

Fecal Microbiota Transplantation in Patients With Recurrent *Clostridium difficile* Infection: A Four-Year Single-Center Retrospective Review

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Abstract

Background: *Clostridium difficile* infection (CDI) is a common cause of hospital and community-acquired diarrhea with an annual incidence of 453,000 cases in the USA. The white race, female gender, and age over 65 years are known risk factors. Recurrence of CDI is a major problem in patients taking antibiotics for prolonged periods. These patients are observed to have reduced diversity of the intestinal microbiome. Fecal microbiota transplantation (FMT) can restore the healthy flora in the gut, thus breaking the cycle of recurrent infection. Our study aimed to analyze the efficacy of FMT and the recurrence of CDI after FMT. We also aimed to investigate the effects of comorbidities on the outcome of FMT.

Methods: After obtaining approval from the institutional review board, we included 64 patients who had received FMT at our institution from October 2015 to November 2019. All the patients over 16 years of age in both inpatient and outpatient settings were included. Patients under 16 years of age and patients treated without FMT were excluded. Frozen stool from a standardized stool bank (OpenBiome) was used. The thawed specimen was instilled into the terminal ileum or the cecum. Patients were followed up for the next 1 year for analysis of improvement in symptoms, recurrence, and repeat FMT.

Results: On the 2-months follow-up, 75% of patients reported symptomatic improvement, 15.6% reported no improvement while 9.4% did not follow up. Twenty-six (40.6%) patients had CDI recurrence in the following year; and 69.2% of patients with recurrence underwent a repeat FMT. There was no statistically significant correlation between CDI recurrence and the age (P value = 0.68), gender (P value = 0.61), previous use of proton pump inhibitors (PPIs, P value = 0.11) or antibiotics (P value = 0.45). There was a statistically significant correlation noted with the use of immunosuppressants and recurrence (P value = 0.04).

Conclusions: FMT is a successful treatment modality for refractory and recurrent CDI. Repeat treatments can be beneficial if there is a lack of initial response. Being immunosuppressed with medications is associated with the risk of recurrence.

Keywords: Fecal microbiota transplant; *Clostridium difficile* infection; Frozen stool sample; Colonoscopy

Introduction

Clostridium difficile infection (CDI) is a common cause of hospital and community-acquired diarrhea with an annual incidence of 453,000 cases in the USA. Every year 29,000 people die of CDI in their first 30 days after diagnosis in the USA [1]. A higher incidence of CDI has been reported in the white race, female gender, and 65 or older population [2]. The recurrence of CDI is a challenging problem in patients taking antibiotics. These patients are observed to have reduced diversity of the intestinal microbiome resulting in recurrent CDI. Fecal microbiota transplantation (FMT) from healthy individuals to these patients can restore healthy flora in the gut, thus breaking the cycle of recurrent infection [3].

Historically, coprophagy (ingestion of fecal material) has been observed in many animal species likely contributing to the prevention of colonization of pathogens [4, 5]. The earliest use of fecal material in human history for the treatment of diarrhea dated to the fourth century in China. Later records of ancient gastrointestinal remedies refer to fecal products as “yellow soup” or “golden syrup” for the treatment of several gastrointestinal and systemic diseases such as diarrhea, malaria, severe food poisoning, and fever [6, 7]. In modern medicine, Eiseman et al in the year 1958 successfully treated four patients with pseudomembranous colitis through fecal enemas prepared from healthy donor stool [8]. Currently, FMT is mostly used for the treatment of recurrent *Clostridium difficile* colitis. The Infectious Disease Society of America (IDSA) in its updated clinical practice guidelines for the treatment of CDI strongly recommends FMT for patients with multiple recurrences of CDI despite appropriate antibiotic treatments [9]. Both frozen and fresh microbiota can be used for transplant. The rates of clinical resolution among frozen and fresh FMT were comparable (75% versus 70%) in a randomized clinical

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trial including 219 patients with the added advantage of using frozen microbiome stool banks for better screening [10]. In recent years there has been much debate regarding the safety of FMT which mainly stems from the idea of potentially introducing harmful bacteria in recipients through donor feces. Although, FMT is Food and Drug Administration (FDA) approved only as an experimental treatment for recurrent CDI, yet it has multiple potential applications in both intestinal and extra-intestinal disorders, some of them being inflammatory bowel disease (IBD), irritable bowel syndrome, and metabolic syndrome.

The purpose of our study was to analyze the efficacy of FMT in decreasing the recurrence of CDI and assess comorbidities and their relationship with the outcomes in this patient population.

Materials and Methods

Study design and sample

After institutional review board (IRB) approval, a retrospective electronic medical record chart review was performed on 64 patients in the institutional FMT registry who underwent FMT between October 1, 2015 and November 20, 2019 at Albany Medical Center, Department of Gastroenterology. During these 4 years, seven cases of FMT were performed in 2015, 21 cases of FMT were performed in 2016, 16 cases were performed in 2017, 17 cases were performed in 2018 while 26 cases were performed in 2019. Data were collected from electronic medical records of the patient visits to the gastroenterology clinic, endoscopy reports, and hospital admissions. Patients were followed up to 1 year after FMT. The patient population variables examined were age, gender, history of antibiotic use before FMT, prolonged proton pump inhibitor (PPI) use (defined by more than 1 month of PPI use), inpatient versus outpatient location, in-house versus outside referral, use of immunosuppressants, colonoscopy findings, time of stopping antibiotics before FMT, number of recurrences of CDI before FMT, number of FMT done in past, time to symptom improvement, duration of hospital stay, subsequent recurrence, subsequent FMT, and adverse events after the procedure. Besides, data on comorbidities such as immunocompromised state, diabetes, and hypertension were collected. Other variables included were the use of vancomycin, metronidazole, fidaxomicin, or all three before FMT. Recurrence was defined as relapse of CDI symptoms 2 weeks after the procedure. A successful FMT was defined as more than 50% improvement in the number of episodes of diarrhea after FMT. Both hospital and follow-up clinical records were reviewed to determine how many bowel movements patients were having before and after FMT. Patients were followed up for 2 months for symptomatic improvement. Patients with less than 50% improvement or no improvement in 2 months following FMT were deemed a failure.

Donor stool preparation and delivery

Pre-screened donor stool was obtained from the stool bank (Open Biome) in the form of frozen specimens. Both frozen

and fresh stool preparation is used for FMT, but since our facility uses only frozen stool, fresh stool samples were not used in our study. Preparation of stool specimens for transplant was done in the endoscopy suite before administration. Colonoscopy was performed using minimum air insufflation and the specimen was instilled into the terminal ileum or the cecum. Patients were advised to remain supine after the procedure for as long as possible to retain the transplanted stool.

Outcomes

Greater than 50% improvement in symptoms within 2 months after the fecal transplant was the primary outcome of the study. Secondary outcomes included recurrence of CDI after FMT and the need for subsequent FMT. After the transplant, patients had follow-up appointments setup with our gastroenterology clinic in 6 - 8 weeks to evaluate for symptom improvement. Telephone calls were also made by staff during this period to evaluate response to transplant and documented in electronic medical records. Questions were asked regarding adverse effects of the procedure, consistency of stools, and frequency of bowel movements. The patients were not tested for CDI after FMT to determine the resolution of infection as per guidelines to prevent false-positive results [11]. Patients experiencing persistent or recurrent symptoms after FMT were evaluated for a repeat procedure.

Statistical analysis

Statistical analysis was performed using IBM SPSS (Version 22). Frequency tables, Chi-square tests, Fisher's exact test, and cross-tabulations were used to analyze any correlation between variables under investigation and outcomes of the study. A P value of < 0.05 was determined to be statistically significant.

Ethical compliance with human study

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

Patient population

The study included 64 patients. Their ages ranged from 16 to 91 years. Thirty-seven patients (57.8%) were female, and 27 patients (42.2%) were male.

Role of antibiotic use

About 59.4% of patients had a history of antibiotic use before CDI (n = 38). Forty-six patients (71.9%) had antibiotics for CDI stopped > 48 h before the procedure, while 18 patients (28.1%)

Table 1. Demographic Variables (N = 64)

	N (%)
Gender	
Male	27 (42.2%)
Female	37 (57.8%)
Referral	
In-house	55 (85.9%)
Outside	9 (14.1%)
Inpatient	37 (57.8%)
Outpatient	27 (42.2%)
Comorbidities and risk factors	
History of PPI use	27 (42.2%)
Antibiotics used before CDI	38 (59.4%)
Use of immunosuppressants	12 (18.8%)
Diabetes	17 (26.6%)
Hypertension	38 (59.4%)
Immunocompromised state including IBD	25 (39.1%)
Antibiotics used for the treatment of CDI before FMT	
Vancomycin alone	14 (21.8%)
Fidaxomicin alone	0 (0%)
Metronidazole alone	2 (3.1%)
Vancomycin + metronidazole	16 (25.0%)
Vancomycin + fidaxomicin	10 (15.6%)
Fidaxomicin + metronidazole	0 (0%)
No antibiotic therapies	1 (1.5%)
All three	21 (42.1%)
Antibiotics stopped > 48 h before FMT	46 (71.9%)
Adverse events from FMT	12 (18.8%)
Abnormal colonoscopy findings	39 (60.9%)

PPI: proton pump inhibitors; CDI: *Clostridium difficile* infection; IBD: inflammatory bowel disease; FMT: fecal microbiota transplant.

had antibiotics stopped < 48 h before the procedure. Vancomycin was the most common antibiotic used in these patients for CDI before FMT, with 61 (95.3%) patients using vancomycin either in combination or monotherapy. Fourteen patients (21.1%) used vancomycin alone while 16 patients (25%) used a combination of vancomycin and metronidazole, 10 patients (15.6%) used a combination of vancomycin and fidaxomicin. Metronidazole monotherapy was observed in two patients (3.1%). Monotherapy with fidaxomicin or a combination of fidaxomicin and metronidazole was not observed in any patients. Twenty-one patients (42.1%) had used all three antibiotics to treat CDI before FMT.

Other variables

Twenty-seven patients (42.2%) had a history of prolonged PPI use (more than 1 month), while 37 patients (57.8%) did not

Table 2. Primary and Secondary Outcomes (N = 64)

	N (%)
Improvement in 2 months	48 (75.0%)
FMT failure	10 (15.6%)
Patients lost to follow-up	6 (9.4%)
Recurrence of CDI after 2 months	26 (40.0%)

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplant.

have a history of PPI use. Twelve patients (18.8%) were on immunosuppressant therapy before FMT (Table 1). Patients were either referred for FMT from our hospital's gastroenterology clinic/inpatient facility (in-house referrals) or outside clinics (outside referrals). Fifty-five patients (84.9%) had an in-house referral and the success rate of FMT in these patients (defined by more than 50% improvement in 2 months) was 78.2%. Both Chi-square and Fisher's exact test showed a significant correlation between referral type and the result of FMT ($P = 0.002$). Only one variable, referral type had a statistically significant correlation with the primary outcome (improvement in 2 months). This was likely due to better follow-up in patients with in-house referrals as four out of six patients who were lost to follow-up were referred from outside facilities.

Primary outcome

The overall success rate of FMT in our study was 75% with 48 out of 64 patients showing improvement in the first 2 months after FMT (Table 2). Six patients (9.4%) were lost to follow-up of which four patients were outside referrals. Ten patients (15.6%) reported no improvement and were deemed treatment failure. Among these 10 patients who had failed treatment, four patients underwent a repeat FMT with improvement in symptoms of which three patients improved, while one failed repeat FMT requiring a colectomy. Among the remaining six patients who had failed treatment but did not receive repeat FMT, three patients died from various etiologies before getting the repeat FMT, two patients showed improvement after the first 2 months while one patient underwent colectomy. Thirty-nine (60.9%) patients had abnormal colonoscopy findings with pancolitis being the most common (18.8%, Fig. 1). Twelve patients (18.8%) reported adverse events after FMT. The most reported adverse event was abdominal pain/cramping (10.9%). Other adverse events included worsening diarrhea in three (4.6%) patients, bloating in one (1.6%) patient, and weight gain in one (1.6%) patient.

Secondary outcomes

Secondary outcomes in our study were the rate of CDI recurrence and the need for repeat FMT after the initial procedure. CDI recurrence was defined as a positive *Clostridium difficile* polymerase chain reaction (PCR) test in symptomatic patients at least 2 months after initial FMT. CDI recurrence was reported in 26 patients (40.6%). On average, CDI recurrence occurred 113 days after the initial FMT. Nine patients (34.6%) used antibiotics

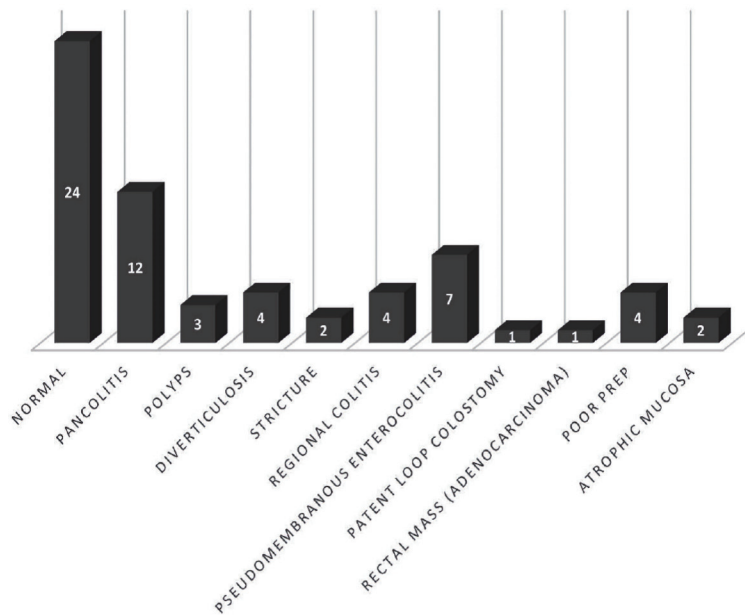


Figure 1. Colonoscopy findings.

for reasons other than treatment of CDI before recurrence. Eight patients (30.8%) were on immune suppressants for either IBD or to prevent transplant rejection while two patients had IBD but were not taking any immune suppressants. Among these eight patients on immune suppressants, six had IBD, one patient was

on chemotherapy for leukemia while one patient was a renal transplant recipient maintained on tacrolimus. Crohn’s disease and ulcerative colitis were observed in three patients each. Being on immunosuppressant therapy had a statistically significant relationship with recurrence of CDI (P = 0.04, Table 3). The ma-

Table 3. Success and Recurrence Rates in Different Demographic Variables and Risk Factors

Demographic variables	N	Success ^a	P value	Recurrence	P value
Gender					
Male	27	23 (85.3%)		10 (37.0%)	
Female	37	25 (67.6%)	0.24	16 (43.2%)	0.61
Referral					
In-house	55	43 (78.2%)		21 (38.2%)	
Outside	9	5 (55.6%)	0.002	5 (55.6%)	0.32
Inpatient	37	30 (81.1%)		17 (45.9%)	
Outpatient	27	18 (66.7%)	0.09	9 (33.3%)	0.31
Comorbidities and risk factors					
History of PPI use	27	21 (77.8%)	0.66	14 (51.9%)	0.11
Antibiotics used before CDI	38	27 (71.1%)	0.05	14 (36.8%)	0.45
Use of immunosuppressants	12	10 (83.3%)	0.72	8 (66.7%)	0.04
Diabetes	17	12 (70.6%)	0.87	6 (35.3%)	0.62
Hypertension	38	30 (78.9%)	0.68	18 (47.4%)	0.18
Immunocompromised state	25	19 (76%)	0.72	11 (44.0%)	0.66
Antibiotics stopped > 48 h before FMT	46	34 (73.9%)	0.90	17 (37.0%)	0.19
Adverse events from FMT	12	7 (58.3%)	0.17	3 (25.0%)	0.22
Abnormal colonoscopy findings	37	26 (70.3%)	0.53	15 (40.5%)	0.62

^aSuccess was defined as more than 50% improvement of symptoms in 2 months. Values were shown as n (%). CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplant; PPI: proton pump inhibitor.

Table 4. Characteristics of Patients With CDI Recurrence (N = 26)

	N (%)
Antibiotic use before CDI recurrence	9 (34.6%)
Immunosuppressant use before recurrence	8 (30.7%)
Crohn's disease	3 (11.5%)
Ulcerative colitis	3 (11.5%)
Organ transplant recipients	1 (3%)
Treatment with repeat FMT	18 (69.2%)
Treatment with antibiotics	7 (26.9%)

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplant.

majority of these patients with CDI recurrence were treated with repeat FMT. Eighteen patients (65.3%) with CDI recurrence were treated with repeat FMT while antibiotics were used to treat seven patients (26.9%). One patient died before receiving a repeat FMT. Of the seven patients treated with antibiotics, vancomycin was used to treat five patients. These findings are summarized in Table 4. Interestingly, three patients who had received a successful repeat FMT after treatment failure during the first 2 months showed CDI recurrence in the next year and underwent a third FMT with 100% success. The success rate in patients undergoing two FMTs was 70.6% while a 100% success rate was observed in patients with three FMTs. The single patient who had four FMTs failed therapy finally underwent a total proctocolectomy.

Discussion

We conducted a single-center retrospective chart review for patients with recurrent CDI undergoing FMT between October 1, 2015 and November 20, 2019 at Albany Medical Center, Department of Gastroenterology. Our results with frozen fecal microbiota were comparable to other studies and showed a success rate of 75%. About 10% of patients were lost to follow-up therefore actual success rate may be higher than 75%. A cure rate as high as 91.9% has been reported in the literature [12]. Both fresh and frozen fecal microbiota can be used for this procedure with comparable results in both groups [10, 13]. A randomized clinical trial by Lee et al [10] showed 70.3% and 75.0% clinical resolution in fresh versus frozen fecal samples. At our facility, only prescreened frozen specimens are used hence our study is based on frozen fecal microbiota.

The patients in our study had a variety of comorbidities such as hypertension, diabetes, immunosuppressed state, and PPI use. Our study noted that among the comorbidities studied, being on an immunosuppressant medication had a statistically significant association with recurrence. There was no statistically significant relationship between being on immunosuppressants and symptom resolution in these patients. In our study, patients on immunosuppressants had a 90.9% success rate. But on the other hand, these patients were also at risk for recurrence as mentioned above. A systematic review of 44 studies showed an 87% success rate in immunocompromised

patients who underwent their first FMT, and the cure rate increased to 93% on subsequent FMTs [14]. A possible reason why being on immunosuppressant therapy had an association with recurrence and the need for repeat FMT is that these patients are more likely to be colonized with *Clostridium difficile* in general, and thus can have a higher recurrence rate. This makes being on immunosuppressants an independent risk factor for recurrent CDI as shown in a previous study [15]. In the past few years, multiple studies and meta-analysis have shown a significant relationship between PPI use and the risk of CDI while some studies have rejected this hypothesis [16-18]. Our study did not show a causal relationship between PPI use and recurrence of CDI.

In our tertiary referral center, there were more in-house than outside referrals. In-house referrals showed better outcomes. This can be explained by a higher loss of follow-up in outside referrals. Of the six patients lost to follow-up, four patients were referred from outside gastrointestinal clinics.

Although the inpatient population tends to be sicker and treatment is challenging, our study showed a success rate of 81% in inpatient versus 66.7% in outpatient cases. This can be explained by a higher number of inpatient cases (37 inpatients versus 27 outpatients) and a higher loss of follow-up in the outpatient population as described above. Also, patients with outpatient cases reported subjective changes in symptoms while the inpatient population had their number of daily bowel movements and other symptoms quantified and charted by nursing staff making this data more accurate.

Although FMT offers a higher cure rate, it does not come without its limitations. Our study showed that recurrence of CDI after FMT in the following years is still a major concern despite high symptom resolution rates. Three patients in our study died during the follow-up period due to various reasons. Only one patient died secondary to uncontrolled CDI. In a systematic review of 15 studies, the all-cause 30-day mortality in patients with CDI was seen in 15% of patients while mortality attributed to CDI in these patients ranged from 5.7% to 6.9% [19].

Our study had certain limitations including its retrospective design and small sample size. Since FMT is an innovative treatment option and only approved as an experimental treatment as per FDA, we only had 64 patients over 4 years in our study. To determine the generalizability of our results, larger sample size will be beneficial. Certain confounders can be missed in a small sample population. Despite being limited by our sample size, our study showed a cure rate of FMT comparable to available literature, and we were able to show a statistically significant relationship between the use of immunosuppressants and the recurrence of CDI.

Future studies on FMT should include a comparison of different FMT protocols used these days to help develop a standard FMT protocol [20]. Recently, questions have been raised regarding the safety of FMT. A standard FMT protocol with standardized screening for drug-resistant bacteria in donor stool can make FMT safer [20, 21]. At our institution, stool samples were obtained from "open biome", which is a standardized stool bank providing frozen fecal samples after screening for harmful pathogens (OpenBiome, n.d.). It will be interesting to follow patients for a longer period to determine

the long-lasting effects of FMT on these patients. We followed patients in our study population for up to 2 months for symptom resolution and up to 1 year for recurrence and repeat FMT. Also, more studies are needed to analyze the effects of FMT on other diseases beyond CDI such as IBD, irritable bowel syndrome, metabolic syndrome, and non-alcoholic steatohepatitis [22, 23]. Finally, measures should be taken to reduce the recurrence of CDI, and factors affecting recurrent disruption of colonic flora should be studied in more detail. The risk of symptomatic recurrence of CDI increases after every episode of CDI [24].

Conclusions

In conclusion, our single-center retrospective study showed that FMT is a safe and effective treatment option for patients with recurrent or severe CDI. Being on immunosuppressant medications correlates with the recurrence of CDI. The financial burden of CDI on hospitals may be minimized with frequent use of FMT by limiting the need for long-term use of expensive antibiotics and readmissions due to recurrent CDI. The use of frozen samples for FMT from a stool bank can ensure standardized screening. Universal screening and adoption of a single most effective FMT protocol can help determine the long-term safety and efficacy of FMT, especially in the immunosuppressed population.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

Informed Consent

Not applicable

Author Contributions

MFA and AB conceived and designed the project. MFA, OT, and YN contributed to data collection. MFA and OT analyzed and interpreted the data. YN, MFA, and OT drafted the manuscript. All authors read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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