Optimizing Therapeutic Potential of Fecal Transplant in Inflammatory Bowel Disease

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KEYWORDS

• Fecal microbiota transplant • Gut microbiome • Gut microbial therapies
• Crohn's disease • Ulcerative colitis • Randomized controlled trial

KEY POINTS

- Fecal microbiota transplantation (FMT) currently does not have sufficient evidence to support its use in management of inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's and pouchitis.
- There is a marked lack in standardization around donor screening, stool processing and FMT delivery methods, limiting evidence to support changing practice guidelines.
- A comprehensive review of studies suggests that FMT has a beneficial role as adjunctive therapy for inducing remission in patients with UC.
- The alpha diversity of gut microbiota in individuals with IBD may impact their response to FMT.

INTRODUCTION/BACKGROUND

Inflammatory Bowel Disease and the Microbiome

Inflammatory bowel disease (IBD) encompasses a spectrum of chronic inflammatory conditions of the gastrointestinal tract, and includes 2 main subtypes: Crohn's disease and ulcerative colitis (UC). The pathophysiology of IBD involves a complex interplay of genetic, environmental, immune, and microbial factors[1] (**Fig. 1**). Dysbiosis, an imbalance in the gut microbiota composition, is thought to play a significant role in the development and progression of IBD.[2,3] Patients with IBD exhibit decreased bacterial diversity, with expansion of putative aggressive groups (such as Proteobacteria, Fusobacterium species, and *Ruminococcus gnavus*) combined with decreases in

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Abbreviations	
CDI	Clostridioides difficile infection
FMT	fecal microbiota transplantation
IBD	inflammatory bowel disease
PCDAI	Pediatric Crohn's disease activity index
RCT	randomized controlled trials
SAE	serious adverse events
UC	ulcerative colitis
VLP	viral like particles

protective groups (such as Lachnospiraceae, Bifidobacterium species, Roseburia, and Sutterella).[4] Dysbiosis can lead to alterations in the mucosal immune response, disruption of the intestinal barrier function, and dysregulation of inflammatory pathways, all of which contribute to chronic inflammation. Targeting dysbiosis with fecal microbiota transplantation (FMT) is a potential therapeutic strategy for managing IBD by restoring a healthier gut microbiota balance.[5]

There has been remarkable progress over the past decade in the therapeutic options that are available to help control disease activity, reduce inflammation, and improve quality of life for patients with IBD.[1,6,7] Biologic and small molecule agents have revolutionized the treatment landscape,[1,7] improving long-term outcomes for patients with UC and Crohn's. Due to the growing recognition of the role of the gut microbiome in IBD pathogenesis and the limitations of existing therapies, including incomplete response rates, medication risk profile, and side effects, there has been significant interest in evaluating FMT for the management of IBD, particularly as an

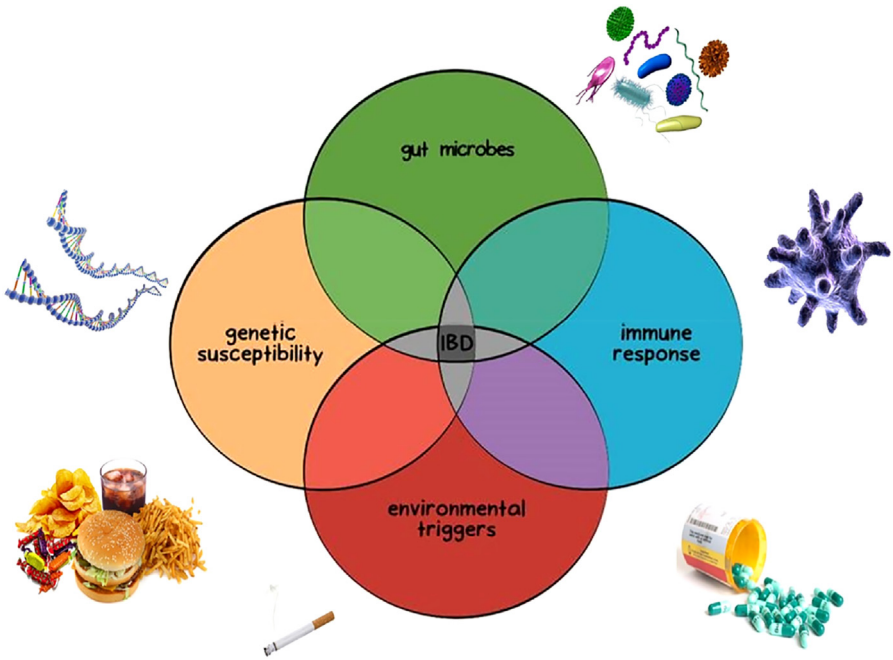

Fig. 1. Pathogenesis of IBD.[1] (*Modified from* Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Sartor RB.Nat Clin Pract Gastroenterol Hepatol. 2006;3(7):390-407.)

adjunct or alternative to current therapeutic modalities. The goal of this article is to delineate the efficacy, safety, and optimal application of FMT in the management of IBD.

Fecal Microbiota-Based Therapies

FMT is the transfer of fecal organisms from a healthy donor into the gastrointestinal tract of a recipient with the goal of restoring a diverse and balanced gut microbiota composition. Currently, oral capsule, bowel enemas, and colonoscopy are used to administer FMT, with the studies below using different forms of administration.[8] The donor, preparation of stool, volume and weight administered, number of administrations, route of delivery and control against which FMT is being compared vary widely across different studies.[9] This heterogeneity in studies to date is one of the challenges in evaluating the data in IBD.

Current Evidence for Fecal Microbiota Transplantation in Inflammatory Bowel Diseases

The most recent American Gastroenterology Association clinical practice guidelines on FMT-based therapies, published in 2024, only recommend FMT for prevention of recurrent *Clostridioides difficile* infection (CDI).[8] These guidelines specifically recommend against use of FMT in UC, Crohn's disease, and pouchitis except within the context of clinical trials. Many of the studies that guided the panel on their recommendations are discussed below, notably the Cochrane systematic review and published randomized controlled trials (RCTs).[9] Similarly, the European consensus guidelines from 2017 indicated that the only clinical indication with sufficient evidence of benefit from the implementation of FMT in clinical practice is CDI.[10]

To date, the most comprehensive analysis of the role of FMT in IBD is a Cochrane systematic review and meta-analyses of 12 RCTs and observational studies that evaluate the efficacy and safety of FMT in IBD.[9] All included FMT, based on a consensus definition using whole stool from the donor, for their intervention arm. The control groups included autologous FMT, placebo, standard of care medication or no intervention. The primary analysis was intention-to-treat with additional sensitivity analyses to assess for random and fixed-effects. Study heterogeneity and reporting biases were analyzed and the overall certainty of the pooled evidence was assessed using grading of recommendations assesssment, development and evaluation (GRADE) criteria.

Current evidence for fecal microbiota transplantation in ulcerative colitis

Fecal microbiota transplantation for induction of clinical remission in ulcerative colitis. The meta-analysis in the Cochrane review compared 10 studies on FMT versus control for *induction* of clinical remission. Key findings of select RCTs are detailed in **Fig. 2**. The primary analysis suggested that FMT led to increased rates of induction of clinical remission at the longest follow-up period with pooled results (risk ratio [RR] 1.79 with 95% confidence interval [CI] 1.13–2.84) based on low-quality evidence due to risk of bias. Sensitivity analysis to evaluate composite clinical outcomes based on endoscopic and histologic data rather than clinical score similarly showed 2-fold increased rates in the FMT arm for induction of remission (RR 2.13, 95% CI 1.51–3.02). Subgroup analysis on studies that evaluated induction of remission at 8 and 12 weeks were similar with possibility of no effect in the 12-week cohort (8 weeks: RR 1.68, 95% CI 0.93–3.05; 12 weeks: RR 1.54, 95% CI 0.89–2.66). Serious adverse events (SAE) were reported in 10 of the 11 UC studies. These included worsening UC requiring intravenous steroids or surgery, development of infection including

	Rossen 2015	Moayyedi 2015	Paramsothy 2017	Costello 2019	Brezina 2021	Haifer 2022
Subjects Enrolled (Donor / Control)	50 (23/25)	75 (38/37)	81 (41/40)	73 (38/35)	45 (23/22)	35 (15/20)
Duration (weeks)	12 weeks	6 weeks	8 weeks	8 weeks	12 weeks	8 weeks
FMT Delivery Route (number of doses)	Nasoduodenal (2)	Enema (6)	Colonoscopy (1) + Enema (39)	Colonoscopy (1) + Enema (2)	Enema (10)	Oral capsule Daily x 8 wks
Donor stool	Single	Single	Pooled (3-7 donors)	Pooled (3-7 donors)	Single	Single
Remission Induction (FMT vs control)	30% FMT 20% Placebo	24% FMT 5% Placebo	27% FMT 8 % Placebo	32% FMT 9% Placebo	52% FMT 36% control (mesalamine)	53% FMT 15% Placebo

Fig. 2. Select RCTs in UC.

pneumonia, and small bowel perforation. The evidence was of very-low certainty and the estimate included the possibility of no effect on adverse events (RR 1.77, 95% CI 0.88–3.55).

Brezina and colleagues conducted a multicenter, open-label RCT on the efficacy of FMT in adults under 70 years with clinically and endoscopically active left-sided UC over 3 months.[11] Eligible patients had a total Mayo score of 4 to 10 and an endoscopy subscore of at least 2 on stable doses of maintenance therapy. Exclusion criteria included recent use of biologic therapies, certain infections, and specific gastrointestinal conditions. The experimental group (n = 23) received FMT via enema from a single donor, administered 6 times over 6 weeks, while the control group (n = 22) received mesalamine (4 g) via enema for the same duration. The primary outcome was clinical remission at week 12, defined as a total Mayo score of $\leq$2 with no subscore greater than 1, with secondary outcomes including clinical response and endoscopic remission at weeks 6 and 12, along with adverse events. The authors used a modified intention to treat (ITT) analysis, focusing on treatment success relative to those who received treatment. At week 12, 57% of the FMT arm achieved the primary study endpoint compared to 36% in the 5-aminosalicylates (5-ASA) enema group, confirming noninferiority within a 10% margin. No significant differences were observed between groups for secondary outcomes, including clinical response and endoscopic remission at both weeks 6 and 12.

Similarly, a multicenter, double-blinded RCT in Australia assigned participants (Mayo score 4–10) to receive either multiple-donor feces via an intensive sequential enema regimen following an initial dose by colonoscopy (n = 41) or saline infusions (n = 40), with FMT demonstrating superiority to the control group in achieving steroid-free clinical (27% vs 8% of those receiving placebo) and endoscopic remission.[12] They also found distinct differences in ribosomal ribonucleic acid (rRNA) stool analysis of microbial changes between the 2 groups. Another prominent single-center, double-blinded RCT in Canada assigned a similar patient population to single-donor FMT via enemas (n = 38) versus placebo enema (n = 37) for 6 weeks with the primary outcome of Mayo score $\leq$2 and endoscopic Mayo 0 at week 7. The study was stopped early for futility, but all enrolled patients were able to continue (n = 70). The authors found that 24% of the FMT arms compared with 5% of placebo arm were in remission at week 7. Stool samples were also provided before and after intervention, with post-intervention stool analysis revealing significantly increased alpha diversity from baseline in the FMT patients. Of note, analysis revealed that treatment success in the

intervention cohort was donor dependent with 7/18 patients in remission receiving stool from the same donor. The family Lachnospiraceae and genera Ruminococcus were notably higher in this donor's stool. SAE were the same in both groups as were quality of life scores.[13]

Oral FMT delivery has been less extensively studied, with 3 RCTs included in the Cochrane review examining its role in inducing remission and none on maintenance. A subgroup analysis was performed looking at route of administration divided by upper gastrointestinal, lower gastrointestinal, and mixed (upper and lower) in the FMT versus control groups with no significant differences found (Chi^2 $P = .63$). One single-center, double-blind RCT administered FMT via colonoscopy and oral capsules with alternating 2-donor feces over the course of 12 weeks (n = 7) and compared this to the control group who received sham capsules and sham colonoscopy (n = 8). Participants, who were required to be on stable doses of IBD-directed therapies, excluding corticosteroids, for at least 6 weeks before screening, received up to 85 administrations of FMT. They found no significant differences in clinical outcomes or adverse events.[14] Another study conducted by Haifer and colleagues was a multicenter, double-blind RCT where they administered FMT using only oral capsules (n = 15) or sham capsules (n = 20) anywhere from 2 to 6 times daily at varying intervals over the course of 48 weeks. However, different from other studies, patients received antibiotic therapy before this. At week 8, (53%) of 15 patients in the FMT group were in corticosteroid-free clinical remission with endoscopic remission or response, as were 3 (15%) of 20 patients in the placebo group (difference 38·3%, 95% CI 8·6–68·0; $P = 0·027$; odds ratio 5·0, 95% CI 1·8–14·1). For the maintenance phase of the study, 10 subjects who had achieved remission were randomized to continuation of FMT versus withdrawal of therapy. At week 56, the 4 patients assigned to open-label FMT remained in remission compared to none of the 6 patients that did not continue therapy. SAEs were comparable in the initial treatment and control arms.[15] The last study using oral FMT delivery allocated 50 UC patients to receive either donor FMT (n = 23) or autologous FMT (n = 25) via nasoduodenal tube at the start of study and then 3 weeks later.[16] Donor FMT included feces from a mixture of related and unrelated donors. There was no significant difference in clinical remission in both ITT and per-protocol analyses at 12-week follow-up. However, microbiota composition was also evaluated with phylogenetic microarray showing higher amounts of Clostridium clusters IV and XIVa in the group receiving heterologous donor stool, which resembles that of healthy donors.

While the majority of studies focus on outpatients, one single-center, open-label RCT in China[17] recruited 20 adults hospitalized with active UC (Mayo score 4–12) and randomized them to receive either a single dose of multiple-donor FMT via colonoscopy versus control treatment with mesalamine and steroids. Feces from children were specifically used in this study. FMT significantly improved Mayo scores and gut microbiota composition, with 90% of FMT patients achieving the primary endpoint compared with 50% in the control group. No SAE were reported.

The role of concomitant dietary changes with FMT was evaluated in a multicenter, single-blind RCT conducted in both Israel and Italy.[18] Patients with active mild-to-moderate UC refractory to standard-of-care medication were randomized to either the experimental group or one of 2 control groups. The treatment arm was given FMT via colonoscopy on day 1, enemas on day 2 and 14, dietary preconditioning and a UC exclusion diet (UCED). Control arm 1 received the same FMT and enemas without dietary preconditioning and control arm 2 received only dietary treatment for 12 weeks. The control arm receiving only UCED had higher rates of clinical and endoscopic remission than either the experimental or control FMT groups.

Pai and colleagues performed a multicenter, single-blind RCT in Canada in 25 children between ages 4 to 17 with UC.[19] Patients received either multiple-donor FMT via enema (n = 13) or placebo via enema (n = 12) twice weekly for 6 weeks. Efficacy was measured by a composite clinical endpoint (improvement in fecal calprotectin, serum inflammatory markers, and clinical disease activity scores) without endoscopic examination at week 6. Taken together, 91.7% if children treated with FMT achieved the composite clinical outcome versus 50% of those treated with placebo. Specifically, FMT treated patients experienced C- reactive protein (CRP) response (66.7% vs 18,2%), fecal calprotectin (FC) change (−881.1 vs −390.4), and improvement in baseline pediatric ulcerative colitis activity index (PUCAI) score (58.3% vs 33.3%) compared to placebo at week 6. At 12 months 75% of FMT patients maintained clinical response, which suggests durability of FMT and that it may be beneficial when used as induction therapy.

Further subgroup analysis in the Cochrane review looked for differences in induction of clinical remission at longest follow-up stratified by type of donor (single vs multiple), age (pediatric vs adult), and frequency of FMT (single vs multiple infusions). There was no significant found in any of the subgroups.

Fecal microbiota transplantation for maintenance of clinical remission in ulcerative colitis. The Cochrane review compared only 2 studies on FMT for *maintenance* of remission to the control group. There was a large distribution across the data with very uncertain evidence to support the role of FMT in maintenance of remission (RR 2.67, 95% CI 0.26–34.42). A sensitivity analysis with fixed-effects and a per-protocol analysis showed a small increase in rates of maintenance of remission (RR 1.53, 95% CI 1.13–2.07, RR 1.66 95% CI 0.47–5.81 respectively). No SAEs were reported.

Among these studies was the multicenter, double-blind RCT by Costello and colleagues in Australia that allocated patients with a total Mayo score of 3 to 10 on stable maintenance therapy to receive FMT from multiple-donors (n = 38) or the control, autologous FMT (n = 35), both administered via colonoscopy and enema. Using an ITT analysis, 32% of the intervention group achieved the primary outcomes of steroid-free and clinical remission at week 8 versus 9% of the control group (OR 5.0, 95% CI 1.2–20.1, P =.03) At the 12-month follow-up, 42% of the intervention group maintained clinical remission versus 25% of the control group. There were 3 SAE in the treatment arm versus 2 in the control. Of note, at 9 months, 13 patients had worsening UC and 9 patients required colectomy but this was not categorized by study arm.[20]

Current evidence for fecal microbiota transplantation in Crohn's disease

There is a general paucity of data surrounding the role of FMT in patients with Crohn's disease. In the aforementioned Cochrane review, only 1 study of the 12 included in the review studied Crohn's disease. This was the first RCT looking at the role of FMT in maintenance of Crohn's disease.[21] There are no studies on the effect of FMT on induction of remission in Crohn's.

Sokol and colleagues performed a small randomized, single-blinded, sham-controlled pilot study of FMT for 17 adults with ileocolonic or colonic Crohn's disease (CD) on oral corticosteroids for active CD.[21] Once patients were in clinical remission, they were randomized to FMT (n = 9) or sham (n = 8) via colonoscopy followed by a second colonoscopy, to assess disease activity, at week 6. Longitudinal collection of fecal samples was performed up to week 24. None of the patients reached the primary endpoint of donor microbiota colonization at week 6. The steroid-free clinical remission rate at 10 and 24 weeks was 44.4% (4/9) and 33.3% (3/9) in the sham transplantation group and 87.5% (7/8) and 50.0% (4/8; one patient loss of follow-up while in

remission at week 12 and considered in flare at week 24) in the FMT group. Patients receiving FMT had a lower incidence of flares compared to the sham group, although this difference did not reach statistical significance. Furthermore, FMT was associated with a significant decrease in the CD endoscopic index of severity at 6 weeks post-FMT (8.5 [4.6; 13.0] vs 3.5 [1.0; 8.9]; P=.03) but not after sham (2.4 [0.0; 8.3] vs 2.7 [0.7; 10.0]; P=.8; (P = .03).

These findings could potentially be explained by the microbiota analysis, which demonstrated that successful FMT (treatment arm colonized with donor microbiota) was associated with a transient increase in alpha diversity and a shift toward the donor microbiota profile. Specific taxa linked to FMT success included an increase in the relative abundance of Ruminococcaceae, Coprococcus, and Desulfovibrio, while taxa associated with flare risk were primarily within the Gammaproteobacteria class and the Clostridiales order, including Ruminococcus gnavus.

Since publication of the Cochrane review, there has been a systematic review and meta-analysis looking specifically at efficacy and safety of FMT for induction of remission in a total of 228 adult and pediatric patients with active CD based on clinical score.[22] It included 11 noncomparative cohort studies and 1 nonplacebo controlled RCT, published between 2015 and 2021. The primary endpoint was rate of clinical remission defined as Harvey–Bradshaw index less than 5, Crohn's disease activity index less than 150, pediatric Crohn's disease activity index (PCDAI) less than 10, or IBD questionnaire (IBDQ) greater than 170. Secondary outcomes included clinical response, endoscopic remission, and endoscopic response.

Results were divided by clinical endpoints in adult and pediatric populations. Among 6 studies in the adult population, a pooled proportion of 57% of patients who received FMT achieved clinical remission. A pooled proportion of 5 studies showed a 72% clinical response rate to FMT. There was no endoscopic remission at 8 weeks in the 2 studies that evaluated this. In the pediatric population, 64.7% of patients who received FMT (of note, only 17 patients total) achieved clinical remission based on PCDAI score after 2 to 4 weeks. Two cohort studies evaluating clinical response, which included only 8 patients, yielded a pooled proportion of 79%. There were no studies on endoscopic remission. All these outcome measures across the adult and pediatric had a low risk of heterogeneity among the pooled data.

There were adverse events reported during and after FMT in most of the studies. The pooled proportion of major adverse events was 19%, but these were primarily gastrointestinal complaints that were self-limiting. The pooled proportion of SAE was 3%, totaling 5 patients, which the authors felt were not associated with FMT.

While quality of life is an important consideration in evaluating IBD treatment, there are currently no studies on the role of FMT on IBDQ for induction or maintenance of remission in CD.

Current evidence for fecal microbiota transplantation in pouchitis

There is limited evidence on FMT for pouchitis. A systematic review by Kayal and colleagues looked at one RCT, 2 cohort studies and one prospective trial. They reported that while FMT was found to have a generally favorable safety profile, there were variable clinical response and remission rates and thus overall limited effectiveness of FMT. Due to differences in study characteristics, the authors emphasized the need for additional research to better understand the role of FMT in treating pouchitis.[23]

SUMMARY OF CURRENT CLINICAL EVIDENCE

FMT may be effective in inducing clinical remission and improving endoscopic outcomes in patients with mild-to-moderate UC. However, the heterogeneity among

study characteristics and small-scale, single-center studies has limited the generalizability of findings and adoption of FMT into treatment algorithms for IBD. Furthermore, the risk of SAE remains uncertain, and the long-term effects on remission and quality of life need further investigation. There are no significant differences in the induction of clinical remission for patients with UC by method of administration, donor type, age, or FMT frequency.

Evidence for FMT in CD is limited. While 1 study showed potential benefits in reducing disease flares and improving endoscopic outcomes, more research is necessary to confirm these findings. Studies on FMT for pouchitis are limited, with variable clinical response rates and overall limited effectiveness reported. Importantly, there is limited evidence on FMT's impact on quality of life in both CD and UC, with inconclusive results from existing studies.

The alpha diversity of gut microbiota in individuals with IBD after FMT with successful donor colonization and evidence of clinical remission resembled the microbial composition of healthy patients in both UC and CD, albeit with limited sample sizes and statistical significance. However, these data support that both host immunologic and microbiome factors may affect IBD patients' response to FMT or other disease-related therapies. At this time, FMT is not recommended for IBD in any clinical practice guidelines; however, the data to support FMT in UC are compelling. In order for FMT to become standard therapy in UC, future trials must explore which patients may benefit, positioning with regards to other therapies, necessary donor microbiota characteristics, and appropriate dosing for both induction and maintenance. Finally, a reliable source of donor material acceptable to regulatory agencies is critical for FMT to become part of our treatment armamentarium.

MECHANISMS OF FECAL MICROBIOTA TRANSPLANTATION IN INFLAMMATORY BOWEL DISEASE

Though data from clinical trials clearly demonstrate efficacy for the use of FMT in the treatment of some patients with mild-to-moderate UC, this effectiveness is limited to a subset of patients leading researchers to work toward identifying which aspects of FMT are responsible for inducing remission.

Some early studies using FMT for the treatment of IBD have advanced the idea that individual compositions of some microbiomes may account for therapeutic efficacy FMT. In an early study by Moayyedi and colleagues,[13] patients with active UC were randomized to receive 50 mL enemas from healthy donors or placebo once weekly for 6 weeks. 9 of 38 patients receiving FMT were in remission at 7 weeks, whereas only 2/37 who received placebo were in remission. Intriguingly, 7 of the 9 patients achieving remission received material from the same donor, suggesting a possible *Super Donor effect*. This outcome supported the idea that individual specific factors may be responsible for the efficacy of FMT in IBD.

FECAL GENOMIC AND METABOLIC CHARACTERIZATION

One approach to identifying specific mechanistic factors is to understand the microbial and metabolic state of successful FMT recipients versus those who do not achieve remission. To this end, Paramsothy and colleagues performed a double-blinded trial in which the treatment group received endoscopic infusion of FMT followed by 5 enemas per week for 8 weeks.[24]

In broad terms, they found that FMT increased microbial diversity, and that diversity was greater in fecal and colon samples collected when FMT treatment achieved remission; though they do note that those achieving remission often had higher

richness at baseline. Increased presence of *Eubacterium hallii* and *Roseburia inulinivorans*, were the strongest predictors of achieving the primary outcome; however, this did not reach statistical significance. The authors note that *E hallii* has previously been reported to be a beneficial microorganism in gastrointestinal (GI) tract, able to produce large quantities of the short chain fatty acids butyrate and propionate.[25] They further used a combination of sequencing and mass spectrometric analysis to identify metabolic pathways and specific metabolites correlating with a positive response to FMT. This analysis showed increased short chain fatty acid (SCFA) metabolism, secondary bile acid synthesis and biosynthesis of ansamycins among others correlating with a positive response. Many of these pathways have been posited to play beneficial rolls in gut homeostasis including the beneficial roles of secondary bile acids and ansamycin synthesis; the latter being microbial generated metabolites, which can act as antimicrobials against gram-positive bacteria as well as bacteriophages. The same data set demonstrated that increased presence of several bacteria was associated with a negative outcome including *Fusobacterium gondiaformans, Suterall wadsorthensis, Haemophilius,* and Escherichia species; several of which have been previously described as possible instigators in IBD.[25,26] Several biochemical pathways associated with a negative response were identified including heme, lipopolysaccharide, and peptidoglycan biosynthesis. Metabolomics confirmed that heme was a strong negative predictor of positive response to FMT. The use of multi-donor batches of feces limited the ability to identify any *super donor* traits. There was an association with effective donor batches containing Bacteroides species, where Streptococcus containing donor samples were associated with lack of remission. Overall, this deep dive using sequencing and metabolomics helps to further confirm many previous findings and shed light on new and interesting associations linking positive or negative FMT response with specific bacteria and metabolites.

IMMUNOGLOBULIN A COATED BACTERIA HELP IDENTIFY IMPORTANT PLAYERS IN FECAL MICROBIOTA TRANSPLANTATION

The mucosal immune system is a complex network of both innate and immune regulatory networks. A primary mediator of host defense is immunoglobulin A (IgA). This unique immunoglobulin exists as a homodimer, which is secreted into the gut lumen and binds both commensal and pathogenic bacteria.[27] Previous groups have shown that in IBD patients, those bacteria which are more highly coated with IgA represent more *colitogenic* bacteria.[28] The technique used to isolate and identify these IgA coated bacteria from feces is termed *IgA-Seq*.

Given the previous findings that IgA-seq can be used by to identify bacteria which are heavily immunoglobulin bound and likely important to the immune system, Lima and colleagues[29] looked at the IgA coated portion of the microbiome in responders and nonresponders from a previously successful FMT trial.[30] Of 29 IgA coated species identified to be differentially abundant post FMT, only the relative abundance of *Odoribacter splanchinicus* at 4 weeks post FMT and its increase post FMT were found to significantly correlate with decreased Mayo score. They go on to show that colonization of germ-free mice with Odoribacter, but not other patient derived bacterial species, almost completely abrogated body weight loss in a DSS colitis model and further increased the abundance of CD4 + Tregs (RORγT/Foxp3+). Finally, rectal biopsies from FMT recipients showed increased regulatory T cells correlating with the abundance of Odoribacter. Overall, they show a transferable microbiota component associated with clinical remission post FMT. Further, their work demonstrates

mechanism in this strains capacity to expand regulatory T cell activity within the mucosal microenvironment.

SERUM PROFILING OF ULCERATIVE COLITIS PATIENTS

Whereas most groups have focused on the specific components of the feces itself to identify responsible factors for the efficacy of FMT in treating UC, others have focused on patient serum to identify key immune signaling pathways or circulating metabolites to better understand the mechanisms behind responsive individuals.

In one study, Zhang and colleagues treated 19 UC patients with moderate to severe UC with FMT via gastroscope delivered to the small bowel.[31] Serum was collected on the day before FMT delivery and then again 3 days post FMT, and patients were followed for response to FMT for a minimum of 3 months. In this study, 11 of 19 patients achieved clinical response, whereas only 2 of 19 achieved clinical remission. Their data showed that serum interleukin (IL)-6 and tumor necrosis factor receptor (TNFR) 2 were significantly higher in UC patients as compared to healthy controls, whereas IL-2 and IL-4 were significantly decreased. However, of 11 cytokines measured, none showed significant difference between pre-FMT and post-FMT treatment regardless of whether the patient benefited from the FMT.

In another study looking to identify biomarkers of successful FMT, 44 total patients with active UC (Mayo >3) and poor response to conventional therapy or acute UC underwent FMT.[32] FMT was delivered via gastroscope or nasojejunal (NJ) tube in a total of 44 patients with a step-up protocol in place for lack of initial response. In this study, 29.5% of patients achieved clinical remission from the FMT. Venous blood samples were collected 7 days post FMT and subjected to untargeted metabolomic analysis by liquid chromatography mass spectrometry (LC-MS). The top 2 most significantly altered pathways in the responding group were vitamin B6 metabolism and tRNA biosynthesis. The authors did note that most metabolites experienced the same trend after FMT, regardless of remission or response achievement.

In the response groups, cholic acid, Nabilone, L ascorbic acid 2 sulfate, arachidonic acid, and cascardilin significantly increased post FMT, while some proinflammatory metabolites like spiroxamine, butralin, and carbofuran showed a significant decrease. They also showed that in the nonresponding group, many toxic metabolites post FMT were increased over baseline.

Vitamin B6 is associated with scavenging reactive oxygen species (ROS) and inversely correlates with inflammatory markers. As IBD patients commonly have B6 deficiency, the authors speculate these findings may represent mobilization of B6 to sites of inflammation or serve as a cofactor in immune cell functions. Vitamin B6 is further an essential cofactor in amino acid synthesis and therefore the finding of elevated levels of amino acid transfer ribonucleic acid (tRNA) biosynthesis metabolites is in good concordance with this result. The authors suggest these elevations likely contribute to improvement in restoring normal immune signaling pathways.

BENCH RESEARCH

Basic scientific efforts using mice as a model organism for studying FMT and gut homeostasis provide unique opportunities, not available when studying humans, including the capacity to perform large sample numbers on nearly genetically identical individuals with the capacity to perform advanced tissue sampling and necropsy. Furthermore, they allow for unique treatment paradigms that would be unreasonable or unethical in human clinical trials.

To understand the efficacy of FMT in rodent models and any parallel relevant biologic mechanisms, Burerello and colleagues treated mice with DSS to induce acute colitis, and then subsequently treated with 3 doses of FMT from normobiotic mice.[33] They found that FMT ameliorated weight loss and histopathologic evidence of inflammation on colonic H + E as well as reduced expression of IL1-beta in the colonic mucosa. They go on to show that FMT reduced the number of TNF producing intestinal dendritic cells and macrophages while increasing the frequency of IL-10 producing dendritic cells and monocytes. Given the evidence of FMT efficacy in this model as well as relatively increased abundance of IL-10 producing cells, they looked to test whether IL-10 played a functional roll in this process. They repeated their initial experiment while treating one group with an IL-10 receptor blocking antibody. IL-10 receptor blockade inhibited the previously beneficial effects of FMT on body weight loss and colon length. Overall, this data highlights the use of DSS colitis models utility in paralleling acute colitis in human disease, and further shows functional capacity of FMT to improve colitis in an IL-10 dependent manner.

Other groups have further validated the roll of mouse modeling for the study of FMT in acute colitis. In a recent paper, Li and colleagues demonstrate that FMT from healthy control can protect mice from DSS colitis, and that several common inflammatory pathways seen in humans are paralleled in this model.[34] They found improved body weight loss and histopathologic scoring in those mice treated with FMT and further saw mice treated with FMT had reduced serum levels of signal transducer and activator of transcription (Stat) 3, nuclear factor kappa B (NFκB), and IL-6. Finally, they show that DSS colitis treatment reduces the alpha diversity of the intestinal microbiome, and FMT can restore this effect, a finding modeling human studies. Works such as these highlight the usefulness of mice as a model organism for understanding FMT, and demonstrate disease pathology mirroring humans.

COLONIZING MICE WITH HUMAN FECES

To better understand the role of the IBD microbiome and its response to FMT, Britton and colleagues began by colonizing germ-free mice with defined cultured microbiotas from 3 patients with IBD.[35] Three weeks later, the mice received 1 of 5 defined cultured healthy donor FMT and were subsequently individually housed. They then performed metagenomic sequencing of stool samples from premicrobial and postmicrobial transplant as well as healthy donor treated mice, showing that 58% of the strains from the IBD donors remained detectable following transplant into mice. Next, they focused on which fecal transplants resulted in the greatest shifts in T helper 17 (Th17) cells, a cell population previously shown to be associated with increased susceptibility to IBD.[36] The first of 3 IBD donors, IBD-A, was able to induce the greatest TH17 response in the recipient mucosal surface, and further treatment with healthy donor fecal transplant significantly reduced the Th17 response observed.

They then created 16 subcommunities of bacteria from donor IBD-A and used these to colonize germ-free mice looking to identify specific strains responsible for the induction of Th17 cells in the mucosa. By assessing for induction of IL17 A + Th17 cells they showed *Escherichia coli* A6, a variant of *E coli* 0157H7 strongly induced Th17 cells.[37] They repeated this initial experiment on germ-free mice using the IBD-A donor stool sample with *E coli* A6 removed. This result showed that *E coli* A6 was the key component of this stool sample able to induce Th17 cells. Finally, they showed that mice receiving FMT from IBD patients showed minimal induction of tolerogenic RORyt Tregs. However, with subsequent FMT from healthy donors, the presence of these important cells increased in all settings tested. No super donor

effect was found, as mice colonized with all IBD donor microbiotas were all responsive to healthy donor transplantation.

These data nicely show that specific strains of pathogenic bacteria can modulate the mucosal immune microenvironment. Further, FMT from healthy donors was able to increase the presence of tolerogenic RORyt Tregs, shaping a more quiescent gut mucosal landscape.

VIROME IN FECAL MICROBIOTA TRANSPLANTATION

Given the close interplay between bacteria and gut homeostasis and relative ease of identifying bacterial profiles, efforts to evaluate the mechanism of FMT in IBD has been mostly focused on bacterial components. However, bacteriophages play an important role in gut homeostasis and have been demonstrated to be different between healthy controls and IBD patients.[38]

Sinha and colleagues explored the roll of bacteriophages in FMT.[39] They began by colonizing germ-free mice with healthy donor or UC-patient pooled bacterial communities. Mice were then given viral like particles (VLPs) isolated from healthy controls and UC patients with active disease and treated with DSS to induce colitis. Similar to results seen in other studies, mice receiving FMT from UC patients showed enhanced sensitivity to colitis induction, but they furthermore demonstrated worsening colitis phenotype in the UC-FMT transplanted mice receiving VLPs from UC patients. Finally, they demonstrated that when the VLPs are heat treated before administration their effect is lost, suggesting these VLPs are biologically active and their intact structure is required for the obtained result. Overall, these data nicely demonstrate that bacteriophages may play a role in the utility and capacity of FMT to induce remission in UC patients.

Another study by Gogokhia and colleagues[40] isolated bacteriophages targeting adherent invasive E coli from an individual with IBD. Three separate phages were propagated and purified; all belonged to the order Caudovirales, which were previously demonstrated to be elevated in IBD patients.[38] Germ-free mice treated with bacteriophage preparations elicited an immune response to the bacteriophages, despite lacking intestinal bacteria, as evidenced by expansion of immune cells within the Peyer's patches, including interferon gamm (IFNγ)-producing cluster of differentiation 4 (CD4) T cells among others. They went on to show that pretreatment of specific pathogen free mice with bacteriophages which had tested negative for *E coli*, worsened colitis severity during DSS challenge, suggesting a direct host interaction not related to the phages infectious capacity toward *E coli*. They next examined differences in bacteriophage communities in patients with UC treated with FMT and compared responders to nonresponders. Patients with a clinical response to FMT had a lower relative abundance of Caudovirales bacteriophages at the time of transplant as compared to nonresponders. Furthermore, Caudovirales relative abundance increased in nonresponders but did not change in responders post FMT. Finally, they showed that IFNγ-production from rectal mucosal biopsies showed positive correlation with the relative abundance of Caudiovirales specifically. Overall, these data elegantly delineate that specific types of bacteriophages can have a direct impact on mammalian host gut immune landscape and that these viruses may play a role in the response to FMT.

ANTIBIOTIC EFFECTS

Several studies have used antibiotic pretreatment of patients receiving FMT with the hope of improving engraftment of the donor microbiome.[41] In a unique study, Strati

and colleagues aimed to determine what effects antibiotic treatment of the donor would have on the capacity of FMT to treat experimental colitis.[42] Colitis was induced with DSS, and mice were subsequently given donor stool from normobiotic mice treated with metronidazole, vancomycin, streptomycin or untreated control. Their data showed that those mice receiving microbiota conditioned with streptomycin or vancomycin were characterized by blooming Bacteroides, Parabacteroides, and Streptococcus, which have been previously associated with poor outcomes in human FMT IBD studies as well as reduction in health promoting Bifidobacterium and Akkermansia.[43,44] They further showed that exposure of lamina propria mononuclear cells from UC patients exposed to vancomycin or streptomycin-conditioned gut microenvironments (fecal water) enriched microbial derived metabolites driving a proinflammatory TH1/Th17 phenotype with excessive production of proinflammatory mediators like TNF alpha. Finally, they show that exposure of human invarient natural killter T (iNKT) cells to metronidazole-conditioned fecal water, promoted secretion of IL10, supporting previous assertions that metronidazole may shape the gut microenvironment in a more tolerable fashion to reduce colitis severity. Overall, their data show that antibiotics can shape the microbial landscape and may facilitate engraftment of donor microbiota, allowing recipients to achieve remission with FMT.

UNDERSTANDING HOST GENE INTERACTIONS IN FECAL MICROBIOTA TRANSPLANTATION

Although a great deal of attention has been given to transferable factors such as bacteria and bacteriophages, understanding the host response to the FMT poses a unique way to identify important pathways and potential sites for therapeutic intervention. Various bench and translational studies related to these host factors have been conducted to determine host factors that may explain some of the variability of response to FMT in IBD.

Guanylate binding protein 5 (GBP5) is a protein capable of sensing and lysing bacteria and has previously been shown to be upregulated in patients with UC. In a study of genetic pathways in biopsy samples from a subset of patients from a previous FMT clinical trial,[45] Luu and colleagues[46] found that 78 genes were regulated by FMT and delineated responders from nonresponders; of these, only GBP5 showed no sign of regulation in nonresponders, and its expression was linearly correlated with Sutterella OTU29—an important finding as levels of *Sutterella wadsworthensis* were associated with lack of FMT efficacy in this cohort. Furthermore, this group showed GBP5 knockout mice are resistant to DSS colitis. Other host factors which have been shown to modulate or regulate the gut microbiome, play a role in attenuating colitis severity, or whose effects result in transferable changes in the gut microbiome include claudin 3,[47] IL-2,[48] the potent neutrophil chemokine, chemokine ligand 1 (CXCL1),[49] and ESRRA-estrogen related receptor alpha, an orphan nuclear receptor with critical function in mitochondrial biology and autophagy.[50]

CHALLENGES AND FUTURE DIRECTIONS

While FMT shows promise as an adjunctive therapy for IBD, particularly UC, challenges such as standardization of donor screening, optimization of delivery methods, long-term safety monitoring, and the need for personalized approaches remain areas of active investigation in the field (**Fig. 3**). (see R. Balfour Sartor's "Beyond random fecal microbial transplants: Next generation personalized approaches to normalize dysbiotic microbiota for treating IBD," in this issue). Across the current literature, there is marked heterogeneity in

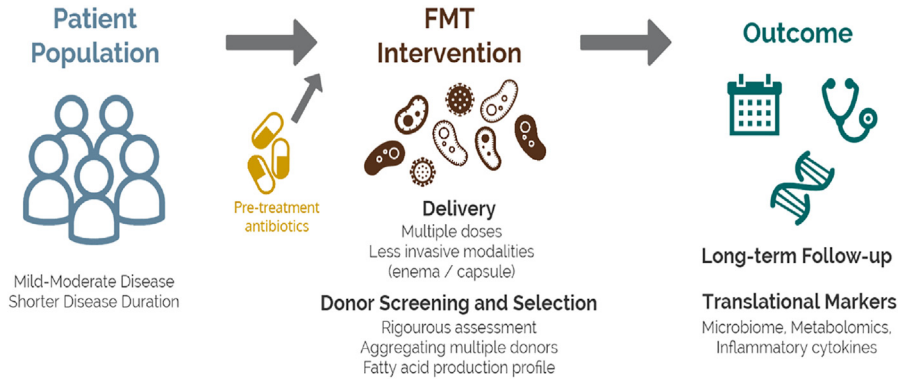

Fig. 3. Unanswered questions.

- Donor microbiota source, including related versus unrelated and adult versus pediatric
- Dosing: weight and volume of stool and number of organisms transferred
- Colon preparation before FMT
- Antibiotic pretreatment
- Stool processing and storage methods
- Method of administration: including oral, enteral feeding, enema, and colonoscopy
- Number of administrations: range from single to up to 85 FMT doses

Given these unanswered questions and that there is no FDA approved fecal microbiota preparation for the indication of IBD, current practice guidelines do not recommend FMT in management of IBD outside of a clinical trial setting. Though generally safe, in a minority of IBD recipients FMT can lead to infection, worsening IBD, and need for surgical intervention.[51]

Treatment with FMT from healthy donors has demonstrated beneficial alteration in the fecal microbial milieu of recipients, with specific taxa linked to clinical remission in IBD. However, the relationship between microbiota changes and clinical outcomes remains complex with a wide range in findings across studies and generally small sample sizes. Salient themes from review of the literature highlight the need for standardization in FMT therapy, larger patient cohorts, and multicenter collaborations to delineate both donor and host factors and the role of gut microbiota in IBD patients to advance our understanding of the underlying mechanisms of successful FMT. These continued and refined research efforts are essential to elucidate the intricate interactions between the gut microbiota in IBD, paving the way for the development of novel therapeutic strategies to realize the potential of FMT.

CLINICS CARE POINTS

- Inbalance in gut bacteria, or dysbiosis, contributes to the development of IBD and may be a therapeutic target.
- There is increasing evidence that FMT may be beneficial in some patients with UC.
- Given unanswered questions around the optimum donor, delivery, and dose and a need for more efficacy and safety data, FMT is not yet recommended for routine clinical use.

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