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ORIGINAL ARTICLE

Fecal microbiota transplantation in recurrent *Clostridium difficile* infection: A retrospective single-center chart review

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Abstract

Background and Aim: Fecal microbiota transplantation (FMT) has been proposed as a treatment option for patients with recurrent *Clostridium difficile* (*C. difficile*) infection but remains a novel option. We examined if FMT is an effective means of treating recurrent *C. difficile* infection.
Methods: A retrospective review of 35 patients who underwent FMT was completed. Demographics and other variables, including the use of proton pump inhibitor therapy and history of inflammatory bowel disease, were collected.
Results: Twenty-five patients (71.4%) belonged to a high-risk population (working in a hospital setting, rehabilitation center, or nursing facility) and a total of 74.3% of patients (n = 26 patients) had no history of proton pump inhibitor use. Twenty-five patients (71.4%) had used metronidazole prior to transplantation, 35 patients (100%) had used vancomycin, and 7 patients (20%) had used fidaxomicin for prior infection. Four patients (11.4%) had used all three antibiotics during prior treatment. Of the eight patients who had a history of inflammatory bowel disease, six (75%) experienced resolution of symptoms after transplantation. A total of 30 patients (85.7%) had resolution of their symptoms 6–8 weeks' posttransplant, while 5 patients (14.3%) continued to have symptoms.
Conclusions: Our retrospective chart review supports that patients benefit from FMT in the setting of recurrent *C. difficile* infection.

Introduction

Clostridium difficile (*C. difficile*) has long been recognized as the most common infectious cause of nosocomial diarrhea[1–5] and has led to ever expanding health-care costs.[2] In the United States, the rates of *C. difficile* infection (CDI) are not accurately known as it is not a reportable illness.[3] In 2011, almost 500 000 patients were diagnosed with CDI, and this led to almost 29 000 CDI-related deaths.[6,7] According to the Centers for Disease Control and Prevention, the mortality rates due to CDI from 1999 to 2004 increased from 5.7 per million population to 23.7 per million.[8] The average length of stay attributed to CDI treatment in the hospital was found to be 11.1 days in a recent meta-analysis published in 2016, and the annual cost of CDI is estimated to be $6.3 billion, with a range of $1.9 to $7 billion.[9]

The rate of infection and recurrence has increased as more virulent strains of *C. difficile* arise.[1,2] Recurrence is defined as an occurrence of symptomatic diarrhea or abdominal pain, with positive results of a stool test within 56 days of a previous episode after interim symptom resolution.[1] In one randomized trial that included 163 cases of CDI, a total of 73 or 44.8% of patients had at least one episode of recurrence within a 2-month period on standard medical therapy.[10] Once a patient experiences a recurrent episode of CDI, 45–65% continue to have repeated episodes.[10] In addition, literature documents that CDI recurrence was 31% with tapered vancomycin and 14% with pulsed metronidazole and vancomycin regimen.[2]

Fecal microbiota transplantation (FMT) has been proposed as a treatment option for patients with recurrent CDI. This treatment has been found to have high cure rates and is considered to be safe, superior, and a less costly treatment option than repeated antibiotic use.[2] In a landmark study conducted by van Nood E, Vriezen A, Nieuwdorp M, et al., patients with recurrent CDI were randomized as receiving 500 mg vancomycin orally four times a day for 4 days followed by donor feces infusion via nasoduodenal tube *versus* standard vancomycin oral regimen of 500 mg orally four times a day for 14 days *versus* the standard oral regimen with a bowel lavage.[11] The cure rate was found to be 81% (13 of 16 patients) for those patients who received donor feces via nasoduodenal tube compared to 31% of patients who received 500 mg vancomycin orally four times a day for 14 days alone. Due to the high cure rate in the FMT group, this study was prematurely discontinued.[11] In a systematic review of 27 studies and case reports including 317 patients with recurrent CDI treated via FMT, they found an overall success rate of 92%,

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with 89% of patients responding after a single treatment, with the highest response rate found for those patients who received FMT via enema[1] *versus* a more recent review of seven randomized controlled trials with 30 case series that found a 92% cure rate, ranging from 68% to 100%, which took into account more than one infusion to achieve cure.[12] In a 2016 study examining the success of FMT in recurrent CDI in 146 elderly patients, they found a cure rate of 82%.[13] In another recent study, the use of FMT to treat CDI was examined in immunocompromised patients, including those with inflammatory bowel disease (IBD), and a cure rate of 78% was found.[14] Given the growing evidence supporting the use of FMT, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recently published new guidelines recommending the use of FMT at the second recurrence of CDI.[15]

However, as FMT remains a novel treatment option, there has been no standardization of treatment delivery. Existing research publications have varied in the form of delivery, amount of fecal delivery, donor stool sample preparation, and pre- and post-FMT procedures.[7,16–18] For instance, FMT can be performed via nasogastric tube, nasoduodenal tube, esophagoduodenoscopy (EGD), colonoscopy, or enema.[1,16,18] The volume of sample delivered has varied from 25 to 50 mL via nasogastric tube *versus* 250–500 mL when delivered via enema or colonoscopy.[2] Some studies have used fresh *versus* frozen samples and have recommended that transplantation occur within 24 h of stool collection *versus* 6 h.[2,16] Moreover, there have been differing pre- and post-transplant procedures, with some suggesting bowel lavage prior to FMT to help flush residing flora and some suggesting loperamide after colonoscopy FMT *versus* use of probiotics.[16]

Materials and methods

Study design and sample. A retrospective electronic medical record chart review of 35 patients who underwent FMT at Allegheny General Hospital (AGH) or Forbes Regional Hospital between January 2016 and April 2017 was completed. The following patient population variables were examined: age, gender, history of smoking, history of alcohol use, recent antibiotic use within 3 months prior to CDI diagnosis, use of proton pump inhibitor (PPI) or immunosuppressive therapy, history of malignancy, history of end-stage renal disease, history of diabetes, history of cirrhosis, and history of IBD as well as whether the patient belonged to a high-risk population, meaning employed in a health-care setting, including hospitals, rehabilitation centers, or nursing facilities. Other variables included if there was a family member with CDI and if the patient had the hypervirulent strain of *C. difficile*, which was defined as being positive for the 027 NAP 1 B1 strain. We also examined the number of documented CDI recurrences before FMT was completed; the use of prior antibiotics for CDI treatment, including metronidazole, vancomycin, or fidaxomicin; whether the recipient underwent OpenBiome donation *versus* adult donor stool; and the resolution of symptoms at the time of outpatient follow-up. After transplant, patients were contacted by nursing staff via telephone at weeks one and four posttransplant to discuss any adverse effects and were also scheduled for a follow-up office visit within 6–8 weeks to evaluate for any signs of recurrent infection.

FMT recipient criteria. The institution's existing FMT protocol states that a patient is a FMT candidate if they had a laboratory confirmed diagnosis of CDI and if they were evaluated by Infectious Disease and/or Gastroenterology (GI). According to the institution's protocol, prior to transplant, if a patient was considered to be immunocompromised, their cytomegalovirus (CMV) status was checked. If the recipient's CMV status was negative, the donor was then screened for CMV, and the patient was unable to use OpenBiome as OpenBiome does not screen stool samples for CMV. If the recipient was found to have a positive IgG for CMV, they were eligible for FMT from an adult donor or from OpenBiome, and if the recipient was found to be positive for CMV IgM, FMT was determined at the discretion of the gastroenterologist. Participants were instructed to complete all testing at the two clinical campuses where FMT is offered, unless this would cause unreasonable burden on the donor.

Seven days prior to FMT, the stool transplant recipient was required to submit a stool sample for *C. difficile* testing per the hospital's algorithm. Prior to FMT, all recipients were pretreated with a 4-day course of 125 mg oral vancomycin every 6 h with the last dose given the evening prior to FMT. The night prior to transplant, the recipient was instructed to eat nothing by mouth, and to complete a bowel preparation.

FMT donor selection criteria. The existing institutional FMT protocol states that patients are to be given the option of using OpenBiome or selecting their own stool donor. Adult donors were defined as individuals who had close physical contact with the patient, a family household member, or a healthy donor. Contraindications to adult stool donation included the following: the current use of immunosuppressants or chemotherapy, antibiotic use or hospitalization within 6 months, history of travel within 6 months where diarrheal illness is prevalent, new tattoos/piercings within 6 months, history of GI malignancy or GI disease such as celiac disease or IBD, history of prior incarceration, or high risk sexual behaviors.

The institutional protocol states that if a recipient used an adult donor outside of OpenBiome, stool donors were required to complete a questionnaire to assess for any contraindications to adult stool donation as discussed above. Donors were screened for HIV-1 and HIV-2; hepatitis A, B, and C; CMV; and syphilis within 30 days of transplantation, along with CBC, using a differential and complete metabolic panel. Donor stool was screened for ova and parasites, per the department's protocol, and pathogens, such as *C. difficile*. If FMT was to be performed via nasojejunal (NJ) tube, the stool donor underwent *Helicobacter pylori* fecal antigen testing. If the recipient was considered immunosuppressed, donor stool was additionally screened for Cyclospora, Isospora, and Cryptosporidium. If any of these laboratory tests were found to be positive, this was an absolute contraindication for stool donation.

Participants were instructed to complete all testing at either of the two clinical campuses unless this would cause unreasonable burden on the donor.

Stool preparation and delivery. Donor stool and OpenBiome stool samples were prepared in a designated area in the GI laboratory on the day of transplant. Per the institutional FMT

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protocol, stool samples were obtained less than 6 h prior to the procedure, into a disposable medical hat, and were stored in a sterile container that was then placed in a biohazard bag. The required stool specimen volume was 20–30 mL, which was then mixed with 250 mL of sterile 0.9% normal saline in a 1-L sterile fluid canister or sterile disposable blender canister. The canister was then sealed and mixed via a disposable blender purchased for this purpose or by manually agitating the container for at least 1 min. If necessary, this process would be repeated for an additional 2–4 min until the sample was found to have a liquid consistency that could easily pass through the colonoscope or an NJ tube.

At our institution, FMT is only delivered via colonoscopy or NJ tube. If transplant was to occur via NJ tube, the tube was placed prior to transplant, and an abdominal x-ray was performed no more than 2 h prior to transplant to confirm positioning of the tube. After NJ tube placement, 25 mL of sterile saline was flushed into the NJ tube; then, 50 mL of prepared stool was pushed into the tube slowly to ensure no stool leaks around the end of the NJ tube, and following this, the NJ was flushed with another 25 mL of sterile saline following stool transplant. Per the department's FMT algorithm, for those recipients who received transplant via colonoscopy, a total of 100 mL of stool suspension was aspirated into a syringe, which was then instilled into the recipient via the biopsy channel of the colonoscope. The colonoscope was then slowly withdrawn, and transplant stool was deposited every 10 cm throughout the large intestine.

Statistical analysis. Statistical analysis for this study was performed using IBM SPSS (Version 22; Armonk, NY, USA). Cross tabulation, frequency tables, Chi-square tests, Fisher's exact test, and a logistic regression model were used to detect any associations between the different variables under study and the results of the stool transplant. A P-value < 0.05 was considered statistically significant. Approval from the Institutional Review Board for research ethics was obtained before conducting chart review of the study subjects.

Results

Of the total of 35 patients, 20 patients (57.1%) were under the age of 65, and 15 patients (42.9%) were over the age of 65; 85.7% were females (n = 30). A total of 19 patients (54.3%) had a history of smoking, and 12 patients (34.3%) had a history of alcohol use. Only one patient had a family member with a previous history of CDI, and 25 patients (71.4%) belonged to a high-risk population, including working in a hospital setting, rehabilitation center, or nursing facility. Eight patients had a history of IBD, 74.3% of patients (n = 26 patients) had no history of PPI use, and only 25.7% of patients (n = 9) had used PPIs previously. A total of 28 patients had mild to moderate CDI; 6 had severe CDI; and only 1 patient was found to have had severe, complicated CDI; 25 patients (71.4%) had used metronidazole prior to FMT, all 35 patients had used vancomycin, and 7 patients (20%) had used fidaxomicin for treatment of prior CDI. Four patients (11.4%) had used all three antibiotics for treatment of their CDI. Eight patients (22.9%) were on immunosuppressant therapy prior to FMT (Table 1).

Five patients (14.3%) were found to have the hypervirulent strain of *C. difficile*, and the success rate of FMT in those with this strain of *C. difficile* was 60%. The results of Fisher's exact test showed a significant relationship between the FMT result and having the hypervirulent strain of *C. difficile* (Fisher's exact test, P = 0.04). A binary logistic regression was performed to analyze if any of the variables were predictors for the results of the fecal transplant (Table 2). Only one variable, having the hypervirulent strain, was a statistically significant independent predictor (P-value of 0.009). Being on immunosuppression was close to significance, with a P-value of 0.052. All other variables were not statistically significant. A logistic regression model was performed and only one variable was a significant predictor of outcome which was having the hypervirulent strain of *C. difficile*, with a P value of 0.034 and an odds ratio of 13.795, with a 95% confidence interval of 1.226–155.289. However, these findings have limitations. The large odds ratio may be due to a small sample size (n = 30). There could also be confounding factors that cannot be considered in this analysis.

Of the 35 patients, 2 used an adult donor (5.7%), and 33 recipients (94.2%) used OpenBiome. Of the two patients who used an adult donor, FMT was successful 50% of the time. A total of 30 patients (85.7%) had resolution of their symptoms after FMT, while 5 patients (14.3%) continued to have symptoms and were deemed FMT failures (Table 3). Of the eight patients who had a history of IBD, six experienced resolution of symptoms after FMT (75%), and only two of these eight patients had experienced relapse (25%).

Of the 35 patients who underwent FMT, 8 were on immunosuppression therapy prior to transplantation. Of these eight patients on immunosuppression, six patients were noted to have IBD, and two were non-IBD patients on immunosuppresive therapy. In the subset of patients who were on immunosuppressive

Table 1 Demographic characteristics and variables

Demographic variable	Yes	No
High-risk population[†]	25 (71.4%)	10 (28.6%)
History of PPI	9 (25.7)	26 (74.3%)
Use of immunosuppressants	8 (22.9%)	27 (77.1%)
Tobacco use	19 (54.3%)	16 (45.7%)
Alcohol use	12 (34.3%)	23 (65.7%)
Family member with *C. diff*	1 (2.9%)	34 (97.1%)
History of malignancy	3 (8.6%)	32 (91.4%)
Diabetes	4 (11.4%)	31 (88.6%)
Cirrhosis	0 (0%)	35 (100%)
ESRD	0 (0%)	35 (100%)
History of IBD	8 (22.9%)	27 (77.1%)
Antibiotic use within 3 months	25 (71.4%)	10 (28.6%)
Prior use of metronidazole for *C. diff*	25 (71.4%)	10 (28.6%)
Prior use of vancomycin for *C. diff*	35 (100%)	0 (0%)
Prior use of fidaxomicin for *C. diff*	7 (20%)	28 (80%)
Hypervirulent strain of *C. diff*	5 (14.3%)	30 (85.7%)

[†]defined as patients who are employed in a health-care setting, including hospitals, rehabilitation centers, or nursing facilities.

Values as n (%).

C. diff, *Clostridium difficile*; ESRD, end-stage renal disease; IBD, inflammatory bowel disease; PPI, proton pump inhibitors.

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Table 2 Univariable Binary logistic regression predictors of fecal microbiota transplantation (FMT)

Demographic variable	*P*-value
Age (≥65 or < 65)	0.411
Gender (male or female)	0.695
Previous antibiotic use within 3 months	0.545
Use of immunosuppressants	0.052
Tobacco use	0.494
Alcohol use	0.477
Previous hospitalization (not for *C. diff*)	0.545
Previous hospitalization (for *C. diff*)	0.558
Family member with *C. diff*	1.00
High-risk population[†]	0.650
History of malignancy	0.999
Diabetes	0.999
Cirrhosis	0
ESRD	0
History of IBD	0.337
History of GI surgery	0.584
History of PPI use	0.753
Imagining	0.283
Colonoscopy	0.999
Leukocytosis/leukopenia (>15 000 cells/mm^3 or <2000 cells/mm^3	0.999
Serum albumin <3 g/dL	0.999
ICU admission	0
Severity of *C. diff*	1.00
Frequency of bowel movements	0.337
History of chemotherapy	1.00
Prior use of metronidazole for *C. diff*	0.545
Prior use of vancomycin for *C. diff*	0
Prior use of fidaxomicin for *C. diff*	1.00
Number of recurrences before FMT	0.999
Type of stool transplanted	0.999
Hypervirulent strain of *C. diff*	0.009

[†]defined as patients who are employed in a health-care setting, including hospitals, rehabilitation centers, or nursing facilities.
C. diff, *Clostridium difficile*; ESRD, end-stage renal disease; GI, gastroenterology; IBD, inflammatory bowel disease; ICU, intensive care unit; PPI, proton pump inhibitors.

Table 3 Fecal microbiota transplantation (FMT) outcomes

Specific variables	Success	Failure
Rate in inflammatory bowel disease	6 (75.0%)	2 (25.0%)
Rate in high-risk population	20 (80.0%)	5 (20.0%)
Rate in proton pump inhibitor use	7 (77.8%)	2 (22.2%)
Rate in immunosuppressant use	5 (62.5%)	3 (37.5%)
Overall rate	30 (85.7%)	5 (14.3%)

Values as *n* (%).

treatment and did not have IBD, two patients, the FMT success rate was 50%. Of the six patients on immunosuppression due to IBD, three of the patients had controlled IBD symptoms, two patients had uncontrolled IBD symptoms, and the last patient was newly diagnosed with IBD during FMT colonoscopy. The two patients who had documented uncontrolled IBD symptoms both had successful FMT, the one patient diagnosed during FMT colonoscopy had an unsuccessful FMT, and two of the three patients with documented controlled IBD had successful FMT. Overall, the six patients who had IBD and were on concurrent immunosuppressive therapy had an FMT success rate of 66.7%, and the overall cure rate of CDI with FMT in the immunosuppression group was 62.5% (Table 4).

Discussion

CDI is a leading cause of infection in hospitalized patients and continues to plague the health-care system. As the number of recurrences of CDI increases, novel approaches to treating CDI have been studied, including FMT. We performed a retrospective chart review of all 35 patients who underwent FMT at our institution. A total of 30 patients (85.7%) had resolution of their symptoms 6–8 weeks post-transplant, while 5 patients (14.3%) continued to have symptoms. This is a rate of success similar to those seen in previous studies.[1,16,18,19] Of note, there was no correlation found between the five patients who failed the FMT.

One subset of patients that was taken into account in this study included patients with PPI use. As previous studies have mentioned, PPI use may have a correlation with CDI.[1–3,20,21] In reviewing the data from our study, only about one-fourth of the patients with CDI were exposed to PPI therapy, and the use of PPI therapy did not affect the success of FMT. Of the nine patients on PPI therapy, the cure rate after first-time FMT was 88.9% (seven of nine patients). Of the 14.3% of patients who continued to have symptoms after FMT, only two patients had previous exposure to PPI use.

Another subset of patients in our review included those on immunosuppression. On further review, these patients included both IBD and non-IBD patients. Our study showed that there was no statistical significant difference in the success of FMT in patients on immunosuppressive therapy when compared to patients not on immunosuppression, which is in alignment with existing literature.[5] Although our population of patients on immunosuppression was small, our cure rate in this subset population on immunosuppression was 62.5% after first FMT compared to existing literature that has reported a cure rate of 78%.[14] Furthermore, when examining the patients with IBD, there was no statistically significant difference in the success of FMT for patients with active or inactive IBD. The overall cure rate after first-time FMT in the IBD patient population, regardless of immunosuppressive therapy, was 75%. The use of FMT in IBD patients is particularly interesting as the incidence of CDI is approximately 2.5–8 times higher in this patient population than the general population.[4] The existing literature suggests that the success rate after first FMT in the IBD population is 74–79%,[4,14,19] and our result is comparable to existing literature reports. Even with a small sample size, this can support the notion that patients on immunosuppression and with active or inactive IBD had no statistical significant difference in success of FMT. We propose that the cure rate might have been higher if patients underwent another FMT as existing literature shows that the cure rate after up to three FMTs can be as high as 90% in the IBD population.[4]

We found a statistically significant relationship between FMT success rate and the hypervirulent strain of *C. difficile* and

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Table 4 Fecal microbiota transplantation (FMT) outcomes in patients on immunosuppression

	Immunosuppression with IBD			
	Controlled IBD	Uncontrolled IBD	Newly diagnosed IBD	Immunosuppression without IBD
FMT success rate	3 (66.7%)	2 (100%)	1 (0%)	2 (50%)

Values as *n* (%).
IBD, inflammatory bowel disease.

that this variable was also a significant predictor of outcome ($P = 0.034$), with an odds ratio of 13.795. In our study, of those with the hypervirulent strain of *C. difficile*, 60% had an FMT cure. A previous literature review showed an 89% cure rate after FMT in those with hypervirulent strain at 12-week follow-up.[1] As mentioned previously, this finding has its limitation due to the small sample size and other confounding factors. Although our sample size was small, the type of strain of *C. difficile* may have an important impact in predicting the success rate of FMT in patients and may be an area for future study.

The existing literature on FMT for recurrent CDI does not consistently report the materials and methods used when conducting FMT.[7] For instance, in one review of 85 studies, it was found that 96% of the time studies did not include the materials utilized for stool collection and that donor criteria are not listed 47% of the time.[17] In our review, we delineated the criteria used for stool donor selection, recipient criteria, and the process used for stool collection along with infusion. By sharing this process, we hope to be able to help reproduce our findings and add to the existing literature on FMT.

Our study is limited by our small sample size and its retrospective design. As FMT is a novel treatment option, we only had 35 patients in our study. Due to the size, there may be other confounding factors not considered in this analysis that may be impacting our results. It would be beneficial to include a larger population to see if there is generalizability in our results, especially with the immunocompromised or IBD population. Even with our limited sample size, our cure rate is similar to existing literature, and we were able to find a statistically significant relationship between the hypervirulent strain of CDI and FMT success. Potential future directions of FMT should include following patients for a longer period of time posttransplant to assess the longevity of success as our population only had follow-up of 6–8 weeks post-transplant. In addition, looking further into alternative methods of delivering FMT in the setting of recurrent *C. difficile* would be interesting to determine if one method has more likelihood of success. Finally, the fecal microbiome has been implicated in multiple disease processes, and it may be beneficial to look at larger populations of these patients, such as patients with IBD, and the efficacy of FMT.

We believe the utilization of FMT to treat CDI recurrence will continue to increase given the newest IDSA recommendations and as more studies continue to show the efficacy of FMT. Given the relative novelty of FMT treatment, the long-term consequences of FMT are not readily known.[19] In a 2018 publication examining the long-term effects of FMT treatment in recurrent CDI on average for 3.8 years, they found that patients who had undergone FMT had no statistically significant difference in the new development of autoimmune disease, including IBD, allergies, malignancy, or disease of the nervous system, between patients who had received FMT and those who had not for CDI.[22]

In conclusion, as seen in previous studies, our study demonstrates that FMT is an effective treatment option for those patients with recurrent CDI. Although our population size is small, we were able to demonstrate that FMT was successful 85.7% of the time. As success rates are high, FMT is becoming the standard of care for recurrent CDI. This may have important future implications on antimicrobial stewardship and costs to the health-care system by minimizing the number of times patients are exposed to antibiotics as well as limiting the number of hospitalizations or office visits needed for recurrent CDI.

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