

Fecal microbiota transplantation in recurrent clostridium difficile infections: our experience in patients with and without inflammatory bowel disease

Abstract

Purpose: Fecal microbiota transplantation (FMT) has been used to reintroduce typical microbiota to reestablish balance in the setting of recurrent *Clostridium difficile* infection (CDI). The purpose of this study was to assess the safety and efficacy of FMT with concurrent CDI and inflammatory bowel disease (IBD).

Methods: This is a retrospective study performed at Med Star Georgetown University Hospital reviewing all patients with a history of recurrent CDI that were treated with FMT between December 1st, 2012 to August 30th, 2015.

Results: We identified 42 patients with recurrent CDI who were treated with FMT. Nine of the 42 patients had IBD. At 48 hours after FMT, 38 patients experienced resolution or improvement of diarrhea, 1 patient had persistent diarrhea and abdominal pain, and 3 patients had no documentation of symptoms reported. Eleven of the 24 patients experienced abdominal pain prior to FMT, and 9 of these patients had resolution or improvement. Of the 9 patients with IBD, 5 had resolution of diarrhea, and 1 had a repeat episode of CDI, 1 required surgery, and 2 or undocumented. Of the four patients with IBD that had abdominal pain, all experienced resolution or improvement initially, with one that recurred with resolution after another dose of vancomycin.

Conclusion: Recent studies have shown FMT as a successful treatment of recurrent CDI. There are ongoing studies evaluating the benefit of FMT in the treatment of IBD but there is limited evidence that FMT reduces symptoms in IBD. Of the 9 patients treated with FMT with concurrent IBD, all reported resolution of diarrhea and improvement in abdominal pain initially with FMT. Further studies are needed to assess these patients long term benefits after FMT and correlation with IBD flares as well.

Keywords: recurrent clostridium difficile infection; fecal microbiota transplantation; inflammatory bowel disease

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Abbreviations: FMT, fecal microbiota transplantation; CDI, clostridium difficile infection; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, crohn's disease; EIA, enzyme immunoassay

Introduction

The gastrointestinal tract harbors approximately 100 trillion bacterial cells that exist symbiotically to maintain the integrity of the intestinal mucosa and the gut immune system.^{1,2} Intestinal homeostasis is achieved by the symbiotic relationship between the host immune system and these microbes. Disruptions of this homeostasis predispose the gastrointestinal tract to increased incidence of enteric infections. This phenomenon is believed to play a role in several intestinal and extra-intestinal diseases such as asthma, atopic diseases, obesity, colon cancer, irritable bowel syndrome, and inflammatory bowel disease.^{2,3} Antibiotic use and immunocompromised states have been associated with an increased incidence of *Clostridium difficile* infection (CDI) [4].

Recent studies have established the role of environmental factors (such as diet, antibiotic use, and NSAID use), and their effect on the gut microbiome in the development of inflammatory bowel

disease (IBD) in genetically susceptible individuals.^{1,5} Ulcerative colitis (UC) is characterized by continuous inflammatory changes of the superficial layers of the colon, while Crohn's disease (CD) is characterized by transmural inflammation that can affect any area of the gastrointestinal tract in a patchy manner.⁶ Similar gut dysbiosis that occurs in antibiotic use, has also been found in patients with IBD.⁴ It is well established that patients with IBD have a higher incidence of CDI than the average population.^{1,5,7}

One proposed mechanism of CDI after exposure to antibiotics is the eradication of Bacteroides and Firmicutes bacteria which are present in the healthy colon. Standard therapies include metronidazole, vancomycin, or fidaxomicin, but recurrences are common.⁷⁻⁹ The estimated efficacy of antibiotics for the first recurrence is 60%.⁶ Most recent data suggest that fecal microbiota transplantation (FMT) is a safe and effective therapy for patients with recurrent disease to reintroduce typical microbiota and reestablish balance.^{1,3,5}

One longstanding theory of IBD pathogenesis includes disruption of the intestinal wall and immune dysregulation against altered commensal gut bacteria.⁶ Patients with IBD are highly susceptible to CDI due to immunosuppressive agents used for treatment,

intermittent hospital courses, and altered gut microbiota as well.⁷ Current studies are underway to determine the safety and efficacy of FMT in the treatment of CDI in this population. Kelly et al.⁷ noted 89% of immunocompromised patients that underwent FMT were asymptomatic after treatment.⁷ However, there are mixed outcomes in anecdotal reports and small studies utilizing FMT in patients with IBD.^{7,10-13}

It remains unclear whether the dysbiosis in patients with IBD causes the disease manifestations or is a result of the active inflammation.¹⁴ Questions also remain as to the optimal FMT scheduling protocol, route of administration, and appropriate diseases for FMT use. In this study, we describe our experience with FMT in treating patients with recurrent and refractory CDI, along with a subset of patients with concurrent CDI and IBD.

Methods

Between December 1, 2012 and August 30th, 2015, 42 patients with a history of recurrent or refractory CDI treated with FMT at MedStar Georgetown University Hospital were identified. A retrospective chart review was performed with approval by the institutional review board at Georgetown University. Patients' records were reviewed to determine demographic data, details of FMT, route of administration, response to FMT at 48 hours, and laboratory data. Gastroenterologists completed all of the colonoscopies. We identified 42 patients with recurrent CDI who were treated with FMT. Twenty-nine were females (69%) and 13 were males (31%). The mean age at treatment was 60.23 years old (5-95). Patients underwent a standard split-dose bowel preparation prior to FMT. Twenty-two patients used polyethylene glycol (PEG)-3350 and electrolytes oral solution, twenty-three patients used PEG-3350, eleven patients used PEG-3350, electrolytes, sodium ascorbate, and ascorbic acid oral solution, three patients used sodium picosulfate, magnesium oxide, and anhydrous citric acid, three patients used magnesium citrate and two enemas, four with unknown prep type, and one patient did not use a prep. The donor laboratory evaluations included stool for ova and parasites, bacterial culture and sensitivity, *C. difficile* PCR or enzyme immunoassay (EIA), Cryptosporidium antigen and Giardia antigen. Serum test included HIV-1, HIV-2, hepatitis A IgM, hepatitis B surface antibody, hepatitis C antibody, liver enzymes, and rapid plasma reagin. All donors were generally healthy, without autoimmune diseases, had normal pretesting labs, and were without current or recent antibiotic use. The donor provided 8 ounces of stool the morning of the procedure and blended it with 500-1000mL of water. The blended stool was strained and the remaining slurry was collected. The donor stool was labeled upon arrival to MedStar Georgetown University Hospital with the donor present and with the appropriate patient identifiers. Ten patients used stock stool from Open Biome. All patients discontinued antibiotics the day prior to the procedure. Loperamide 4mg by mouth was administered immediately after the procedure and 4 hours after discharge. Patients were called 48 hours after the procedure to evaluate symptom control. While this is not current standard protocol, a repeat stool *C. difficile* EIA or PCR test was performed 7 days after the procedure.

Results

Twenty-nine of the 42 patients (69.05%) were Caucasian, 4 unknown (9.52%), and 9 (21.43%) were African American. All patients had at least 2 documented episodes of recurrent CDI. Nine of the 42 patients (21.42%) had inflammatory bowel disease. Five patients had ulcerative colitis and 4 patients had Crohn's disease.

Twenty-one of the patients had donor stool from a family member (50%), 9 from a spouse (21.4%), 2 from a friend/coworker (4.8%), and 10 from banked samples from Open Biome (23.8%). One patient had a total of 1000mL of slurry transplanted, one had 540ml, one with 350ml, eight with 250ml, two had 100ml, one with 50ml, 2 with undocumented amounts, while the remaining patients had 500mL of slurry transplanted. Twenty-five patients (59.52%) had all the slurry deposited into the terminal ileum, 7 patients (16.67%) into the cecum, 2 into the splenic flexure (4.76%), 4 patients into the small bowel (9.52%), 2 patient (4.76%) throughout the entire colon, 2 via G-tube (4.76%), and 2 patient (4.76%) into the rectum via enema. Two patients could not undergo a full colonoscopy due to extensive cardiopulmonary disease that prevented him from safely undergoing a sedated colonoscopy. Of note, one patient had S pouch formation with ileostomy and underwent sigmoidoscopy and one patient underwent FMT via jejunostomy.

Prior to FMT, all 42 patients had diarrhea as defined by having three or more loose or liquid bowel movements per day. At 48 hours after FMT, 23 of 24 patients experienced resolution or marked improvement of diarrhea. The sole patient with persistent abdominal pain and diarrhea has resolution of symptoms by 90-day follow-up. One patient who had FMT via enema experienced a recurrence of diarrhea with positive *C. difficile* stool EIA and recurrent diarrhea. These symptoms resolved after an additional course of vancomycin, 125mg orally four times daily for 14 days, with negative repeat *C. difficile* stool EIA. One additional patient had an episode of recurrent CDI which was treated successfully with fidaxomicin. Eleven of the 42 patients (26.19%) had abdominal pain prior to FMT, with 9 of these patients experiencing resolution or improvement of abdominal pain. Two of the 11 patients (4.76%) with abdominal pain had unchanged abdominal pain.

Nine of the 42 patients had inflammatory bowel disease. Five patients had UC and 4 patients had CD. One of the patients with CD had a history of perianal fistulae with no small bowel involvement. One patient with CD had colonic involvement with a small ulcer in the ileum. The last patient with CD was being treated with Lialda and was asymptomatic. Of the four patients with CD, 3 patients remained asymptomatic with resolution of CDI, while 1 had repeat episode of CDI after FMT, but was successfully treated with vancomycin. One patient with UC had severe pancolitis with diffuse pseudopolyps. After declining escalation of therapy to biologic agents, this patient agreed to starting infliximab (IFX) two months later. He ultimately underwent total colectomy after the first two induction doses of IFX. The other patient with UC, had resolution of CDI but abdominal pain returned requiring narcotics for control. Of the 9 patients with IBD, 7 had resolution of diarrhea, and 2 had improvement of diarrhea to baseline prior to CDI. Of the 5 patients with IBD that had abdominal pain, 4 of 5 experienced resolution or improvement initially, however only 1 patient had recurrent abdominal pain later in the disease course.

Discussion

In our study, Forty-two patients underwent FMT for recurrent CDI. Of those, nine patients were also diagnosed with concomitant IBD. Follow-up after treatment revealed resolution of CDI in 90.5% of patients of those reported. Seventeen patients are still to be determined. Abdominal pain resolved initially in all patients with IBD, but later returned in 2 patients.

Fecal microbiota transplantation has been reported to successfully treat patients with recurrent CDI. Analysis of the cost-effectiveness of

strategies to combat recurrent CDI showed that FMT by colonoscopy is the most cost-effective approach, compared to vancomycin, metronidazole, or fidaxomicin.¹⁵ FMT confers cure rates greater than 96.4%, recurrence rates below 6.9%, with costs of less than \$1223. The varying routes for delivery include: enema, colonoscopy, and nasogastric tube. Despite several different routes of administration of microbiota there has not been a reported optimal protocol identified.

FMT is currently reserved for patients with recurrent or refractory CDI. FMT has most recently been investigated in the treatment of inflammatory bowel disease as well. There is currently conflicting data in the literature on the utility of FMT to treat IBD. It is well-documented that CDI is more common in patients with IBD than the general population with a prevalence of 3.7% in UC, 1.1% in CD, and 0.5% in the general population.⁹ Due to these rates, there have been trials to determine the typical bacterial environment to determine possible susceptibilities. Brace et al.⁵ described the fecal microbiota composition of one patient with CDI and UC and noted that prior to FMT the composition resembles non-IBD patients with CDI with predominance of Proteobacteria and scarcity of Firmicutes and Bacteroides. Patients experiencing an active UC flare and without CDI also have dominant Proteobacteria. After FMT in this patient, both CDI and UC symptoms resolved.⁵ This suggests that a common factor among patients with IBD and those more susceptible to CDI both have decreased flora variety, with predominance of Proteobacteria.

Available data on FMT in IBD are limited to case vignettes and small case series. To date, there are limited data from the few ongoing controlled, prospective, clinical trials designed to monitor IBD effects after FMT. Moayyedi et al.¹⁵ described their placebo controlled trial of FMT in active ulcerative colitis in abstract form. Sixty-three patients with active UC and no evidence of CDI were randomized to 6 weekly FMT enemas or water placebo enema. There were no major adverse events and no differences in endoscopic or clinical remission.¹⁵ A systematic review by Anderson et al.¹⁶ found 17 studies with 41 total patients treated with FMT for IBD and CDI or IBD alone.¹⁶ Of which, 26 were treated with FMT for IBD alone and the remaining 15 treated with FMT for both CDI and IBD. The outcome of the IBD alone group was a 76% improvement of symptoms. Of the trials that reviewed FMT in the CDI and IBD group, data could only be extracted from 10 of 15 patients. Six of seven were initially refractory to IBD medications, and subsequently had a response to medications after FMT, 3 patients restarted prior medications without mention of symptoms, and 5 patients' symptoms were not reported. Most of this data did not report a standardized scale for reporting IBD disease activity before and after FMT ([Table 1](#)).

Our study has several limitations including, retrospective nature and the small number of patients with both concomitant IBD and recurrent CDI. However, FMT in this review, does reveal that 90.5% were initially CDI negative, with only three requiring additional treatment after fecal microbiota transplantation. Of the concomitant CDI and IBD, 88% has resolution of CDI, and of those with follow-up documentation, 60% endorsed subjective improvement associated IBD pain. From our report and others, FMT plays a positive role in the resolution of CDI in patients with concurrent IBD, but may also become helpful in symptom control as well. Further studies are needed to assess patients with both recurrent CDI and IBD on the resolution of CDI, objective measures of resolution of IBD symptoms, prolonged monitoring for duration of effects of FMT on disease process, and the implications for IBD management to help elucidate the appropriate

role for FMT as a potential therapeutic option in inflammatory bowel disease.

Conclusion

Fecal microbiota transplantation is understood to provide excellent treatment success for refractory or recurrent CDI. There are ongoing studies evaluating the benefit of FMT in the treatment of IBD but there is limited evidence that FMT reduces symptoms in IBD. For this reason, FMT cannot be recommended for the treatment of such patients. There is, however, a valuable role for FMT in patients with CDI and underlying IBD. The successful treatment of the CDI helps clinicians focus on treating the inflammatory component more effectively. This data also supports prior results of the safety of FMT in patients undergoing immunosuppressant therapy for their IBD.

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Conflicts of interest

The authors declare there is no conflict of interests.

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