Fecal Microbiota Transplantation for Inflammatory Bowel Disease

Joanna Lopez, MD, and Ari Grinspan, MD

Dr Lopez is a gastroenterology fellow and Dr Grinspan is an assistant professor of medicine at Icahn School of Medicine at Mount Sinai in New York, New York.

Address correspondence to:
Dr Ari Grinspan
Mount Sinai Hospital
1 Gustave L. Levy Place
New York, NY 10029
Tel: 212-241-8100
Fax: 646-537-8921
E-mail: ari.grinspan@mountsinai.org

Abstract: The gut bacterial microbiome, particularly its role in disease and inflammation, has gained international attention with the successful use of fecal microbiota transplantation (FMT) in the treatment of *Clostridium difficile* infection. This success has led to studies exploring the role of FMT in other conditions, including inflammatory bowel disease (IBD). Both Crohn's disease and ulcerative colitis are chronic inflammatory conditions of the gastrointestinal system that have multifactorial etiologies. A shift in gut microbial composition in genetically susceptible individuals, an altered immune system, and environmental factors are all hypothesized to have a role in the pathogenesis of IBD. While numerous case reports and cohort studies have described the use of FMT in patients with IBD over the last 2 decades, the development of new sequencing techniques and results from 2 recent randomized, controlled trials have allowed for a better understanding of the relationship between the microbiome and the human host. However, despite these efforts, knowledge remains limited and the role of FMT in the management of IBD remains uncertain. Further investigation is necessary before FMT joins the current armamentarium of treatment options in clinical practice.

Keywords
Fecal microbiota transplantation, ulcerative colitis, Crohn's disease, inflammatory bowel disease

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic, relapsing, and remitting inflammatory diseases of the intestines that lead to significant morbidity and mortality in affected individuals. The underlying pathophysiology of these conditions remains unknown, although it is hypothesized to be multifactorial (ie, an altered immune system, environmental exposures, genetic predisposition, and an aberrant interaction of gut microorganisms with the intestinal mucosa).[1,2] Current treatment modalities center on the modulation of the immune system and are limited by side effects, few therapeutic options, and a lack of efficacy.[3,4]

The role of the microbiome in human disease has gained interest among physicians and patients alike as a means for alternative treatment, with a marked increase in the number of studies over the last few years. The successful use of fecal microbiota transplantation

(FMT) in the treatment of *Clostridium difficile* infection (CDI) propelled this concept. Newer sequencing technologies have complemented the efforts to understand the role of the gut endogenous flora in the pathophysiology of many diseases, including inflammatory bowel disease (IBD). However, despite growing knowledge, the available data are conflicting, with a suggested beneficial effect that may be limited.

The Microbiome in Health and Disease

The human microbiome consists of bacterial, fungal, and viral communities that inhabit the human body. There has been growing interest and intensified research in recent years, primarily focusing on the bacterial component of the microbiome. As a result, the understanding of the microbiota and its symbiotic relationship with the human host is improving. Both environment and diet are thought to influence a delicate balance of commensal and pathogenic organisms. Microbial populations take hold in the human host shortly after birth and remain mostly stable for years in the absence of any antibiotic or significant dietary changes.[5] The bacterial communities that reside in adult humans are believed to collectively consist of as many as 25 to 50 trillion cells, with the largest concentration found in the gastrointestinal tract.[6] The number of gut species, which has been possible to enumerate through ribosomal RNA sequencing, is calculated to be 500 to 2000, representing only a fraction of the existing world bacteria.[5,6] This core microbiota functions as an organ in the human body, with important physiologic roles in energy metabolism and modulation of the immune system.

CDI is an increasingly prevalent enteric infection that is a direct result of the imbalance of normal gut microbiota and is effectively treated by restoration of intestinal flora.[7,8] As a result, guidelines for management of CDI from the major gastrointestinal societies are now available to support the use of FMT.[9,10] Multiple other diseases are believed to be a result of a similarly disturbed microbial state, including atopic diseases,[11] obesity and metabolic syndrome,[12] colorectal cancer,[13] and irritable bowel syndrome.[14,15] Although in its infancy, the use of FMT to treat other conditions, including IBD, has become an exciting area of interest in the scientific community, and is expected to continue to grow in the future.

Current Understanding of Inflammatory Bowel Disease

The 2 major disorders that comprise IBD have distinct yet overlapping pathologic and clinical manifestations. Characterized by transmural inflammation, CD can affect any portion of the gastrointestinal tract from the mouth to the perianal area. UC, differentiated by inflammation of the mucosal layer, is limited to the colon.

The etiology of IBD is currently unknown and is hypothesized to be multifactorial, with genetic and environmental components that result in altered intestinal homeostasis. To date, there are over 160 genetic loci that are associated with IBD.[16] The mechanisms through which the affected genes contribute to disease include microbe recognition, lymphocyte regulation, cytokine release, and intestinal barrier defense.[17] The increased incidence of both UC and CD in the last few decades and their expansion to developing countries highlight the role of environmental factors and their effect on the gut microbiota. The interaction between the intestinal microorganisms and an altered immune system in a susceptible individual is suspected to be central to the development of IBD. Whether the pathogenesis of IBD results from a dysregulated mucosal immune system response to commensal flora or from an imbalanced gut microbiome inducing an alteration in the immune system of a susceptible host remains unclear.

Current management of IBD results from the understanding of the inflammatory cascade that ensues in the unbalanced host. Therapies aimed at modulating this immunologic response include salicylates, corticosteroids, thiopurines, anti–tumor necrosis factor agents, and antiintegrins. The limitations of these treatments include side effects, infections, secondary malignancies, and lack of response. New treatment approaches, with a focus away from the host and onto restoring microbial balance, may prove efficacious and provide an alternative and complementary approach to the management of IBD.

Current Understanding of the Gut Microbiome in Inflammatory Bowel Disease

Bacteria were reported to play a role in colitis as early as the 1900s.[18] Over the last 2 decades, studies have highlighted the pivotal role of gut microbiota in the pathogenesis of IBD.[19,20] For instance, in almost all mouse models of IBD, the presence of intestinal bacteria is required for clinical symptoms of colitis to develop.[21,22] In both UC and CD patients, antibiotic use and the resulting imbalance of the natural microbial composition have been shown to contribute to disease activity.[23] Alternatively, probiotics have been shown to have some efficacy in remission in UC patients,[24] and fecal diversion is an acceptable management strategy in patients with CD to alleviate downstream inflammation.[25]

The fecal bacterial flora of IBD patients has been shown to be different from healthy individuals.[26,27] The ratio of pathogenic to commensal flora is shifted in IBD patients, and a decreased bacterial load is present in areas

Table. Studies of FMT in Patients With IBD

Study	Disease	Patients (n)	Disease Severity	FMT Delivery	FMT Frequency	Follow-Up
Bennet et al[56]	UC	1	Severe	Enema	Multiple times	6 months
Borody et al[57]	UC, CD	2	Active	–	–	1-12 months
Borody et al[58]	UC	3	In remission	Enema	Daily for 5 days	8-28 months
Borody et al[59]	UC	6	Severe	Enema	Daily for 5 days	1-13 years
Borody et al[60]	IBD	3	Refractory disease	Enema	Daily and weekly	1-4 years
Borody et al[61]	UC	1	Relapsing	–	–	–
Vermeire et al[50]	CD	4	Refractory disease	NJT	3 times within 36 hours	2 months
Kunde et al[42]	UC	10	Mild-moderate	Enema	Daily for 5 days	6 weeks
Kellermayer et al[62]	UC	4	Refractory disease	Colonoscopy	–	>5 months
Kump et al[49]	UC	6	Refractory disease	Colonoscopy	Once	1 year
Angelberger et al[46]	UC	5	Severe	NJT, enema	Daily for 3 days	>1 year
Kao et al[63]	IBD	1	Moderate-severe	Colonoscopy	3 times at weeks 0, 4, and 10	2 months
Landy et al[64]	UC	5	Refractory pouchitis	NGT	Once	4 weeks
Zhang et al[65]	CD	16	Refractory disease	Gastroscopy	Once	1 month
Suskind et al[66]	CD	9	Mild-moderate	NGT	Once	6 weeks
Damman et al[47]	UC	8	Mild-moderate	Colonoscopy	Once	12 weeks
Vaughn et al[44]	CD	9	Active	Colonoscopy	Once	12 weeks
Suskind et al[43]	CD	9	Mild-moderate	NGT	Once	12 weeks
Moayyedi et al[37]	UC	75	Active	Enema	Weekly for 6 weeks	7 weeks
Rossen et al[38]	UC	37	Mild-moderate	Nasoduodenal	2 times at weeks 0 and 3	12 weeks

CD, Crohn's disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; NGT, nasogastric tube; NJT, nasojejunal tube; UC, ulcerative colitis.

of active inflammation. Bacterial RNA sequencing has shown an increase in pathogenic organisms such as *Escherichia coli*, *Campylobacter* species, and *Mycobacterium avium* in CD, while organisms from the Bacteroidetes and Firmicutes phyla are decreased.[28] This microbial imbalance may be a potential therapeutic target for IBD. In mouse models, a specific bacterium, *Faecalibacterium prausnitzii* from the Firmicutes phylum, has been shown to have significant anti-inflammatory properties through the secretion of metabolites that reduce the secretion of inflammatory cytokines and, therefore, prevent active colitis.[29] Other mechanisms through which commensal organisms contribute to the anti-inflammatory response include inducing regulatory CD4 T-cell activation and anti-inflammatory cytokine secretion.[30,31]

The bacterial mucosal surface component of CD and UC patients is also known to differ from that of non-IBD patients. A recent study of children with new-onset, treatment-naive CD demonstrated a marked dysbiosis in mucosa-associated bacteria compared with healthy controls.[32] Bacterial invasion of the mucosa is evident in both CD and UC patients, while rarely found in healthy patients.[33,34] Furthermore, there is an increase in entero-adherent bacteria and a decrease in health-promoting bacterial communities in these patients.[35]

The interaction of the microbiome with the immune system is complicated. Physicians have seen that patients with IBD have altered fecal and mucosal bacterial microbiomes when compared with healthy controls. Microbiome manipulation that restores intestinal microbial homeostasis has been considered as a therapeutic option given the aberrant immune response and downstream inflammatory cascade.

The Use of Fecal Microbiota Transplantation in Inflammatory Bowel Disease

Twenty studies that include a combination of case reports; cohort studies; and randomized, controlled trials have been published on the use of FMT in IBD, with the earliest case report published in 1989 (Table). A rigorous systematic review of 18 studies that used FMT as the primary therapeutic agent in IBD summarized the limitations and potential benefits of this strategy.[36] Overall, 122 patients who underwent FMT were found to have a remission rate of 45%. Publication bias from case reports was eliminated through a subgroup analysis of cohort studies only, and the results fell to a 36% efficacy rate in this group.[36] The subgroup analysis suggested that CD patients were more likely to have a response to FMT, with an estimated response

of nearly 61% of patients achieving clinical remission, in comparison to a modest 22% rate in UC patients.

Two randomized, controlled trials were published in 2015 with conflicting results. A study by Moayyedi and colleagues included 75 adult patients with active UC on stable doses of immunosuppressants who were randomized to weekly FMTs or water enemas for 6 weeks and evaluated for remission at week 7.[37] Remission was defined as a total Mayo score of 2 or lower with an endoscopic subscore of 0. The authors found that patients who received FMT were significantly more likely to achieve remission than those who received placebo (25% vs 5%; *P*=.03). An interesting observation was that although this study included 6 donors, 1 donor in particular seemed to be more effective than the others; stool from Donor B induced remission in 7 of 18 (39%) patients, while stool from Donors A, C, D, E, and F induced remission in only 2 of 20 (10%) patients (*P*=.06). Another observation was the increased efficacy seen in recently diagnosed patients (<1 year), in which 3 of 4 patients randomized to FMT achieved remission. Although the sample size was smaller than planned due to early termination, this study provides thought-provoking data that suggest a pathway for mucosal healing in UC through alteration of the gut microbiome. Study limitations include small sample size due to early study termination (as mentioned above) and only short-term follow-up.

Concurrent to the study conducted by Moayyedi and colleagues,[37] Rossen and colleagues conducted a randomized, controlled trial that included 48 adult patients with mild to moderate UC who were randomized to receive 2 FMTs at weeks 0 and 3 from either healthy donors or their own stool (autologous transplant).[38] FMT was delivered via nasoduodenal tube. Only 37 patients were included in the per-protocol analysis for the primary endpoint of clinical remission and at least a 1-point decrease in the Mayo endoscopic score at week 12. The authors found no significant difference between the 2 groups, with 7 of 17 (41.2%) patients who received FMT and 5 of 20 (25%) patients who received placebo achieving the primary endpoint (*P*=.29).

Important differences between these 2 trials, and previous published data, may contribute to the discrepancy in results. The mode of administration of FMT may have an important effect in UC patients. The positive study[37] performed FMT via enemas (lower gastrointestinal route), and the negative study[38] performed FMT via nasoduodenal tube (upper gastrointestinal route). Studies of the use of FMT in patients with CDI suggest that nasoduodenal tube administration may be less effective than colonoscopic infusion.[39-41] In UC, the underlying pathophysiology may favor distal as opposed to proximal FMT administration.

The total number of treatments also differed between the 2 randomized, controlled trials, with 6 enemas by Moayyedi and colleagues[37] as opposed to 2 nasoduodenal infusions by Rossen and colleagues,[38] and raises the possibility of a dose response to allow for an effective microbial engraftment in the host. Interestingly, 4 of the previously published cohort studies found clinical improvement after a single endoscopic administration.[42-45] The variability in methodology and conflicting results in these studies highlight the need for further studies that expand on optimal delivery route, dosage, and frequency.

The microbiotal analysis of responders vs nonresponders in the few studies that have analyzed these data emphasizes the important role that specific bacterial phyla or classes may play in disease activity, as well as the changes in microbial composition that occur after FMT. An increase in Bacteroidetes and Proteobacteria phyla and *Bacilli* class in autologous FMT responders vs nonresponders is seen in the study by Rossen and colleagues.[38] In contrast, responders to the donor FMT had a shift in their profile that was characterized by an increase in *Clostridium* clusters IV, XIVa, and XVIII, and a reduction in Bacteroidetes, which mirrored the donor stool.[18] In several studies, UC patients who responded to FMT resembled the donor with similar shifts in their microbiome[46-48]; however, 1 study showed a shift that was not associated with response.[49] The 2 studies of CD patients that included microbiome analysis found differing results, with a microbial shift toward the donor profile in only 1 study.[44,50]

The study by Moayyedi and colleagues suggests that FMT may be more efficacious in patients currently on immunosuppressive therapy and that donor effect may play a significant role in treatment success.[37] This last observation may be the basis for the identification and transplantation of specific microbial communities that restore intestinal homeostasis. Further studies on what makes an effective donor are paramount to understanding how and why FMT may be a successful treatment. A significant effect was also seen in patients with recently diagnosed UC, an observation that must be corroborated in future studies.

The safety profile of FMT is based on the few small studies that have been published. Reported adverse events have included transient fevers, abdominal tenderness, elevation in inflammatory markers, and vomiting (after duodenal infusions).[36] Serious adverse events are rare, although IBD flares and infection have been reported after FMT.[51-53] Therefore, if FMT can shift the gut profile for the better, it stands to reason that the procedure could also make it worse. The previous reports of flares emphasize the need for larger clinical trials that focus on both the short- and long-term efficacy and safety of FMT.

Future Directions

The role of FMT in the management of IBD remains unclear. The limited published studies to date show that FMT does not have the same dramatic impact in IBD as it does in CDI. While both CDI and IBD are characterized by an altered microbiome, IBD is a far more complex disease with multifaceted interactions between the host and its environment. More studies are required to determine if there is a beneficial effect in this population and to assess for any possible detrimental outcomes.

If FMT proves to be effective in the management of IBD, which component makes it successful will remain an important question, including whether the most significant role is played by a single species, a community of bacteria, bacterial metabolites, or a nonbacterial component. There are recent data highlighting the role of viruses and fungi in IBD.[54,55] It is unknown if a particular patient population might benefit most from microbial manipulation, or if FMT might be better suited as an induction or maintenance agent. Likewise, the long-term consequences of microbial manipulation of the gut, if any, need to be studied.

There are multiple studies being conducted worldwide exploring the use of FMT in IBD, including both investigator-initiated and industry-driven trials. These trials should shed more light on the clinical utility of FMT and microbial manipulation in IBD. Guidelines that standardize the collection, preparation, dosing, and delivery of FMT are lacking and require further investigation in larger trials. Safety data are currently scarce and require systematic collection of outcomes moving forward.

FMT is a rapidly evolving therapy. Standard delivery via enema, colonoscopy, or nasoduodenal tube may soon be obsolete. A growing number of physicians, stool banks, and pharmaceutical companies have each designed microbiota-based pills that are currently in clinical trials for a number of different conditions, including IBD. Hopefully, these efforts will lead to the refinement of synthetic stool that may have a beneficial effect in IBD and other diseases. As the age of personalized medicine occurs, the future of FMT may involve microbiome profiling of patients with individualized microbial treatments as opposed to a one-microbiome-fits-all approach. However, while the future holds promise, there are not enough data at this time to support the routine use of FMT for IBD.

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