tube, gastroscope, colonoscope, or enema nozzle. Stool is most commonly suspended in a nonbacteriostatic saline solution; however, water and other diluents (eg, milk), as described previously, also have been used.[20] Although there are no consistent differences in resolution or relapse rates among diluents, saline solution and milk may give slightly lower resolution (86.2% and 88.6%, respectively) and recurrence (3.0% and 3.2%, respectively) rates, whereas water may give higher resolution (98.5%) and recurrence (7.8%) rates.[20] These data must be interpreted with caution because they comprise heterogeneous studies, including case reports, and the use of diluents other than nonbacteriostatic saline solution has not been studied in detail.

How much stool is needed?

The amount of stool to be used for FMT has not been standardized; however those who regularly perform FMT favor 50 to 60 g of 250 to 300 mL of diluent, respectively. It seems that more favorable outcomes are seen with larger amounts of stool, and standard practice now includes the use of about 300 mL for colonic FMT and 60 to 75 mL

for upper tract FMT. The use of smaller stool volumes for upper tract FMT given by this route possibly explains the lower cure rates seen with lower tract administration, although an impressive cure rate has been seen with a nasoduodenal tube when larger stool volumes were used.[30] Thus, in a study by Van Nood et al,[30] 500 mL of suspended stool administered via a nasoenteric tube over the course of 20 to 30 minutes resulted in cure rates of 81% and 94% after 1 and 2 infusions, respectively. In a large systemic review that did not distinguish the route of FMT, an administered volume of less than 200 mL gave a resolution rate of 80% and a relapse rate of 6.2%, whereas a volume greater than 500 mL gave a resolution rate of 97.3% and a relapse rate of 4.7%.[20] Use of less than 50 g of stool was associated with resolution and relapse rates of 82.8% and 3.8%, respectively, whereas more than 50 g of stool had resolution and relapse rates of 86.2% and 1.0%, respectively.[20] Although the use of larger stool volumes is now favored, these data must be interpreted with caution because this systematic review evaluated heterogeneous studies including case reports.

Is fresh or frozen stool better?

Standard practice includes the use of fresh stool (passed within 8 hours); however, this mode of FMT has not been compared with other types of stool preparation. One study compared outcomes in 43 patients with RCDI who underwent FMT with fresh stool or a previously frozen stool preparation and found similar cure rates of 92% and 90%, respectively.[69] In this study, stool was weighed and homogenized in a commercial blender under N_2 gas within 2 hours of collection. The slurry was passed through stainless steel sieves to remove particulate matter, then centrifuged, and ultimately suspended in one half the original volume of nonbacteriostatic saline solution. The concentrated fecal bacteria suspension was admixed with glycerol at a concentration of 10% and stored at −80°C for 1 to 8 weeks. Thawing was done over 2 to 4 hours in an ice bath, and once thawed, the aliquot was diluted to 250 mL with nonbacteriostatic normal saline solution before infusion.[69] The use of frozen stool significantly simplifies the practical aspects of FMT by enabling the use of a universal donor[69] as well as shipping to distant locations. Additional studies are needed to confirm the use of frozen stool as a viable alternative to fresh stool.

How do patients feel about FMT?

FMT has been so publicized in patient chat rooms and on the Web that patient acceptance does not seem to be a concern. In our experience, most patients with RCDI have been so frustrated by their disease, its recurrence, and the failure of all treatments that they have had to resolve the problem that they initiate the search for someone to do FMT; some have even tried to do it themselves before seeking professional help. They are well informed and knowledgeable about technique, potential risk, and, most important in their opinion, expected outcome. In the multicenter long-term follow-up study cited previously,[43] 97% of patients who had undergone FMT for RCDI reported willingness to undergo another FMT in the future should they need it, and 53% stated that they would choose FMT as first-line treatment before antibiotics. Patient perceptions of the aesthetics of FMT and their willingness to consider it as a treatment option were explored in a study that enrolled medical and surgical ambulatory patients to complete an extensive survey that included hypothetical case scenarios of RCDI.[72] When provided with only efficacy data and not knowing the specifics of the treatment ("floral reconstitution"), 85% chose to receive FMT and 15% chose antibiotics alone.[72] When made aware that fecal infusion was the means of treatment, only 4% of patients changed their choice from FMT to antibiotics alone, with no significant change in the total number of participants choosing FMT.[72] Of note, women found all aspects of FMT less appealing than men, whereas older patients (65 years of age and older) found all aspects more appealing than younger patients.[72] The nasogastric route was reported to be the most unappealing mode compared with administration via fecal enema and colonoscopy.[72] The majority of respondents preferred to undergo FMT in the hospital (48%) or physician's office (39%) rather than in their own home (13%).[72] Of the respondents, 77% stated that they personally would be willing to pay for the FMT.[72]

FMT: HOW SAFE IS IT?

In the only long-term follow-up study of FMT to date, a 5-medical center, cross-country effort, 77 patients who had had FMT and were followed for more than 3 months experienced and maintained a 91% primary cure rate and a 98% secondary cure rate, the latter defined as cure enabled by use of antibiotics to which the patient had not responded to before the FMT or by a second FMT.[43] It is not unusual for transient GI symptoms or altered bowel habits to develop in some patients for several days after FMT, including the absence of bowel movement, abdominal cramping, gurgling bowel sounds, and increased feelings of gaseousness. Of the 77 subjects in this study, an autoimmune disease (rheumatoid arthritis, Sjögren syndrome, idiopathic thrombocytopenic purpura, and peripheral neuropathy) developed in 4 subjects at some time after the FMT, although a clear relationship between the new disease and FMT was not evident.[43] The safety of FMT in immunosuppressed patients needs to be established, although limited experience by 1 of the authors (L.J.B.) in 20 patients would suggest that this is not of concern: FMT was performed safely in patients who were either taking glucocorticoids, immunosuppressive (6-mercaptopurine,

azathioprine), or biologic (infliximab, adalimumab) agents or who had diseases or therapies associated with immunocompromise (kidney transplantation, chronic lymphocytic leukemia, lymphoma, primary immune deficiency, Schwachman-Diamond syndrome). Nonetheless, safety remains the prime consideration and larger numbers of observations in controlled circumstances are needed.

CONCLUSION

FMT is a highly effective and acceptable therapeutic intervention for the treatment of RCDI and may play a role in treating a variety of other GI and non-GI diseases. Donors must be appropriately screened for potentially transmissible diseases before FMT. FMT can be performed via a nasogastric or nasoenteric tube, upper endoscopy, colonoscopy, flexible sigmoidoscopy, or enema. Although there are few studies that directly compare routes of administration, FMT via the upper tract seems to be less effective than via the lower tract. Choosing the route of administration, however, should be individually tailored to the patient undergoing FMT. Regardless of the route, safety remains the prime consideration and larger numbers of observations in controlled circumstances are needed; the rest will follow. Emerging data now suggest that ingestion or infusion of a defined bacterial mixture can successfully cure CDI, obviating the need to use donor feces. One recent study showed that CDI results in intestinal dysbiosis in the mouse model and that infusion of donor feces from healthy mice into mice with CDI resulted in resolution of disease; moreover, the authors of this very elegant study[77] isolated bacteria from healthy mice and created a mixture of 6 phylogenetically diverse bacteria that were able to disrupt intestinal dysbiosis and, as a result, resolve disease and contagiousness when given to mice with CDI. In another study, use of a stool substitute preparation made from purified intestinal bacterial cultures derived from a single healthy donor after recovering 33 isolates was used to treat RCDI in 2 patients in whom repeated standard antibiotics had failed. The fecal substitute was infused colonoscopically in both patients, and each patient reverted to his or her baseline bowel habits within 2 to 3 days and remained symptom free at 6 months after infusion.[78] These studies set the stage for a time in the not too distant future when a "designer" capsule of selected micro-organisms will be given to restore a balanced microbiota or correct a deficiency of a commensal organism, thereby curing a recalcitrant disease or reversing an underlying metabolic condition.

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