Update on FMT 2015: Indications, Methodologies, Mechanisms and Outlook

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Abstract

The community of microorganisms within the human gut (or microbiota) is critical to health and functions with a level of complexity comparable to an organ system. Alterations of this ecology (or dysbiosis) has been implicated in a number of disease states, the prototypical example being *Clostridium difficile* infection (CDI). Fecal microbiota transplantation (FMT) has been demonstrated to durably alter the gut microbiota of the recipient and has shown efficacy in the treatment of recurrent CDI. There is hope that FMT may eventually prove beneficial for treatment of other disease associated with alterations in gut microbiota, such as inflammatory bowel disease, irritable bowel syndrome and the metabolic syndrome, to name a few. Although the basic principles that underlie the mechanisms by which FMT demonstrates therapeutic efficacy in CDI are becoming apparent, further research is needed to understand the possible role of FMT in these other conditions. Though relatively simple to perform, questions regarding both short- and long-term safety, as well as the complex and rapidly evolving regulatory landscape has limited widespread utilization. Future work will focus on establishing best practices and more robust safety data than exist currently, as well as refining FMT beyond current "whole stool" transplants to increase safety and tolerability. Encapsulated formulations, full spectrum stool-based products and defined microbial consortia are all in the immediate future.

Keywords

FMT; fecal transplant; gut microbial therapeutics

Introduction

It is now understood that the gut microbiota coevolved with the human host over thousands of years and are integral to overall human physiology, playing a pivotal role in metabolism, immune system function and maintenance of gut homeostasis.[1, 2] Fecal microbiota transplantation (FMT) involves administration of fecal material containing distal gut microbiota from a healthy individual (donor) to a patient with a disease or condition related to dysbiosis, or an alteration in their "normal" gut microbiota. The goal of FMT is to treat disease by restoring phylogenetic diversity and microbiota more typical of a "healthy" individual.

Though previously considered fringe-therapy and the "last resort" for patients with *C. difficile* infection (CDI), FMT has become more widely practiced, and interest around FMT among patients, researchers and industry has surged over the past 2–3 years. Numerous case reports, retrospective case series and a single randomized controlled trial have demonstrated benefit of FMT in patients with severe or recurrent CDI with cure rates as high as 100% and a mean cure rate of 87–90% for the over 500 cases reported in the world literature to date.[3–5]

Moreover, the restoration of more typical microbial communities, which come to resemble those of the donor post-transplant, persists in a durable fashion after FMT.[6, 7] This has resulted in speculation that FMT may eventually prove beneficial in other conditions associated with dysbiosis, such as inflammatory bowel disease (IBD), the metabolic syndrome, and many others. This overview will describe the history of FMT, basic methodologies, and the potential mechanisms of effect in CDI and other diseases. We will present efficacy data, including a review of the real and theoretical risks of the procedure. In addition, this overview provides a discussion of the future of microbial-based therapeutics and the complex regulatory issues around this rapidly evolving field.

History of FMT

Fecal transplantation dates back to 4th century China where human fecal suspension by mouth was used to cure food poisoning and severe diarrhea[8] and has been widely used in veterinary medicine to treat ruminal disorders since the 17th century.[9] Anecdotal reports of the use of parental feces to treat antibiotic-associated diarrhea in children had existed, but these cases were largely unknown until the publication of the first case series in 1958 of four patients with pseudomembranous enterocolitis by the American surgeon, Ben Eiseman.[10] For years, FMT remained a rarely used, if not forgotten, therapy. The first documented case of confirmed CDI treated with FMT was reported in 1983.[11] Since that time, a growing number of case series and a single randomized controlled trial[4] have described the administration of donor stool using various modalities to successfully treat patients, mostly with recurrent or refractory CDI.

Driven by an epidemic of increasingly virulent and severe *C. difficile* infections[12, 13], our greater understanding of the human gut microbiome, and favorable headlines in the media, the practice of FMT has recently shown a significant increase in utilization. Some of this interest may be because the perceived "natural" properties of FMT make it appealing to both physicians and the lay public. We have also come to realize that FMT enables use of a logical, low tech, and relatively inexpensive approach to effectively treat a difficult clinical problem. Despite overwhelmingly positive anecdotal experience from the growing number of physicians who have performed this procedure, and evidence from hundreds of published cases, FMT is not yet universally available, though its acceptance is growing. The apparently high efficacy of FMT in treating CDI, compelling animal data on the impact of fecal microbiota in metabolism,[14] and case reports describing successful FMT for treatment of other intestinal disorders, has led to growing interest in the potential of FMT to treat other conditions associated with dysbiosis such as the metabolic syndrome, obesity, food allergies, IBD and irritable bowel syndrome (IBS). A number of clinical trials studying FMT for these conditions and others are ongoing[15].

Current Treatment Guidelines and Methods

Indications

In 2010, members of various specialty societies with an interest in FMT formed a working group for the purpose of creating a consensus on FMT for practitioners. As outlined by the workgroup,[16] the primary indications for FMT are:

1. Recurrent or relapsing CDI:

   a. Three or more episodes of mild-to-moderate CDI and failure of a 6–8 week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide or fidaxomicin).

   b. At least two episodes of CDI resulting in hospitalization and associated with significant morbidity.

2. Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least a week.

3. Severe (even fulminant CDI) with no response to standard therapy after 48 hours.

The 2013 American College of Gastroenterology *Clostridium difficile* treatment guidelines also recommend FMT as a therapeutic alternative for recurrent cases of CDI which have failed to respond to a pulse/tapered regimen of vancomycin.[17] The evidence supporting FMT for treatment of severe, complicated disease (e.g. toxic megacolon) is less robust, with fewer published cases, however a few case reports suggest that it may be safe and effective even in critically ill patients[18–21]. Certainly patients with severe CDI are at greater risk for poor outcomes and decisions to proceed with FMT, versus surgery or other standard of care modalities, should be made with caution. In all cases, primary consideration must be given to the severity and progression of the patient's CDI when deciding whether early use of FMT is appropriate to prevent further clinical deterioration.

Donor selection

The donor may be an intimate, long-time partner, friend, or unrelated volunteer. For the purposes of informed consent, donors should be over the age of 18. However, children could also potentially serve as donors as long as both parental consent and child assent (i.e. agreement to serve as a donor) are obtained. At this time, limited data are available to suggest that any factors other than specific exclusion criteria based on medical history and laboratory testing would endorse a particular donor as optimal.

A number of advantages and disadvantages may be considered during donor selection. Intimate contacts (e.g., spouse) have the advantage of shared environmental risk factors, which may minimize the risk of transmitting an infectious agent. Maternal-line first-degree relatives may have a theoretical advantage of sharing the greatest number of microbial species in their intestinal microbiota with the recipient. Therefore, it is conceivable that adaptive immune elements in the mucosal immune system (e.g., antigen-specific antibodies) may be more tolerant of microbiota derived from such donors. Similarly, it is possible to speculate that men might be preferred donors over women as women may, theoretically, harbor microbiota that are more likely associated with autoimmune disease and IBS. Others have hypothesized that age- and gender-matched donors may be advantageous, although currently there is no data to support this hypothesis. Finally, there may be advantages in using unrelated, healthy, but rigorously screened donors, particularly when FMT is being used to treat diseases where genetics play a contributing role, such as IBD. Availability of a healthy, pre-screened donor pool may facilitate broader ability to perform FMT. These unrelated volunteer donors may even be preferable, as family members may feel coerced to

donate and deny relevant infectious risk factors. Indeed, directed blood donors have higher viral marker rates than volunteer donors.[22] Furthermore, as intestinal microbiota have recently been theorized to potentially be involved in the pathogenesis of a number of systemic diseases, rigorously screened, healthy volunteer donors may have advantages, especially for young patients, who may acquire additional risk factors for disease over their lifetime.

Donor Screening

Potential donors should be screened for behaviors which may confer increased risk for transmitting infection (e.g. injection drug use). Current guidelines[16] recommend using a donor questionnaire that is similar to current protocols for screening blood donors, (see AABB Donor History Questionnaire Documents available at http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/ucm164185.htm Furthermore, donors should be free of diseases or conditions which may, even theoretically, be transmissible by stool. Those who meet eligibility criteria should have serologic and stool testing to screen for infectious agents, preferably within 4 weeks of donation. The donor testing described in the first two columns of Table 1 should be considered minimal and testing for additional pathogens, as also detailed, may be considered in certain clinical situations, such as when the recipient is immunocompromised or in cases of potential donor exposures.

   i.   Donor exclusion criteria:

   - A history of antibiotic treatment during the 3 months preceding donation

   - A history of intrinsic gastrointestinal (GI) illnesses, including IBD, IBS, chronic constipation, Gl malignancies or major GI surgical procedures

   - A history of autoimmune or atopic illnesses or ongoing immune modulating therapy

   - A history of chronic pain syndromes (fibromyalgia, chronic fatigue) or of neurologic or neurodevelopmental disorders

   - Metabolic syndrome, obesity (body mass index >30), or moderate-to-severe malnutrition

   - A history of malignant illnesses or ongoing oncologic therapy

Stool Preparation and Methods of Administration

The material must be diluted and homogenized to a form that can be administered. Published data do not demonstrate a significant difference in success with FMT whether the donor stool is mixed in tap water, milk, or normal saline (sterile, nonbacteriostatic), although the latter is presumed to be less likely to affect the microbiota of the donor specimen. In general, the donor specimen is homogenized (using blender, manual effort, or other method), and filtered if necessary (e.g., gauze, coffee filter, strainer). This processed specimen is then either directly infused into the GI tract or further centrifuged, placed into gelatin capsules, and swallowed. Several series have described freezing the fecal microbiota, which can then be thawed for later use.[7, 23]

As with preparation of the stool, there is no clear consensus on the best method of instillation. Routes of administration have included the upper GI tract (via endoscopy, nasogastric/nasointestinal tubes, or ingestion of pills,[4, 23–29] the proximal colon by colonoscopy,[6, 7, 30–35] or the distal colon by enema, rectal tube, or sigmoidoscopy[36–40] or a combined approach[41]. Nasogastric or nasointestinal routes may be uncomfortable and less appealing to the patient, require radiology assistance to confirm tube placement and carries some risk of vomiting and aspiration. Retention enema is inexpensive, with little procedural risk, but it may be difficult for some patients to retain the donor material and it may require multiple treatments. Endoscopic routes of administration are well tolerated and have the advantage of allowing examination of the colonic mucosa, and exclusion of pathology, such as IBD, which may be contributing to the patient's symptoms and recurrent CDI. Endoscopic delivery carries some procedural risk and increases health care utilization and costs, though a cost-effectiveness study showed FMT dominated (i.e. was less costly and more effective) than vancomycin for initial CDI[42]. FMT is reported to be effective by all of these routes, and the preferred method may vary with the clinical situation. Less invasive methods, such as retention enema or nasointestinal infusion may be safer in patients who are frail or severely ill at the time of FMT. Ileus precludes the upper GI route of administration.

Efficacy data in CDI

FMT has been examined in both young and old, patients with limited comorbidities as well as those considered to be immunocompromised,[43] and the procedure has been shown to be safe, well-tolerated, and effective. The role of FMT for the treatment of CDI in specific situations (e.g., toxic megacolon) is as yet unclear; however, of the over 500 cases reported to date[3], FMT has demonstrated rapid response and a cure rate of nearly 90%, with a negligible significant adverse event rate, regardless of route. Cumulative experience is largely based on data from case reports and series. There has, to date, been only a single randomized controlled trial[4]. This study, conducted in the Netherlands, showed duodenal infusion of donor feces to effectively resolve recurrent CDI in 81% of patients treated, compared to only 31% efficacy of a standard course of oral vancomycin. Furthermore, FMT appeared safe, with no serious adverse events in these subjects. This study was terminated early by the safety monitoring board because it was deemed unethical to continue subjecting patients to the inferior treatment. In a systematic review, Cammarota et al. observed that lower gastrointestinal route (colonoscopy, enema) led to the achievement of higher eradication rates than upper delivery (gastroscopy, nasogastric or nasointestinal tube) (81–86% vs 84–93%, respectively)[3]. Conversely, a small, open label pilot study comparing upper and lower GI routes of administration did not show any differences[44] A recent open-label, single group study[23] at Massachusetts General Hospital assessed the efficacy of fecal material from healthy donors administered as 15 frozen pills on two consecutive days in patients with relapsing CDI. They reported an overall 90% response rate making oral administration a viable alternative to the current practice of administering fecal material via an endoscopic procedure thus decreasing both cost and potential procedural complications.

Mechanisms

C. difficile is an opportunistic organism, which generally causes disease in persons with decreased diversity of the gastrointestinal microflora (typically as a result of antibiotic use). Indeed, studies have demonstrated that patients suffering from recurrent CDI are deficient in phyla of bacteria normally dominant in the colon[6,45] (Figure 1). FMT represents one of the most efficacious treatments available for recurrent CDI, though the exact mechanism of effect still remains to be elucidated.

The greatest risk factor for CDI is the use of antibiotics,[46] though only a small proportion of patients on antibiotics develop the infection. Antibiotic use has been associated with alterations in both gut microbial community structure and function. An early study investigating the effect of antibiotics on gut microbiota function described decreased urobilinogen and fecal tryptic activity as well as decreased conversion of cholesterol to coprostanol following antibiotic treatment.[25] Interestingly these changes were modified following fecal transplant from healthy individuals with increased appearance of coprostanol and urobilinogen.[25] Several studies have since identified the effect of antibiotics on gut microbiome using sophisticated methodology and next-generation sequencing. Dethlefsen et al. investigated the effect of ciprofloxacin in three individuals and found reduced microbial taxonomic diversity, richness and evenness, although the magnitude of effect differed among individuals.[47] A more recent study in mice treated with the antibiotic cefoperazone suggests that antibiotic treatment alters the fecal metabolome related to microbial function.[48] The mice exhibited an increase in primary bile acids such as taurocholate, an increase in sugar alcohols mannitol and sorbitol, a decrease in free short-medium- and long-chain fatty acids, an increase in amino acids such as glycine, proline, cysteine, isoleucine, and a decrease in branched chain fatty acids, all conditions which favor *C. difficile* growth.[48] Differences in susceptibility to infections such as CDI following antibiotic treatment may relate to differential effects of antibiotics across different individuals microbiota, to host factors, and to the type of antibiotic. While antibiotics are a major risk factor for CDI, community acquired CDI is becoming increasingly common in the absence of antibiotic use.[49] There is little information on the gut microbiome in this population, though one may speculate that, in addition to host features, other factors such as diet, environment, and altered GI function may decrease microbial diversity and alter microbial function to favor growth of *C. difficile*.

With the advent of next-generation sequencing, we can now identify specific taxonomic changes that occur after FMT to better understand how the transplant influences gut microbial ecology. FMT appears to result in durable engraftment of new species from donor as well as augmentation of species present at only very low levels prior to FMT[6]. The mechanisms underlying decreased fitness of *C. difficile* following FMT still remain elusive but likely include niche exclusion, competition for nutrients and creation of a nutrient milieu unfavorable for growth, ability of members of healthy gut microbiota to produce antimicrobials that inhibit growth of *C. difficile* and an increase in secondary bile acid production. An important factor determining success of fecal transplant is restoration of microbial diversity following treatment[50]. Additionally, changes in microbial community structure such as restoration of key Firmicutes and Bacteroidetes species with a decrease in

Proteobacteria appear to be required in order to outcompete *C. difficile*.[50] Decrease in Lachnospiraceae has been associated with severe CDI suggesting a protective role for members of this family[51] and administration of a cocktail containing a member of Lachnospiraceae was reported to cure CDI in mice[52]. Furthermore successful FMT restores members of Lachnospiraceae and other butyrate producing organisms supporting their potential role in outcompeting *C. difficile*.[50] *Bacillus thuringensis* secretes a bacteriocin, thuricin CD, with narrow spectrum activity against gram positive bacteria including *C. difficile*; it is likely other members of the gut microbiota secrete similar antimicrobials.[53] Bile acid composition can significantly impact *C. difficile* growth with primary bile acids such as taurocholate favoring germination of *C. difficile* spores. Weingarden and colleagues reported an increase in secondary bile acids following FMT compared to pre-transplant stool samples.[19] A more recent study by Butte et al. showed treatment with either a consortium of bacteria or *C. scindens* both of which harbor the gene encoding 7-hydroxysteroid dehydrogenase required for secondary bile acid synthesis can ameliorate CDI in mice.[54]

FMT in Diseases Other than *Clostridium difficile*

FMT for Inflammatory Bowel Disease

Although the microbial basis of IBD is far more complex and variable than that of recurrent/ refractory CDI, microbiome-based therapies are an important area of investigation for these chronic and debilitating diseases. As early as the 1900s, physicians recognized that bacteria may be playing a pivotal role in colitis.[55] With over a century of research and progress, we are just beginning to understand the microbiological basis for IBD and how FMT and other microbial therapeutics may be useful for IBD.

Advanced molecular techniques have demonstrated fundamental differences in both microbial composition and function in patients with IBD.[56–58] The dysbiosis is characterized by a decreased diversity at the species level, with notable decreases in the Bacteroidetes phylum and the *Lachnospiraceae* group within the Firmicutes phylum and increases in Proteobacteria and Actinobacteria.[59] Studies have also shown lower levels of the protective *Faecalibacterium prausnitzii*, which has been associated with anti-inflammatory properties in patients with Crohn's diseases.[60]

Conventional whole-stool FMT offers an untargeted approach to modify the underlying dybiosis in IBD. Preliminary case reports of FMT enemas in patients with ulcerative colitis (UC) and Crohn's disease (CD) were promising, reporting that patients achieved clinical remission, and maintained remission over long-term follow-up in many of the cases[61, 62] A small number of these case reports also reported endoscopic and histologic remission.[63] These reports were followed by a number of small studies of FMT in children and adults with UC, CD, and pouchitis with mixed results.[64–72] Unfortunately, it is difficult to infer robust conclusions about the safety and efficacy of FMT for IBD from these studies because they were under-powered, open-labeled, lacked uniformity in treatment protocols and delivery approaches, and did not include control groups. In addition, the patient populations for each study varied in disease type, phenotype, severity, and concomitant medications. Also important is the fact that although the donors were screened, they were not otherwise standardized or well-characterized.

A recent systematic review and meta-analysis of 18 studies that included 122 patients with IBD who received FMT found a 45% clinical remission rate.[73] However, the remission rate fell to 36.2% when the case series were excluded in order to minimize publication bias. The pooled estimates were highest in younger patients (7–20 years old) and in patients with Crohn's disease, with 64.1% and 60.5% achieving clinical remission, respectively. These positive result were largely driven by results at two centers with short follow up after FMT[64, 74]. UC patients were much less likely to achieve clinical remission (22%). This review also found that although FMT was not associated with any serious adverse events during short-term follow up, a number of patients experienced fever, chills, and gastrointestinal symptoms including bloating, flatulence, vomiting, diarrhea, and abdominal tenderness.[73] Some UC patients worsened in one study of FMT[71]. Furthermore, flares of FMT in patients with both UC and CD have been described,[43, 75, 76] raising important questions around safety and the potential to worsen disease in some patients.

Two randomized placebo-controlled trials of FMT in IBD were recently published.[77, 78] In the study by Moayyedi et. al, seventy-five patients with active UC were randomized to a weekly FMT or water enema for 6 weeks, and there was a statistically significant difference in remission, the primary outcome, between the two groups. Remission (full Mayo score <3 and complete mucosal healing) was achieved in 24% of patients after FMT and 5% with placebo; stool from patients receiving FMT had greater microbial diversity than that of patients given placebo. The second study, conducted in Amsterdam[78], enrolled 50 patients with mild to moderately active UC and randomized them to donor feces or autologous fecal transplant via naso-duodenal tube. FMT was administered at the start of the study and again 3 weeks later. Only 37 completed assessment for the primary endpoint, clinical remission combined with 1 point decrease in the Mayo endoscopic score at week 12). There was no statistically significant difference in clinical and endoscopic remission between the two groups. It is likely that this study was underpowered to detect these differences.

These initial mixed results do not rule out a possible role of FMT or other gut-microbiota products in the management of IBD. A variety of factors may influence outcome, including patients' IBD characteristics, donor variability, dosage or frequency of FMT, and concomitant medical therapy. Future trial designs may position FMT after induction of remission instead of in the presence of clinically active inflammation. In addition, it is likely that in the future FMT will be replaced by specific manipulation and/or selective transplantation of defined microbial communities that can help restore a healthy enteric commensal community and, hopefully, alter the natural history of IBD.

Obesity

Obesity is recognized as a global epidemic[79]. The lack of effective, non-surgical therapies has led to investigation of potential factors contributing to the development of obesity. Several lines of evidence support the role of gut microbiota in obesity. Lean and obese individuals show marked differences in the gut microbiome.[80] Transfer of gut microbiota from lean and obese individuals can recapitulate the metabolic phenotype in ex-germ free mice.[14] Antibiotic treatment in early life predisposes to obesity in animal models[81] and finally transfer of gut microbiota following roux-en-y gastric bypass to germ free mice leads

to weight loss compared to microbiota from sham surgery.[82] The exact mechanisms by which gut microbiota influence obesity still remain to be elucidated, though recent data from animal models provides valuable insight. Gut microbiota can ferment dietary carbohydrates and provide additional energy to the host in the form of short chain fatty acids. However, microbiota from lean mice produce greater amounts of short chain fatty acids than those from obese mice, suggesting the increased weight gain is not simply from increased energy harvest but rather an effect on the gut neuro-hormonal axis increasing energy expenditure or pathways affecting satiety.[83] A recent double blind randomized controlled study investigated the effect of transfer of gut microbiota from lean individuals to obese individuals and found improved insulin sensitivity and increased gut microbial diversity with increased butyrate-producers following transplant.[84] This pilot study is proof of principle for future randomized controlled trials using fecal transplant or defined microbial consortia for treatment of obesity, metabolic syndrome and diabetes.

Irritable bowel syndrome

IBS is a widely prevalent chronic GI disorder affecting nearly 20% of the North American population[85] and is associated with significant morbidity and health care expenditure. The underlying pathophysiology of symptoms in IBS is not well defined though both central and perpipheral mechanisms have been implicated. Several studies have found alterations in the gut microbiome in patients with IBS.[86–89] However, changes in microbiota composition are not consistent across studies, possibly due to heterogeneous study populations and differing methodologies for sample preparation and analysis. A consistent finding has been decreased microbial diversity, a finding which is reminiscent of alterations in patients with CDI, IBD and obesity. Additionally, recent studies suggest that changes in the gut microbiota may be responsible for underlying mechanisms associated with IBS such as visceral hypersensitivity, altered barrier function, gastrointestinal motility and the gut-brain axis[90–93]. Thus, gut microbiota is an important target for study in the treatment of functional disorders such as IBS, and, in fact, several currently used therapies, such as pre and probiotics, dietary restrictions and antibiotics, modulate the gut microbiota.[89] A few early studies[94] reported improvement in patients with IBS following FMT. For example, in a study reported in abstract form,[95] nearly 90% of patients who were treated with FMT had an improvement in defecation and decreased abdominal bloating after FMT with 60% showing long term benefit from 9–19 months. While these early reports are encouraging, it is important to remember that they are from small, uncontrolled series with high risk of bias. Well-designed, large randomized controlled studies are needed to determine the role of FMT and other bacteriotherapy in the management of IBS.

Other Indications

In addition to specific indications mentioned above, FMT is being actively investigated as a therapeutic strategy for many other diseases including the metabolic syndrome, Type 2 diabetes mellitus, fatty liver disease, multidrug resistant organism eradication, hepatic encephalopathy and pediatric allergy disorders. For example, an investigator at the University of California, San Francisco is currently recruiting patients with human immunodeficiency virus (HIV) on anti-retroviral therapy to determine whether the transfer

of bacterial communities from healthy donors will effect immune activation and inflammatory biomarkers in these patients[96].

Safety of FMT

Evidence regarding the safety of FMT is relatively limited because the very rapid adoption of FMT as a therapeutic modality for CDI has occurred prior to the performance of large, long prospective trials that are typically done to assess the safety of new interventions. Potential adverse events can be categorized as short-term and long-term, and short-term events can further be divided into those related to the method of FMT delivery (e.g., colonoscopy, sedation) and those related to the FMT itself. Due to the recent emergence FMT, little data exists regarding long-term events and many are speculative.

FMT appears to be relatively safe in the short-term, especially when compared to its efficacy in treating recurrent CDI. However, any conclusion regarding short-term safety must be viewed with caution since the data come primarily from retrospective case series with variable assessment and follow-up for adverse events. Furthermore, determining if adverse events are related to FMT is often difficult because patients who receive FMT for recurrent CDI commonly are ill with other comorbidities. Very little information is available regarding the long-term safety of FMT. Table 2 includes reported adverse events associated with or potentially related to FMT in published studies with more than 5 patients identified in a systematic review of FMT for CDI[4,27, 35, 43, 44, 97–107].

Short-term adverse events

Minor events—Minor symptoms immediately following FMT are common, and include abdominal discomfort, bloating, flatulence, diarrhea, constipation, borborygmia, vomiting, and transient fever[4, 70, 71, 78]. The influence of route of administration on development of symptoms after FMT is uncertain. Only one prospective randomized controlled trial is available to compare adverse events with FMT vs. a control group[4]. Among 16 patients receiving FMT via duodenal infusion plus bowel lavage, 15 experienced diarrhea, 5 abdominal cramps, 3 belching, and 1 nausea. These symptoms, which resolved in all patients within 3 hours, were not reported in the control group receiving only bowel lavage.

Serious events—More serious adverse events related to the procedure used to administer the FMT, although rare, may occur. These include complications of endoscopy, such as perforation and bleeding, and side effects related to sedation, such as aspiration[43]. Transmission of enteric pathogens via FMT is also an important concern but appears to be rare with current screening. One center reported 2 cases of documented norovirus infection 2 days and 12 days after FMT[107]. In both cases donors were asymptomatic, and testing for norovirus in one of the donors was negative. The authors speculated that one case was related to transmission via an endoscopy unit employee and the second case was due to community exposure given the time interval between FMT and symptoms. Another potential episode of transmission comes from a case report of fever and E. coli bacteremia 24 hours after FMT via colonoscopy in a patient with IBD[108]. The patient had multiple previous episodes of E. coli bacteremia, the last 9 months prior to FMT. Although other serious adverse events have been reported with FMT (e.g., peritonitis in a patient undergoing

peritoneal dialysis, pneumonia, IBD flares), their relationship to FMT is uncertain. In an effort to quantify adverse events associated with FMT, Kelly, et al recently published a multicenter retrospective study of immunocompromised patients who underwent FMT to treat CDI.[43] Reasons for immunocompromise varied, but included IBD patients on immunosuppressive therapy, solid organ transplant recipients and patients undergoing chemotherapy. Interestingly, there were no infectious complications related to FMT in these potentially "at risk" patients. However, there were two deaths, one an aspiration event related to the procedure used to administer FMT and 17% of IBD patients experienced disease flare post-FMT. The other died 13 days post-FMT secondary to progressive pneumonia, for which she was treated with antibiotics before and after FMT. This death was felt to be unrelated to the FMT.

Potential Long-term adverse events

The greater concern regarding FMT relates to long-term safety. Such risks include the possible transmission of infectious agents via FMT or development of diseases/conditions related to changes in the gut microbiota. The theoretical possibility of transmission of unrecognized infectious agents that causes illness years later, analogous to prior experience with Hepatitis C and human immunodeficiency virus, has been raised, although one would assume that such agents would induce disease in donors as well.

A greater theoretical risk may be the induction of chronic disease based on alterations in the gut microbiota. A partial list of conditions that have been linked to the gut microbiota includes obesity, diabetes, atherosclerosis, IBD, colon cancer, non-alcoholic fatty liver disease, irritable bowel syndrome, asthma, and autism. As mentioned above, transplantation of human fecal microbiota from obese individuals to rodents has been shown to transmit an obesity phenotype[109], and FMT from lean individuals to obese subjects with metabolic syndrome showed an increase in insulin sensitivity[110]. With respect to atherosclerosis, production of the pro-atherogenic metabolite trimethylamine-N-oxide is dependent on the gut microbiota, and increased levels of this metabolite are associated with an increase in major cardiovascular events[111]. Thus, legitimate concern exists regarding the long-term risk of FMT transplantation, especially when used for indications with less well-documented benefit than recurrent CDI. Clinical follow-up of patients over many years, ideally combined with analysis of banked donor and recipient specimens, will be crucial in assessing the possibility that FMT may increase (or decrease) the risk of a number of common chronic conditions.

Patient Perceptions

Patients suffering from recurrent CDI are desperate for a cure and may seek guidance from online communities. Many are willing to travel great distances to undergo FMT. Some have even resorted to performing home-enemas of donor stool when they are unable to find a physician who is willing or able to perform FMT. In fact, a YouTube video describing do-it-yourself FMT has been viewed over 45,000 times.[112] Limited studies on patient perceptions regarding FMT done to date report that patients recognize the unappealing nature of FMT, yet are still open to considering it as a treatment, especially when recommended by a physician. This willingness on the part of patients to try FMT holds true regardless of their

prior experience with FMT or the nature of their disease (CDI, UC or healthy patients).[113–115] For example, in a survey of healthy patients who were presented with hypothetical scenarios related to treatment options for recurrent CDI, 81% of patients chose FMT.[113] Similarly, a survey of UC patients at a single tertiary care center showed that, despite reporting satisfactory to excellent disease control with their treatments, the vast majority were interested in, or willing to consider, FMT.[114] Subjects who had been hospitalized were more willing to undergo FMT (55% versus 34%, p=0.035) suggesting implied risk/benefit assessment by patients. The authors believed that the profound interest in FMT reflects the perception that FMT is a "natural"' treatment for UC, and their dissatisfaction with chronic medical therapy for a variety of reasons. Brandt et al surveyed the perceptions of 77 patients who had experienced recurrences of CDI and were treated with FMT; 97% reported that they would want FMT in the event of another recurrence, and 53% of them would have opted for FMT as primary treatment prior to a trial of antibiotics for their first recurrence if given the option.[32] With the advent of more aesthetically acceptable protocols, including odorless pills, FMT is likely to appeal to a majority of patients who are deemed eligible for FMT.

While no studies about potential barriers to the use of FMT by physicians have been published in full form, a recent abstract reporting a survey of physicians showed that 40% were not willing to try FMT, pending further demonstration of its efficacy, safety and perceived patient acceptance.[116] Although a 'Current Procedural Terminology' (CPT) code for FMT does exist (44705, "preparation of fecal microbiota for instillation, including assessment of donor specimen), lack of adequate reimbursement for the time required by physicians may be a further deterrent. Thus, while patients seem willing to try FMT, it is unknown how willing physicians in various specialties are to offer, perform, or refer patients for this treatment.

Pediatric Considerations

The data regarding safety and efficacy of FMT in pediatric patients to date is quite limited. Currently, the literature is comprised of a handful of case reports and studies which include a small number of children with CDI[23, 28, 97, 117] and/or IBD [67, 118, 11974, 120, 121] who were treated with FMT. Additional larger, controlled, and prospective studies are needed to clarify both the safety and efficacy of FMT in pediatric patients.

In 2010, Russell et al. report the first pediatric patient treated with FMT via nasogastric tube.[118] The case involved a 2 year old child with recalcitrant CDI that had failed an exhaustive course, including probiotics, metronidazole, pulsed-dose vancomycin, rifaximin, and nitazoxanide, who experienced complete resolution of symptoms within 36 hours of FMT. Since this report, others have reported on the safety and efficacy of FMT for children with recurrent CDI without underlying IBD via nasogastric tube, colonoscopy, and capsules with a cure rate of 92% (24/26) and no serious adverse events reported.[117, 121–124] In children with recurrent CDI and underlying IBD, the data the data is mixed, highlighting the difficulty in distinguishing a clinical response to an infection that may have the same symptoms as the underlying disease.[118, 121, 124] Similarly, uncontrolled data on FMT as a primary treatment for IBD, including CD and UC, shows mixed results.[74, 119, 120, 125]

Suskind et al. reported a clinical improvement 7 of the 9 patients with CD who received a single treatment with nasogastric FMT,[74] however, the same approach in 4 patients with active UC showed no benefit.[125] Although these results are promising and suggests that some pediatric patients with Crohn's disease may respond to FMT, it is premature to draw conclusions about the role of FMT in treatment of pediatric IBD. Though no serious short-term adverse events have been reported, some speculate that children may have increased risks as the long-term effects of microbial transplantation and manipulation in children are unknown.

There has also been significant parental interest in FMT for the treatment of other childhood diseases such as food allergies, autism, and chronic diarrhea, however, currently there is no data to support its use for these conditions and studies are ongoing. Parents should be advised not to perform home FMT. They should be counselled about the potential risks of (home) FMT and referred to centers that have ongoing trials (clinicaltrials.gov).

Regulatory issues

Worldwide, regulation of FMT varies greatly between countries. The Therapeutic Goods Administration in Australia, where FMT is not considered a drug or regulated for any indication, has provided no communications regarding FMT. Though several FMT trials are ongoing in China, there has been no indication that The Ministry of Health intends to exercise authority over the procedure. In Europe, the European Medicines Agency has not regulated FMT for CDI thus far.[126] However, Health Canada considers FMT and related synthetic stool therapies as a "New Biologic Drug" and requires any clinical study go through the process of a clinical trial application (CTA) to ensure that quality and safety standards are met.[127] The United States Food and Drug Administration (FDA) has determined that administered stool constitutes a biological product and a drug in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or is intended to affect the structure or function of the body[128]. Though fundamentally different than existing drugs and biologics, the agency has maintained that, at this point, the process of donor eligibility determination and screening, stool processing and infusion defines the FMT "product" and falls under FDA jurisdiction. As such, without large randomized controlled studies to support safety and efficacy, it is an unapproved product and an investigational new drug application (IND) is required in order to administer FMT.

The IND process is largely tailored to the pharmaceutical industry and regulatory experts. The time and administrative burden for any clinician wishing to sponsor an IND to treat his or her individual patients with FMT can be enormous. The initial application may take many weeks to prepare, and once an IND is active, follow up documentation, such as required reporting of all serious adverse events (even if unrelated), institutional review board (IRB) oversight, safety monitoring board meetings and mandatory annual reports to the FDA are similarly time consuming and burdensome. Furthermore, it is not permissible to charge for products which are being administered under IND. Requiring physicians to hold an IND to administer FMT would prevent many from offering this therapy and ensure that only commercial entities with the means to navigate the regulatory process and fund large clinical trials will control this effective therapy. The FDA announced the IND requirement in May

of 2013 at a public workshop to discuss the regulatory and scientific issues around FMT. Physicians, scientists and patient stakeholders argued that the availability of FMT would be adversely affected by this requirement. The Agency agreed and subsequently stated that it would exercise "enforcement discretion" around FMT when used to by licensed physicians to treat CDI not responding to standard therapies.[129] In other words, the FDA will not enforce its own requirement that FMT be done under IND, as long as providers obtain informed consent, detail risks around the procedure, and explain that FMT is considered an investigational therapy. The enforcement discretion policy does not extend to other uses of FMT such as IBD. Furthermore, clinical trials of FMT for *C. difficile* do not fall under enforcement discretion and require an IND.

This policy has enabled many patients suffering from recurrent CDI to receive FMT, but is probably only temporary. The position of the FDA on this matter continues to evolve. Partially in response to stool banks, which were not operating under IND and began shipping preparations of stool to providers across state lines, FDA posted a draft guidance and solicited feedback in early 2014, proposing that the FMT product must be obtained from a donor known to either the patient or to the licensed health care provider treating the patient; and the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient. Although this policy has not been finalized, if fully implemented, such a policy would greatly limit FMT under the stool bank model, which uses volunteer donors who are not known to the patient or provider. Commercialized preparations of human stool are currently in clinical trials and it is conceivable that the FDA might cease to offer enforcement discretion entirely once one or more of these products is approved and commercially available. It is clear that the regulatory landscape will continue to evolve as microbiota-based therapeutics emerge.

Future of FMT & Microbial Therapeutics

While the value of FMT in treating recurrent CDI is clear, its potential long-term detrimental consequences, both beneficial and detrimental, are unknown. The gut microbiota is a complex consortium with many components that have never been characterized. *A priori* knowledge is not available regarding the impact of transferring these complex communities from one individual to another, although many studies in mice indicate that the composition of the gut microbiota can affect host susceptibility to diseases. Despite these safety concerns about transferring a complex and undefined microbial living microbial community from one human to another, there is very little current information about practice of FMT in the U.S. Critical methodological data such as donor/recipient screening, fecal preparation, modality of delivery, and patient consent practices are lacking. Information about the effectiveness of FMT as well as both short- and long-term safety data are not systematically collected, with the only available information being case reports published in the literature. Based on this information void, national societies have attempted to provide guidance to practitioners through published guidelines and editorials[16, 130, 131] but the degree of adherence to these recommendations is unknown.

Patients need to be informed of potential risks and consent to the procedure. Protocols need to be developed about donor sample preparation, characterization, archiving (so that follow-up analyses can be performed), and host preparation/administration/dosing. Registries need to be established for collection of data on donor and recipient characteristics, FMT protocols, and short- and long-term outcomes. Best practices for FMT need to be established, and critically evaluated, and clinically-relevant recipient responses to FMT, both beneficial and adverse, need to be defined and monitored. Recognizing the importance of systematically collecting information about the practice of FMT, there has been considerable interest in the development of a national FMT registry involving collaboration between national professional and advocacy societies. Such a registry would serve as a unique national resource of information about the clinical practice of FMT in the U.S.

In the absence of other therapies FMT remains the mainstay for management of recurrent CDI not responsive to conventional therapy. In the short-term there is a need to improve delivery methods to increase accessibility of this treatment. Frozen preparations of donor material will enable eligible patients to be treated more easily and facilitate clinical research. Openbiome is a stool bank located in Medford, MA USA. This non-profit organization has already supplied over 2000 doses of donor stool to over 200 institutions in the United States at a cost of around $250 USD per dose and has recently secured an IND for this product. However, it is very likely that whole-stool FMT, as currently practiced, is a short-term bridge for the treatment of CDI that will be replaced by commercially developed products. Although the timeline for the development of these products is currently unknown, a number are in late stage development and may be available within the next few years. These include full spectrum stool-based products as well as defined microbial consortia.

Encapsulated formulations of fecal material would help make FMT accessible to many more patients, simplify clinical trials and, if proven safe, could potentially be used earlier in the course of disease. Two recent advances in this area have resulted from efforts to refine FMT in order to isolate and deliver the bacterial species responsible for therapeutic effects. Ser-109, a microbial product comprising a mixture of bacterial spores developed as an ecobiotic by Seres Health, demonstrated excellent efficacy in management of recurrent *C. difficile* diarrhea in a small open-label study.[132] Results from the phase I/II clinical trial showed 100% success at 8 weeks. In an alternate approach using culture techniques, investigators at Queens University and Kingston General Hospital in Ontario, Canada isolated intestinal bacteria from healthy donors using modified continuous culture chemostat system. They then developed a defined microbial community of 33 strains termed *RePOOPulate* based on antibiotic susceptibility profiles, culturability and community robustness and administered it to two patients with relapsing *C. difficile* diarrhea in a proof of principle study. Both patients improved.[133] It is currently believed that the development of specific combinations of bacterial strains whose biological properties have been carefully characterized by genomic sequencing and biochemical/microbiologic analyses, together with standardized methods for human inoculation, with lead to predictable host responses and reduce the risk of pathogen transmission to enhance patient safety. In turn, the safety of such products would be monitored by post-market surveillance registries as required by the FDA for biologics and drugs.

Conclusions

The high therapeutic efficacy of FMT for recurrent CDI is an important proof of concept that substantial modification of the gut microbiota can be an effective modality of the treatment of a disease in humans. Much as the discovery of *H. pylori* revolutionized the treatment of peptic ulcer disease, our greater understanding of the communities of microorganisms residing within the human gut and the role of dysbiosis in various disease states will certainly result in new therapeutics in the coming decade. Rather than something to be feared as disease-causing agents, "germs" are now understood to be integral to human health, and a number of diseases both within and outside the GI tract may soon be treated with microbiota. FMT is the first and crudest way to alter the intestinal microbiome, and both patients and providers have become more aware of this highly effective option for CDI. Though FMT appears to be safe, with few short-term adverse effects or complications directly attributed to the procedure yet reported, more robust safety data is certainly needed as is better understanding of the mechanisms by which FMT is effective. There is speculation that other conditions marked by dysbiosis can be treated with FMT in some form, though these conditions are more complex and the outcomes after microbial manipulation are unlikely to be as dramatic and predictably effective as with CDI. It is certain that fecal therapy will continue to be refined beyond "whole stool" transplants. Rapid advances in DNA sequencing and metabolomic technologies, together with the development of more sophisticated biocomputational tools to analyze large and complex high dimensional datasets, will greatly facilitate the development of defined microbial consortia targeted to treat specific diseases. Though challenges exist, regulatory agencies have been willing to work with stakeholders and will continue to evolve and adapt policy as therapeutics based on human gut microbiome research emerge.

Acknowledgments

Abbreviations

FMT	Fecal Microbiota Transplantation
CDI	*Clostridium difficile* infection
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
GI	gastrointestinal

UC	ulcerative colitis
CD	Crohn's disease
CPT	Current Procedural Terminology
CTA	clinical trial application
FDA	Food and Drug Administration
IND	investigational new drug application

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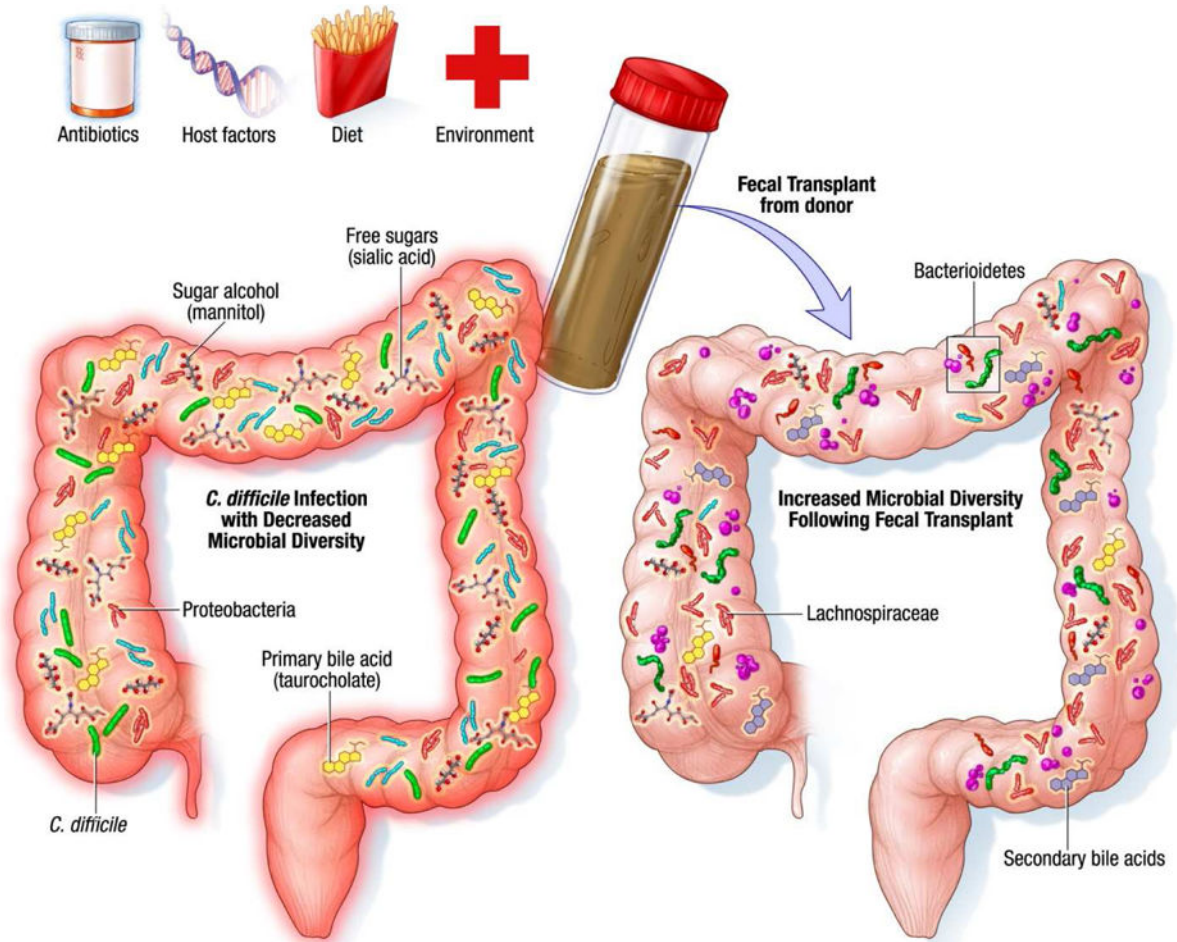
Figure 1.
Mechanisms underlying successful treatment of recurrent CDI with FMT Improvement in symptoms following fecal microbiota transplant has been associated with change in microbial community structure such as a decrease in Proteobacteria as well as restoration of microbial diversity, increase in secondary bile acid production and niche exclusion by other bacteria.

Table 1

Suggested Donor Testing

Serologic	Stool	Consider	Possibly
HAV-IgM	*C. difficile* toxin B (preferably by PCR)	*Giardia*	CMV
HBsAg	Culture for enteric pathogens	*Cryptosporidium*	Human T cell lymphoma virus
anti-HCV-Ab	O+P, if travel history suggests	*Isospora and Cyclospora*	EBV
HIV 1 & 2-EIA		E. coli O157	*Dientamoeba fragilis*
RPR		Rotavirus	*Blastocystis hominus*
		Listeria	*Strongyloides stercoralis*
		Vibrio	*Entamoeba histolytica*
		Norovirus	*Helicobacter pylori*
			Schistosoma
			JC virus
			VRE
			MRSA

Table 2

Adverse events in published series of more than 5 patients receiving FMT for *C. difficile* infection

1st Author	No.	Method of delivery	Follow-up	Adverse events
Van Nood[4]	16	Duodenal infusion	70 days	Diarrhea—5, abdominal cramps—5, belching—3, nausea —1; symptoms resolved in all within 3 hours
Youngster[44]	20	Nasogastric tube or colonoscopy	6 mos	Mild abdominal discomfort/bloating—4; transient fever (day 2)—1
Rubin[97]	75	Nasogastric tube	60 days	No adverse events or deaths
MacConnachie[27]	15	Nasogastric tube	4–24 wks	No adverse events "related to transplant"; upper gastrointestinal bleeding during 1st month post-FMT
Aas[98]	18	Nasogastric tube	90 days	Peritonitis in patient on peritoneal dialysis on day 3 (died "shortly thereafter"); pneumonia in patient with COPD (died on day 14)
Mattila[35]	70	Colonoscopy	1 yr	No complications
Hamilton[99]	43	Colonoscopy	1 yr	No serious adverse events; approximately one-third noted irregular bowel movements and excessive flatulence during 1st couple of weeks after FMT
Patel[100]	31	Colonoscopy	1 yr	1 complication: "microperforation" from colonoscopic biopsy which resolved without surgery
Yoon[101]	12	Colonoscopy	3 wks – 8 yrs	No adverse events
Pathak[102]	12	Colonoscopy—11; nasoduodenal–1	2–29 mos	No complications of FMT
Dutta[103]	27	Enteroscopy + colonoscopy	10–34 mos	Low grade fever—5, bloating—3; resolved within 12–24 hrs
Lee[104]	94	Enema	6–24 mos	No significant adverse events; 10% experienced transient constipation and excessive flatulence
Emanuelsson[105]	23	Rectal catheter	23	"A few" patient experienced temporary constipation (apparently soon after FMT)
Silverman[106]	7	Enema	4–14 mos	No adverse events but reported 1 patient with "post-infectious" irritable bowel syndrome (mixed pattern)
Schwartz[107]	13	Colonoscopy	Not stated	Norovirus—2 (2 days and 12 days after FMT); authors speculated person-to-person rather than FMT transmission
Kelly[43]*	80	Mixed	12 wks	**Potentially related adverse events** *Death*: aspiration during colonoscopy with respiratory failure *Hospitalizations:* IBD flares—4, post-colonoscopy abdominal pain—1; fever, diarrhea, encephalopathy, pancytopenia in lymphoma patient—1 *Non-serious adverse events*: abdominal pain/bloating immediately following FMT—3; "mucosal tear" at colonoscopy—1; self-limited diarrhea-3, fever—1, IBD flare–1

*
Immunocompromised patients (e.g., immunosuppressive therapy for IBD, organ transplant, cancer with antineoplastic therapy)