Fecal Microbiota Transplantation: From *Clostridium difficile* to Inflammatory Bowel Disease

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Keywords
Fecal transplant, *Clostridium difficile*, inflammatory bowel disease

Abstract: Fecal microbiota transplantation (FMT) has evolved from a case report in the medical literature to the basis of major innovations in the treatment of *Clostridium difficile* infection (CDI) and, potentially, inflammatory bowel disease (IBD). In the clinical setting, FMT was noted to significantly lower the risk of recurrent CDI, likely by increasing microbial diversity and altering the metabolic environment in the intestinal tract of recipients. In parallel, advances in the ability to quantify and characterize microbial communities in fecal samples led to the association of IBD with a state of intestinal dysbiosis. Consequently, a number of case series and randomized, controlled trials have evaluated FMT in treating active ulcerative colitis or Crohn's disease. Unlike in CDI, the efficacy of FMT in the treatment of IBD appears to be influenced by a number of factors, including donor microbial profiles, inflammatory burden, and the microbial diversity of the recipient. The therapeutic potential of the microbiome has led to a number of biotechnology and pharmaceutical companies isolating specific strains from healthy stool for use as targeted therapies for IBD in clinical trials. Ongoing studies are likely to determine the missing link between the efficacy of FMT and its impact on microbial communities and mucosal inflammation.

Fecal microbiota transplantation (FMT) currently describes the transfer of fecal material from a healthy donor to a patient for the purpose of increasing intestinal microbial diversity and reestablishing a normal microbiome. The first reported use of FMT in modern medical literature was in 1958 to treat a case of pseudomembranous colitis.[1] This unusual therapy remained a medical curiosity until the 2000s, when the emergence of epidemic strains of *Clostridium difficile*, and major advances in microbial sequencing, resurrected FMT as a novel approach to treat recurrent *C difficile* infection (CDI).[2] In this setting, FMT is a safe, efficacious, and cost-effective alternative to continuous or recurrent courses of antibiotics.[2] At a mechanistic level, the introduction of donor fecal material increases the diversity of the microbiome and alters the metabolic

pathways active in the intestinal flora.[3] Although FMT was initially used to treat recurrent or refractory CDI, it has recently been evaluated in case series and randomized, controlled trials in patients with active inflammatory bowel disease (IBD) without CDI.[4-7]

Impact of *Clostridium difficile* Infection on Patients With Inflammatory Bowel Disease

CDI is a significant complicating factor in patients with IBD who undergo clinical relapse; between 5% and 20% of patients with flare-ups are noted to be positive for the CDI toxin or gene.[8] Risk factors for CDI in hospitalized IBD patients include a diagnosis of ulcerative colitis, recent antibiotic use, proton pump inhibitor use, and low albumin levels (<3 g/dL).[9] In addition, patients taking immunomodulators have a higher rate of CDI than those not taking immunomodulators (74% vs 56%; *P*=.02), although a study in patients with ileal pouches did not confirm this association.[10]

Patients with IBD and CDI appear to fare worse than their non-IBD counterparts.[11-13] In IBD patients hospitalized for infection-related complications, CDI was found to be associated with excess inpatient mortality (odds ratio, 3.2; 95% CI, 2.6-4.0).[13] Odds of colectomy in IBD patients with CDI, particularly those with ulcerative colitis and CDI compared with ulcerative colitis or Crohn's disease alone, increased significantly between the years 1998 and 2007.[11] Similar to non-IBD patients, those with IBD have a high risk of recurrent CDI; nearly 60% of patients with IBD and CDI have recurrent CDI after initial therapy, which is higher than the typical recurrence risk of 15% to 30% in non-IBD patients.[9] A single-center pediatric cohort reported the rate of CDI recurrence in patients with IBD to be 34% vs 8% in non-IBD controls. More than 75% of patients had Crohn's disease, with a greater proportion of CDI patients having colonic involvement (95% vs 67%), as is often seen in pediatric populations.[14]

Thus, there are many reasons to recommend routine screening for CDI in patients with IBD relapse and to initiate an appropriate antibiotic therapy early. The American College of Gastroenterology (ACG) guidelines suggest a test-and-treat strategy for all hospitalized patients with IBD in a flare.[15] Metronidazole therapy is usually sufficient for non-IBD patients with mild to moderate CDI, but the relatively high rates of treatment failure (22%) and early recurrence (28%) limit its value in patients with active IBD.[16] Most patients with IBD have sufficient clinical features to be categorized as moderate to severe CDI, warranting vancomycin therapy for initial infection and prolonged vancomycin pulsed-taper or fidaxomicin (Dificid, Merck) for recurrent infections.[17,18] A conditional recommendation in the ACG practice guidelines supports the ongoing use of immunosuppression in CDI but suggests holding dose escalation or addition of anti–tumor necrosis factor therapy until treatment for CDI has been ongoing for up to 72 hours, although this recommendation was not based on high-quality evidence.[15]

Efficacy of Fecal Microbiota Transplantation in Patients With *Clostridium difficile* Infection

Given the high rates of CDI recurrence, FMT fills an important role in the treatment algorithm of CDI. The rationale for FMT in this setting is based upon both the microbial disruption noted after antibiotic exposure and colonization by toxin-producing *C difficile*.[19] FMT is assumed to initially enhance microbial diversity and diminish the ecologic niche that *C difficile* occupies in patients with CDI. The first published randomized trial of FMT (via nasoduodenal infusion) demonstrated significantly higher rates of resolution of CDI-related diarrhea (81% vs 31%; *P*=.008) and a significant increase in microbial diversity after FMT.[20] A more recent randomized, controlled trial in the United States reported similar rates of resolution of recurrent CDI in patients with recent infection.[21] A case series has repeated these results, with primary and secondary cure rates of 80% to 90% and with no serious adverse events in the short term.[22] It appears that the mode of administration of FMT has little impact on its overall efficacy; oral FMT capsules, FMT enemas, and FMT duodenal infusions all produce success rates in the 70% to 90% range.[23] It should be noted that the endpoint was usually improvement in diarrhea, which is less rigorous of an endpoint than testing negative for *C difficile* by polymerase chain reaction and resolution of diarrhea.

Although none of the randomized, controlled trials were aimed at patients with IBD, a number of groups has published results on CDI, which include some patients with IBD (Table). The largest cohort, by Kelly and colleagues, described outcomes in 36 patients with IBD, including patients on corticosteroids, immunomodulators, anti–tumor necrosis factor therapy, and anti-integrins.[24] The overall cure rate in IBD patients was 94%, with an 86% cure rate after a single FMT. The overall rate of adverse events was 15%, and 4 IBD patients were hospitalized for flare-up early after the FMT. A similar high rate of cure (90%) was reported in a cohort of 10 pediatric patients who received FMT via nasointestinal tube for recurrent CDI.[25] Khoruts and colleagues recently reported that a single colonoscopic FMT cleared CDI from 74% of patients with IBD and 92% of patients without IBD (*P*=.0018).[26] Patients had similar responses to FMT regardless of

Table. Efficacy of Fecal Microbiota Transplantation in *Clostridium difficile* Infection With and Without IBD

Study	Population	Clinical Success	Number With IBD
Agrawal et al[22]	146 patients >65 years	96%	5 (response unknown)
Kronman et al[25]	10 pediatric patients	90%	3 (100% response)
Kelly et al[24]	80 immuno-compromised patients	89%	36 (94% response)
Kelly et al[21]	26 patients	92%	2 (100% response)

IBD, inflammatory bowel disease.

immunosuppression therapy, although 26% of patients with IBD had a clinically significant flare of IBD after FMT.

Potential for Fecal Microbiota Transplantation as a Primary Therapy in Inflammatory Bowel Disease

Given the overlap of dysbiosis between CDI and IBD, recent research has examined whether the composition of microbial communities could be adjusted with therapeutic intent in patients with IBD.

Evidence of a Role for the Microbiome in Inflammatory Bowel Disease Pathogenesis

It is understood from most animal models of IBD that the presence of intestinal bacteria is required for inflammation to occur, regardless of which innate or adaptive defects exist in the host immune system.[27] Not only are commensal bacteria crucial to the development of IBD, but changes in the ecology of the colon may result in what has been termed a colitogenic flora, which might adversely influence the host immune system.[28,29] While no specific pathogens have been identified to cause human IBD, clear associations with the intestinal microbiome have been noted.[30,31] Reduced diversity of bacterial phyla, including Firmicutes and Bacteroidetes, has been noted in these studies, although it is unclear if this is a cause or effect of IBD. Beyond alterations in the composition of the microbiome, the function of the microbiome is notably different, with changes in oxidative stress pathways and carbohydrate metabolism.[28] Thus, the disease process in IBD may be responsive to alterations in microbial diversity if the alterations are introduced at the right time. Oral administration of probiotics has been proven to be therapeutic in controlled trials in patients with ulcerative colitis, and antibiotics prevent recurrence of inflammation at previously affected sites in Crohn's disease.[32,33] Cumulatively, these data suggest that bacteria may play a role in the initiation and propagation of IBD, and therapeutic manipulation of the host microbiome may reduce or prevent the intestinal inflammation characteristic of this condition.

Efficacy of Fecal Microbiota Transplantation in Human Trials in Inflammatory Bowel Disease

Initial data to support a role for FMT in treating IBD came from small case series, often in patients with refractory disease. The first series was in children and reported a transient improvement in colitis symptoms after FMT enema.[34] Later reports of the use of FMT in adults with active ulcerative colitis yielded mostly no or minimal effects in treating active disease.[35,36] Subsequently, 2 randomized, controlled trials of FMT in patients with active ulcerative colitis were published in 2015.[4,5] Rossen and colleagues studied 50 patients in a double-blinded, randomized trial of FMT via nasoduodenal tube.[5] There was no significant difference in the probability of clinical remission between patients who received donor stool or autologous stool (30% vs 20%; P=.5). The FMT did significantly increase bacterial diversity at week 12 in responders of both groups when compared to non-responders, with a shift toward the donor's profile. In the second trial, Moayyedi and colleagues compared the efficacy of 6 weekly fecal enemas to placebo enemas in a group of 75 patients with moderately active ulcerative colitis.[4] A significantly greater proportion of patients who underwent FMT than who received placebo were in remission 7 weeks after the FMT therapy (24% vs 5%). Interestingly, the clinical responders to FMT in this trial were more likely to have received stool from a specific donor (donor B) than from other donors (39% vs 10%; P=.06), suggesting a donor effect that has not been noted as a factor in treating recurrent CDI.

The reported results in Crohn's disease have also been mixed. Vermeire and colleagues noted that none of their refractory patients with Crohn's disease (n=6) had a significant improvement within 8 weeks of FMT.[37] In contrast, an open-label study in patients with moderately active Crohn's disease reported a 58% (11/19) clinical response rate following FMT, with a significant expansion in microbial diversity and improvement in quality-of-life scores.[6] Of note, there was no shift in endoscopy scores or C-reactive protein levels between baseline and week 12 in this small study. Although the results have been heterogeneous, a number of groups are currently exploring the potential anti-inflammatory effects of select bacterial strains in models of colitis as a precursor to clinical trials in IBD.[38]

Regulatory Status of Fecal Microbiota Transplantation in Patients With Inflammatory Bowel Disease

The growing popularity of FMT in the last 5 years has gained the attention of both practitioners and the US Food and Drug Administration (FDA) alike. Fecal matter, if used to alter the physiology of a recipient, meets the federal definition of a drug and, thus, falls under the FDA's regulatory remit. The FDA initially required submission of an Investigational New Drug (IND) application by each provider of FMT, which is typical when developing a new experimental therapy. After much concern from professional gastrointestinal societies, the FDA issued a draft guidance document in 2014 stating that it would exercise enforcement discretion on INDs when FMT is used to treat CDI if certain criteria were met. Criteria included physician consent of the patient for FMT, physician or patient personal knowledge of the donor, and physician screening of the donors.[39] This stipulation would prevent the use of stool banks without an IND application, which is currently the most common mechanism to obtain donor stool in the United States.[40] The authors' experience of using a stool bank (OpenBiome) is that it provides a far more rigorous and quality-controlled screening and distribution process than what had been previously developed locally. A further update to the FDA draft guidance specifically stated that the use of a stool bank for FMT would require an IND application.[39] All other uses of FMT, including as primary therapy for IBD, continue to require investigators to submit an IND application.

Conclusion

FMT is a safe and effective option in the short term to prevent recurrent CDIs in patients with IBD, and will likely remain an important tool in the future. Although the cure rate for CDI may be lower in IBD populations than in non-IBD populations, the impact of CDI on the course of IBD warrants FMT intervention. The potential for microbial therapies to treat IBD seems promising; however, clinical development of a reproducible microbial intervention to FDA standards is currently lacking. Many gaps exist in physician knowledge that can only be answered by well-designed clinical trials. Physicians should understand how FMT alters microbial diversity as a general intervention and which species and/or strains are amenable to colonizing the recipient's intestine in both CDI and IBD. In treating CDI, it remains to be determined if the effects of conventional FMT are due to alterations in host metabolic profiles or bacterial communities, or the introduction of peptides from the donor that alter host immune responses. Whether FMT truly eradicates CDI or merely reverts it to a sporulating state may be answered with follow-up measurements by polymerase chain reaction and toxin production. It is important to determine when microbial interventions might be most effective in the disease course, and in what manner and dosing they would need to be provided to sustain beneficial effects on mucosal immunology and the gut flora.

Dr Moss has acted as a consultant to Seres Therapeutics, Janssen, and Merck on microbiome-based therapies, and has received funding from the Helmsley Charitable Trust to undertake research on FMT. Dr Gianotti has no relevant conflicts of interest to disclose.

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