Fecal Microbiota Transplantation Across the Lifespan: Balancing Efficacy, Safety, and Innovation

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Fecal microbiota transplantation (FMT) is a rapidly growing therapy aimed at reconstituting the dysbiotic microbiota of a patient with the beneficial stool microbiota of a healthy individual. The efficacy rates of FMT are very robust for recurrent *Clostridioides difficile* infection in both children and adults. Although complications of FMT have been reported, it is generally believed to be a safe procedure. Novel indications for FMT are being studied, with the hope that ultimately it may be useful for a variety of disorders. As this field continues to grow, however, it is necessary to consider efficacy, safety, and innovation across the lifespan. There are unique concerns regarding FMT as it pertains to children, adults, and the elderly. In this review, we seek to update clinicians, researchers, and regulators on how these factors must be balanced across the lifespan as we move forward with this innovative therapy.

KEYWORDS: fecal microbiota transplant; *Clostridioides difficile*; biotherapeutics; microbiota; lifespan

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INTRODUCTION

The gut microbiota represents the community of microbes that live within our gastrointestinal tract. Composed of bacteria, viruses, fungi, protozoa, and archaea, these organisms play a key role in human health and disease. Unhealthy disruptions of the gut microbiota result in enteric dysbiosis, which has been implicated in several disorders, from inflammatory bowel disease (IBD) to metabolic syndrome (1,2). This has led physicians and researchers to search for therapeutic approaches to restore microbial health and homeostasis.

The necessity for a restorative approach has become more urgent with the rising incidence of *Clostridioides difficile* infections (CDI) over the past 2 decades. In many cases, vulnerability to CDI results from exposure to antibiotics that drive enteric dysbiosis. This impairs colonization resistance, which is the ability of the microbiota to inhibit colonization by *C. difficile* (3). Moreover, classical antibiotic treatments to treat CDI can perpetuate injury to the gut microbiota. This sets the stage for recurrent *C. difficile* infections (rCDI), which occur in 20%–30% of patients (4). Fecal microbiota transplantation (FMT) emerged largely in response to this challenge and has been shown to repair antibiotic injury and restore colonization resistance to *C. difficile* (5).

FMT involves the delivery of a stool microbiota from a healthy individual to a patient, with the goal of restoring a healthy microbial community in the gut. The US Food and Drug Administration (FDA) currently maintains a policy of enforcement discretion, which allows FMT to be used solely for the treatment of CDI not responsive to standard therapies, without requiring an investigational new drug application (6). This 2013 policy has given clinicians a reprieve from the burden of regulatory paperwork associated with an investigational new drug and has given patients with CDI access to FMT treatment. Through this review, we hope to update clinicians, researchers, and regulators on the efficacy, safety, and innovation of FMT, with an emphasis on how these factors must be balanced across the lifespan (Table 1).

EFFICACY OF FMT

The efficacy of FMT for rCDI has been well established. The first randomized controlled trial evaluating FMT for rCDI was published in 2013 and demonstrated that 81% of patients receiving FMT had a resolution of *C. difficile*, compared with 31% receiving standard antibiotic therapy (7). This striking difference between the treatment and control group resulted in an early stoppage of the trial. Several studies describing the use of FMT for rCDI have since been published, with efficacy reaching 80%–90% (8). FMT is also being used for severe or fulminant CDI, with a 4-week response rate of 88% reported in recent systematic review and meta-analysis (9).

Additional studies have begun examining the role of FMT for indications other than rCDI. Efficacy has been reported for several disorders, including metabolic syndrome, functional gastrointestinal diseases, antibiotic-resistant infections, and IBD (10). For ulcerative colitis, a subtype of IBD, several double-blind randomized controlled trials have been published, with a recent meta-analysis showing a 30.43% clinical and endoscopic remission rate for FMT vs 9.82% for placebo (odds ratio 4.11; 95% confidence interval 2.19–7.72) (11). These efficacy rates are lower

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Table 1. Age-related factors to consider when undergoing FMT for rCDI

	Pediatric	Young adult/middle age	Elderly
Efficacy (%)	80–90	80–90	<80
Safety	Lower rates of adverse events Theoretical long-term concerns of early manipulation of the gut microbiota	Theoretical long-term concerns of manipulation of the gut microbiota Higher rates of co-existing inflammatory bowel disease with rCDI	Higher rates of adverse events, especially procedural complications May have pill dysphagia, limiting use of capsule formulations Higher rates of co-existing microscopic colitis with rCDI
Innovation	Need innovative approaches to administration as there are challenges to capsule and enema administration Need to consider pediatric subjects in innovative trials for emerging LBPs	Most common age group included in LBP clinical trials	Need to consider elderly subjects in innovative trials for emerging LBPs

FMT, fecal microbiota transplantation; LBP, live bacterial product; rCDI, recurrent *Clostridium difficile* infection.

than those for rCDI but provide preliminary evidence that FMT may eventually be useful for other disorders as well. That said, the utility of FMT is not necessarily universal to all microbiota-associated diseases, and clinical trials supporting its use for specific disorders are clearly needed.

SAFETY OF FMT

The incidence of adverse events (AE) after FMT has been reviewed in several studies. A systematic review including subjects of all ages reported an AE rate of 28.5% after FMT (12). However, most AE included mild-to-moderate issues such as abdominal pain, flatulence, increased stool frequency, vomiting, and fever, which were typically self-limited. Serious AE were rare, and only 2 of the 44 (5%) identified were definitively associated with FMT. These studies suggest that FMT is generally a safe procedure for those with rCDI.

Although the overall safety of FMT is well supported, severe complications have been reported. These serious AE, such as aspiration and intestinal perforation, have typically been procedural-related. FMT can be delivered through the upper (nasogastric/nasoduodenal tube or upper endoscopy) or lower (enema or colonoscopy) gastrointestinal tract, and each of these modalities carries some inherent risk. Previous reviews have suggested an increased risk of AE with upper tract FMT delivery (12), although no trials have studied this directly. A recent pediatric study performed FMT in 42 children through a nasogastric tube and described vomiting as the only postprocedural complication (13%) (13). FMT administration directly into the stomach carries additional risks for certain groups; for example, FMT may not be a viable option for medically complex patients who are at risk for aspiration. FMT administration through capsules is an emerging less invasive approach to deliver fecal substrate and may overcome some of the procedural risks described (14,15).

Transmission of infection is also a concern with FMT, although several studies have demonstrated the risk of infection through FMT is low, even in immunocompromised patients (16). Nonetheless, donor screening protocols continue to evolve and adapt to our growing experience and new emerging infections. After a report of FMT-associated cases of extended-spectrum beta-lactamase-producing *Escherichia coli* bacteremia, including the death of 1 patient (17), the FDA advised mandatory testing of stool for common multidrug-resistant organisms (18). More recently, the FDA advised additional donor screening and testing protocols to mitigate the risk of severe acute respiratory syndrome coronavirus 2 and monkeypox transmission through FMT (19). Informed consent of patients and families should include information about the potential transmission of multidrug-resistant organisms, severe acute respiratory syndrome coronavirus 2, and monkeypox (18,19).

Perhaps the most difficult risks that providers and patients must consider with FMT relate to the theoretical possibility of transmitting a microbiota-mediated disease to the recipient. A plethora of chronic diseases have now been associated with the gut microbiota, ranging from neuropsychiatric disorders to autoimmune diseases to obesity (20). Concerns that FMT may actually induce such diseases in recipients have been fueled by reports of chronic disorders such as rheumatoid arthritis, Sjogren syndrome, idiopathic thrombocytopenic purpura, peripheral neuropathy, and obesity in patients after FMT (21,22). Presently, however, there is no evidence to suggest that FMT causes these disorders. Ultimately, more robust, long-term safety data from prospective studies will be required. This will be facilitated by registries such as the Fecal Microbiota Transplantation National Registry, led by the American Gastroenterology Association, which will study short-term and long-term risks of FMT in 4,000 patients for 10 years posttransplant (23).

INNOVATION

FMT is the epitome of an innovative therapy; pioneered in ancient China as a treatment for food poisoning (24), it holds tremendous therapeutic potential for treating disease through manipulation of the intestinal microbiome. The FDA considers FMT both a biologic and a drug; however, its dynamic and variable composition requires a new lens be applied to the development and approval process. In its current form, FMT hovers between an accepted, widely used therapy and an innovative but experimental treatment. Despite robust clinical data supporting its efficacy for recurrent and refractory *C. difficile*, FMT is still considered investigational in many countries including the United States. Indeed, the enforcement discretion policy issued by the FDA was partly driven by a public outcry from patients with CDI and their providers (25). As

such, FMT has not followed standard drug development pathways, which adds to its innovative nature.

FMT represents an entirely new class of therapeutics, which requires development of a new branch of pharmacology that incorporates concepts and sciences that are still new to medicine (26). It requires an updating of the basic germ theory of disease and recognition that entire microbial communities rather than a single pathogen can drive disease pathogenesis. Detailed studies are needed to characterize the distribution of donor microbes along the different compartments within the gastrointestinal tract (e.g., small bowel vs colon and mucosa-adherent vs luminal microbiota). It is also important to consider the structure of the indigenous microbiota, which is highly variable among patients and in its receptiveness of donor microbiota.

FMT is the most basic and straightforward approach to deliver a live bacterial product (LBP) for the treatment of disease. That said, there are a number of novel LBP in various phases of development. RBX2660 is a microbial consortium derived from human stool (27). A recent phase III randomized, double-blind, placebo-controlled trial evaluating the ability of this LBP to prevent rCDI showed a success rate of 70.4% (n = 180), as compared to 58.1% (n = 87) for placebo. Another product, SER-109, is an LBP composed of Firmicutes spores (28). A phase III randomized, double-blind, placebo-controlled trial for this product demonstrated CDI recurrence in 12% of the LBP group (n = 89) vs 40% in the placebo group (n = 93). Notably, most patients with rCDI seen in the real-world clinical practice have been excluded from randomized clinical trials because of strict enrollment criteria (29). Furthermore, these placebo-controlled trials do not allow for comparison among LBP so comparative efficacy data are lacking. Thus, although these results are promising, there remains continued need for further rigorous controlled and pragmatic clinical trials with meaningful long-term end points. Defined microbial consortia may be best suited for conditions that require restoration of specific functions that are missing in a particular disease rather than repair of a decimated microbiome. For the latter, FMT may remain an ideal therapy. In particular, FMT using stool from carefully selected healthy donors generally decreases the overall burden of antibiotic resistance genes in rCDI in both children and adults (30–32). This aspect of dysbiosis may not be fixed with a defined consortium of microbes meant as a bridge to recovery from rCDI.

Finally, there has been a growing interest in nutritional strategies in the treatment of multiple digestive diseases. The combination of FMT and mechanistically informed diets are beginning to be explored in clinical trials and show promise in initial trials for ulcerative colitis (33,34); these will likely be explored for other diseases, including rCDI. In the authors' experience, patients understand the importance of diet as it relates to microbiota health and often ask about dietary instructions after receiving FMT. This question is pertinent to all LBP and certainly deserves more attention.

PEDIATRIC CONCERNS

CDI is frequently described as a disease of the elderly and infirm, but there has been a dramatic increase in the incidence of pediatric CDI in recent decades (35). In addition, although severe CDI is less common in the pediatric population, rCDI occurs in 20%–30% of children, rates equivalent to those described in adults (36). For these reasons, the use of FMT for CDI in children has grown over the past decade.

To date, there are no randomized control trials evaluating the use of FMT for CDI in children. Therefore, most protocols are extrapolated from adult data or retrospective pediatric studies. A retrospective study of 335 pediatric and young adult patients undergoing FMT for the treatment of CDI demonstrated an 81% success rate, which improved to 86.6% if FMT was repeated (37). Smaller case studies in children have reported similar success rates, averaging 80%–90%, mirroring success rates in adults. However, factors associated with success may differ between adults and children. In the pediatric cohort of 335 children, patients were more likely to have a successful FMT with the use of fresh vs frozen stool (odds ratio 2.66; 95% confidence interval 1.04–1.39), whereas previous randomized control trials in adults have not identified a significant difference between the use of fresh vs frozen samples (38). Potential explanations for this include alterations in the microbiome that occur during a freeze-thaw cycle, which may be more critical in children, or issues regarding age match between donor and recipient, which is likely greater with the use of stool banks (adult only) vs family identified (parents and siblings).

In general, FMT in children is well tolerated with infrequent complications. Nicholson et al showed that 17 of 335 (5.1%) patients had an AE after FMT, of which only 2 (0.6%) were believed to be FMT related based on expert consensus (37). Thus, the rate of AE in pediatric FMT seems to be lower than that described in adults. However, issues of long-term safety are particularly relevant in children, where the microbial, metabolic, and immune changes may persist over a lifespan. With limited data on long-term safety, the best screening processes and the most suitable donors for pediatric FMT have yet to be established.

Finally, it is important to note that most new LBP in development are not being studied across the lifespan. Unfortunately, current studies are focused on young and middle-aged adults, excluding the elderly and the young. This is especially problematic for children because the drug approval process typically takes an additional 8–10 years; in short, these LPB will not be immediately approved for pediatric patients for some time. In addition, many microbial therapeutics undergoing study through phase I and II clinical trials are administered through oral capsule or enema use, which limit their pediatric application, and there are no dedicated pediatric LBP trials ongoing.

ADULT/ELDERLY CONCERNS

Older age is a well-recognized risk factor for CDI and rCDI, and changes in the intestinal microbiome and metabolome associated with ageing are consistent with known mechanisms of colonization resistance against *C. difficile* (26,39,40). Older age is associated with decreasing relative abundance of key bacterial taxa, including Lachnospiraceae, Ruminococcaceae, and Bacteroidetes, which have been shown to correlate with rCDI cure after FMT (41). In addition, older age is associated with lower concentrations of secondary bile acids and short-chain fatty acids, which play critical roles in the *C. difficile* lifecycle and protection against *C. difficile* colonization (26,42). These changes may be intrinsic to senescence or result from multiple factors that correlate with older age, such as a greater burden of antibiotics, a restricted diet, and decreased physical activity. In a recent multicenter observational trial, older age (≥65 years) was noted to be a risk factor for FMT failure in rCDI (15). Mechanistic understanding of the factors determining the success of FMT is critical to optimizing the treatment, potentially by altering the dosing regimen and/or using adjunctive dietary measures that would support bacterial taxa that contribute most to protection against CDI.

Although multiple routes of FMT administration are possible, they are not all equivalent with respect to risks and benefits to the patient. The procedure-associated risks of colonoscopy increase with advanced age, whereas the diagnostic benefits decrease. Colonoscopy may be the preferred method of FMT administration in younger adults because of the much higher prevalence of underlying IBD in this patient population (43). In fact, the inability to cure rCDI with antibiotics alone in a young adult should raise suspicion for underlying IBD. However, in most cases, IBD is already known to exist, in which case it is still helpful to document its activity at the time of FMT because it may inform post-FMT IBD management. When physicians and patients were given a choice between a colonoscopic and oral capsule FMT, most treatments were conducted with the oral capsules, given their convenience (15). Notably, older patients have a higher prevalence of lymphocytic colitis, a diagnosis that should be considered when rCDI symptoms fail to resolve, especially after the decolonization of *C. difficile*.

Medical comorbidities are important considerations in identifying the best treatment strategy for individual patients. The older rCDI patient population has a high prevalence of neuromuscular disorders, including a history of stroke, spinal injury, multiple sclerosis, and others (44,45). These conditions can impose significant burdens when preparing for a colonoscopy with a purgative. On the other hand, older patients also have a higher prevalence of pill dysphagia, which may preclude FMT delivery through oral capsules. FMT enema is another alternative to colonoscopic administration that can be useful in medically complex adult patients or those with severe CDI (46,47). It is also critically important to consider a patient's entire infectious disease history. FMT is likely to have minimal benefit when the patient has a high burden of non-CDI antibiotics. For example, many patients with rCDI are older women with recurrent urinary tract infections (48). In these patients, it may be possible to mitigate this problem using acidifying agents such as methenamine with vitamin C and through gut-sparing antibiotic regimens for sporadic uncomplicated urinary tract infections (49). However, in the absence of a plan to limit post-FMT antibiotic exposure, it may be reasonable to maintain patients on prolonged suppressive regimens of daily vancomycin.

FUTURE DIRECTIONS

The emergence of FMT has opened a new frontier of medical therapeutics. Although initially a crude procedure, it is being replaced by more standardized formulations of products manufactured in dedicated facilities that conduct rigorous and comprehensive donor testing, follow Good Manufacturing Practices protocols, and ensure consistent dosing. These elements constitute critical steps for doing rigorous clinical trials, which are necessary for the optimization of dosing regimens. Unfortunately, randomized, placebo-controlled trials of FMT-based products have largely excluded patients of advanced and pediatric ages, and patients with various medical comorbidities (29). Developers of FMT-based products must consider these different age groups in clinical trials moving forward.

The anticipated entry of commercial FMT-based products into the marketplace will also bring forth new ethical challenges that require careful consideration. First, the manufacturing scale-up of FMT-based products involves expansion of the human stool donor recruitment. The demands on these individuals are far more onerous relative to blood donors, given the need for continuous clinical monitoring for many months and the requirement to produce stool in a collection facility. In addition, monetary inducements to increase donor recruitment may also compromise the safety of the donated stool because donors may be less forthcoming about their medical history and infectious disease risk factors. This issue is well recognized in blood banking but has received little attention thus far in commercial FMT manufacturing.

It is hoped that the arrival of commercial FMT-based products will improve access for many patients with rCDI to these curative therapies. However, as noted, these commercial products may not be accessible to all patients, particularly those at either end of the lifespan. Furthermore, access may be limited by reimbursement challenges if these products are priced too high. The encouragement of nonprofit alternatives could mitigate this problem but may face resistance from the pharmaceutical and drug development industry. Despite these financial and access challenges, it is hoped that demonstrable improvements in patient care with FMT-based therapies will draw more investments into research and development of next-generation live biotherapeutics that will benefit a greater range of clinical problems faced by our patients.

Targeting the gut microbiota with FMT and other LBP represents a new therapeutic frontier in medicine. These novel therapeutics have challenged established drug development paradigms, including traditional discovery pathways, the regulatory framework, and the science required for mechanistic understanding. Healthcare providers, researchers, and regulators must gain a greater understanding of the challenges involved in developing these novel and promising therapeutics. Importantly, LBP must not be viewed in a one-size-fits-all paradigm. Instead, rigorous research and a personalized approach that takes into account the lifespan considerations discussed in this review will be critical for the safe and effective use of these therapies in the future.

CONFLICTS OF INTEREST

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