Inpatient and Outpatient Fecal Microbiota Transplant in Pediatric Patients with Clostridium difficile Infections


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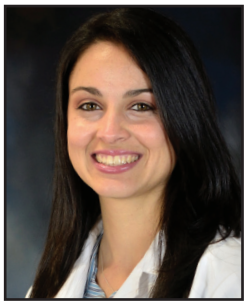
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Objectives: **Fecal microbiota transplant (FMT) has shown a 90% success rate of symptom resolution in adults and pediatric Clostridium difficile infection (CDI). The major aims of this study were to compare the success of inpatient and outpatient FMTs in eradicating CDI and to identify risk factors for failure.**

Methods: **An eight-year retrospective chart review of pediatric FMT to treat CDI in the outpatient or inpatient setting was conducted. Patient demographics and FMT data were extracted.**

Results: **The inpatient (n=19) FMT success rate was significantly higher than the outpatient (n=15) FMT success rate (P=0.018). Significant risk factors for failure were use of a gastrostomy tube versus nasogastric tube as the stool delivery mode (P = 0.034) and having FMT in the outpatient setting (P = 0.027).**

Conclusions: **Inpatient FMT success rate was similar to FMT publications. Most published risk factors for CDI occurrence were not significantly related to CDI recurrence following FMT.**

INTRODUCTION

Clostridium difficile (*C.diff*) is a gram-positive bacteria that produces pathogenic toxins, TcdA and TcdB, and can lead to toxic megacolon, intestinal perforation, and even death.[1-4] The gut is home to over 1,000 different species of bacteria, including *C.diff*. [5] A disruption in the balance between healthy and unhealthy bacteria, commonly linked to antibiotic use, leads C.diff to become pathogenic.[1,4,5] Aside from antibiotic exposure, other risk factors for *C.diff* infection

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Table 1. Patient Characteristics and Risk Factors

Patient Characteristics	Inpatient(n=19)	Outpatient (n=15)	*P*
Mean Age of Diagnosis ± SD	5.1 ± 4.8	6.0 ± 5.5	0.757
Mean Age of FMT ± SD	5.2 ± 4.8	6.0 ± 5.5	0.834
Male (%)	8 (42)	9 (60)	0.300
Race			
White (%)	15 (79)	13 (87)	
African American (%)	4 (21)	1 (7)	0.286
Hispanic (%)	0	1 (7)	
Medicaid (%)	6 (32)	3 (20)	0.461
Risk and Protective Factors			
Presence of a G-tube (%)	3 (16)	9 (60)	0.007*
Inflammatory Bowel Disease (%)	1 (5)	6 (40)	0.013*
Colostomy/ileostomy (%)	0	3 (20)	0.041*
History of Cancer (%)	0	0	-
Non-CDI Treating Antibiotics (%)	8 (42)	3 (20)	0.171
Systemic Immunosuppressants (%)	1 (5)	4 (27)	0.080
Acid Suppression Medications (%)	6 (32)	10 (67)	0.042*
Probiotics (%)	9 (47)	10 (67)	0.261

Abbreviations: SD = Standard Deviation; FMT = Fecal Microbiota Transplant; G-tube = Gastrostomy Tube; CDI = C.*diff* Infection
*Indicates significant findings

(CDI) include malignancy, inflammatory bowel disease, gastrointestinal surgery, acid suppression and presence of a gastrostomy tube (G-tube).[3,6,7]

CDI has recurrence rates of 15%-30% in both adult and pediatric populations.[3,5,6-8] Fecal microbiota transplantation (FMT) studies on adults have found a success rate of around 90%.[9-11] Several pediatric studies involving FMTs have shown CDI symptom resolution similar to the adult population.[6-8,12] These studies have generally been conducted in the outpatient arena and involve a physician.

It is unclear if there would be even higher success rates if pediatric FMTs were conducted in the inpatient setting. Therefore, the primary goals of this study were to evaluate success of FMT in children treated as inpatients compared to the outpatient setting and to identify risk factors for failed FMT treatment. Secondary goals of the study were to compare the number of adverse events and the range of charges for FMT conducted in the two settings.

METHODS

Study Design and Participants

This study is a retrospective chart review of patients within a pediatric gastroenterology outpatient clinic and its affiliated children's hospital in southeastern Louisiana. We included patients between the ages of 1 and 18 diagnosed with CDI (ICD 9 codes 008.45 or ICD 10 codes A04.72) who had an initial FMT treatment between 2012 and 2019. A list was generated of 272 patients who met the age and CDI diagnosis criteria. Forty-five of these patients were treated with an FMT during the study period. For the purposes of this study, we limited data analysis to each patient's first FMT; therefore, 34 patients were included in the final study database.

Procedure notes indicated that FMT typically consisted of 30 milliliters of fresh donor stool

Table 2. Simple Logistic Regression Analysis

Patient Characteristics	OR	95% CI	*P*
Male vs. Female (Referent)	1.354	0.293-6.261	0.698
Other Race vs. Caucasian (Referent)	0.500	0.50-4.978	0.554
Medicade vs. Private Insurance (Referent)	3.200	0.621-16.494	0.164
Outpatient vs. Inpatient (Referent)	7.437	1.25-44.193	0.027*
Risk and Protective Factors			
FMT Delivery Mode GT vs. NG (Referent)	7.500	1.168–8.148	0.034*
Inflammatory Bowel Disease	2.625	0.456–15.112	0.280
Colostomy/ileostomy	1.437	0.114–18.076	0.779
Non-CDI Treating Antibiotics	0.188	0.020–1.739	0.141
Systemic Immunosuppressants	0.656	0.63–6.797	0.724
Acid Suppression Medications	1.591	0.343–7.374	0.553
Hospitalized 12 Weeks Prior	2.656	0.558–12.646	0.220
Probiotics	3.792	0.655–21.961	0.137

Abbreviations: OR = Odds Ratio; CI = Confidence Interval; FMT = Fecal Microbiota Transplant; GT = Gastrostomy Tube; NG = Nasogastric Tube; CDI = C.*diff* Infection
*Indicates significant findings

agitated with 30 milliliters of water that was strained through a sieve and delivered to the patient via G-tubes, nasogastric tubes (NG tubes), enemas, or endoscopies by either a physician, family member, or both (Figure 1). If a feeding pump was used, delivery was set to 30 minutes to avoid intolerance. Transplants done by endoscopy included delivery of stool directly into the duodenum during an esophagogastroduodenoscopy or directly into the ileum and colon during a colonoscopy.

Patient demographics, including gender, ethnicity, age at CDI diagnosis, age at first FMT, relationship of stool donor to the patient, and insurance type were noted. Information on a series of potential risk factors for CDI that might influence FMT success were collected. They included history of inflammatory bowel disease (IBD), presence of an ostomy and/or G-tube, and history of cancer. We also abstracted information from the chart on medications taken within the 30 days leading up to the FMT with a focus on acid suppression medications, immunosuppressant medications, and non-CDI treating antibiotics. Lastly, we gathered information on FMT failure (i.e., recurrence of at least three bowel movements involving diarrhea in a 24-hour period within 12 weeks of FMT), adverse events occurring within 30 days of FMT delivery, and charges associated with the FMT.[6]

The Franciscan Missionaries of Our Lady University institutional review board approved this study as exempt.

Statistical Analyses

We analyzed continuous data using Mann Whitney U and t-tests; frequency counts were analyzed using the Chi Square statistic. These tests and all descriptive analyses were conducted with Graph Pad 5.0. We conducted simple logistic regression analyses to identify risks for FMT failure with SPSS version 23. We considered results to be statistically significant if associated with a *P*-value less than or equal to 0.05.

RESULTS

Description of Patient Sample

As described in Table 1, most of the patients included in our sample were white and had private insurance. Our patients ranged from 1 to 16 years of age, with an average age of 5.5 years.

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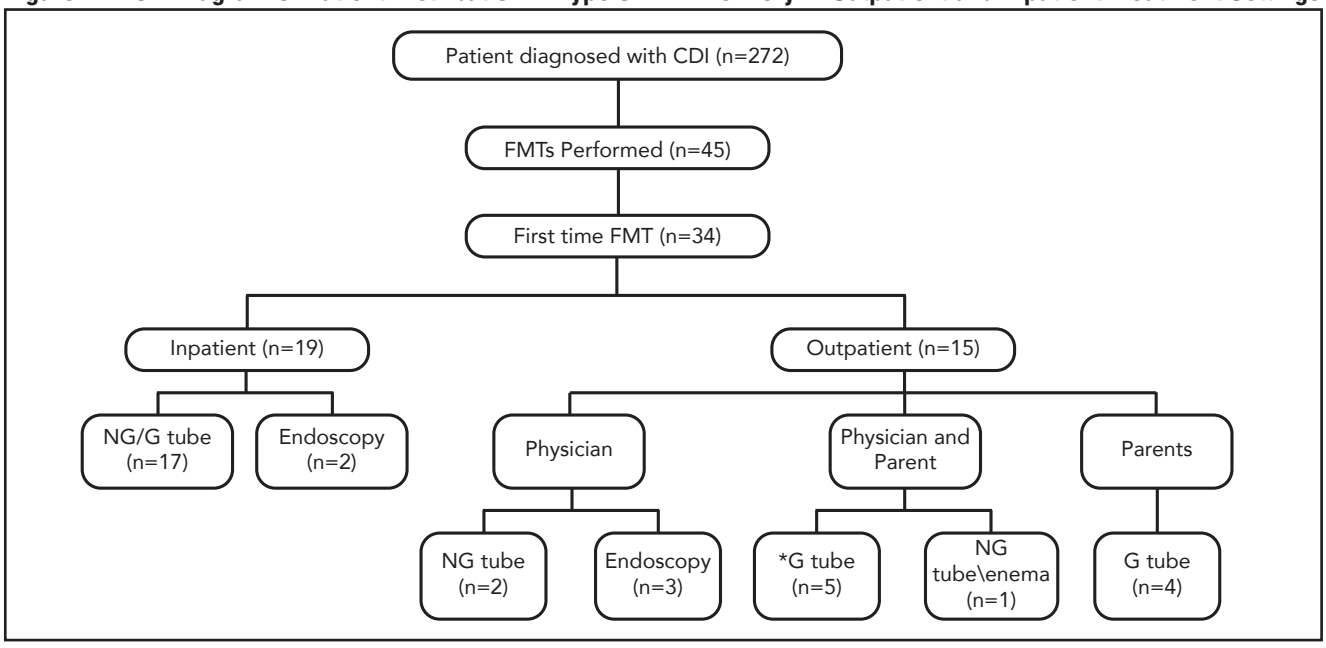
Figure 1. Flow Diagram of Patient Distribution in Type of FMT Delivery in Outpatient and Inpatient Treatment Settings



*There was one patient in this group who received one day of FMT in the hospital and days 2 to 3 completed at home.
Abbreviations: CDI= C.*diff* Infection; FMT= Fecal Microbiota Transplant; NG=Nasogastric Tube; G= Gastrostomy Tube

There were no statistically significant differences between the inpatient and outpatient FMT groups regarding demographic characteristics, including age at diagnosis, age at first FMT, gender, race, and insurance provider.

Description of CDI Diagnosis and FMTs

CDI was most commonly diagnosed using stool polymerase chain reaction (PCR; 79%). Other diagnostic methods used were stool toxin (12%) or visual identification during a colonoscopy (6%). Chart information was missing for CDI diagnostic technique for one patient. Most patients (62%) had an FMT for the third recurrence of CDI after two failed antibiotic attempts.

Nineteen (56%) of the initial FMTs were completed in the inpatient setting and 15 (44%) were completed in the outpatient setting. We defined an inpatient FMT as a hospital admission of three days for FMT transfer and included patients admitted for the sole purpose of FMT via NG tube or G-tube delivery, patients admitted for FMT after endoscopy, and patients admitted for another diagnosis, not CDI, who also had an FMT during the admission. All inpatient FMTs were performed in their entirety by a pediatric gastroenterologist.

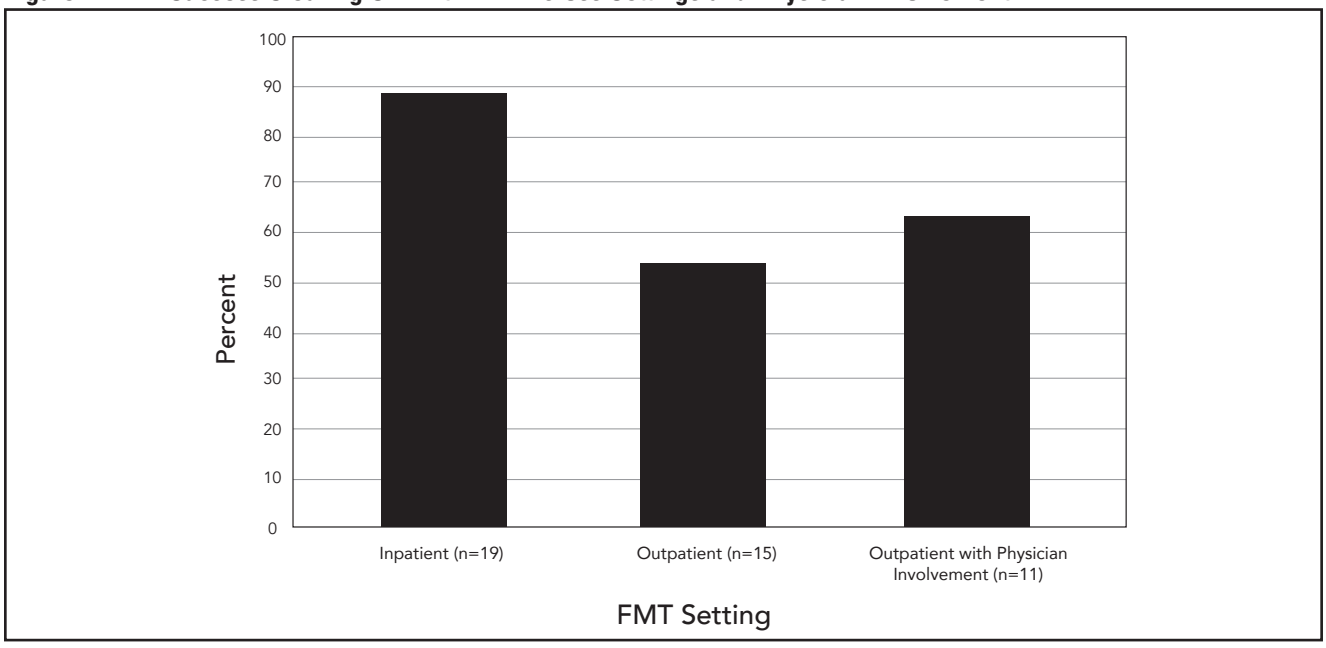
There were three subcategories of FMTs completed in the outpatient setting. One category consisted of FMTs completed exclusively by a physician. These included FMTs involving NG tube insertion in the office and stool transfer over three consecutive days in the office as well as those completed during an outpatient endoscopy. If patients had an FMT during endoscopy, stool was transferred during one day only. The second subcategory consisted of one day of stool transfer by the physician and two days of stool transfer completed by the parents. These patients had stool delivery through a G-tube, NG tube or enema. The third subcategory was comprised of FMTs delivered via G-tube by the patients' parents at home (Figure 1).

All patients received a fresh stool sample from a family member donor, most commonly from a parent (91%). Siblings served as donors for two patients (6%), and a cousin was a donor for one patient (3%). Donors were not screened with stool studies prior to acceptance for transfer; however, each donor was screened clinically by the physician approving the FMT.

Description of Risk and Protective Factors for CDI in the Patient Sample

Among the risk factors identified in the literature, the most common one in our patients was the presence of a G-tube (35%). Twenty-one percent of

Figure 2. FMT Success Clearing CDI with FMT Across Settings and Physician Involvement



Abbreviations: FMT= Fecal Microbiota Transplant; CDI= C.*diff* Infection
*Indicates a significant finding with $P<0.05$

the patients had IBD. Only one patient (3%) had an ileostomy and two patients (6%) had colostomies. None of the included patients had a history of cancer. Three patients (9%) had gastrointestinal surgery other than G-tube or ostomy placement.

Eleven patients (32%) had taken antibiotics for reasons other than *C. diff* treatment during the 30 days before the FMT. Five patients (15%) were on systemic immunosuppressant medications or biologics and sixteen patients (47%) were on acid suppression medication within 30 days of FMT delivery.

The following risk factors were more prevalent among patients in the outpatient vs. inpatient setting: presence of a G-tube ($P = 0.007$), IBD ($P = 0.013$), colostomy/ileostomy ($P = 0.041$), and acid suppression medications ($P = 0.042$). Details comparing the presence of all studied risk factors in the inpatient and outpatient samples are presented in Table 1. When comparing FMT delivery by G-tube vs. NG tube, we found that G-tubes were more often used as the mode of delivery in outpatient FMTs while NG tubes were more often used as the mode of delivery in inpatient FMTs ($P = 0.002$).

We included only one factor in our study, use of probiotics within 30 days before the FMT, which has been identified in the literature as a protective factor against CDI. Overall, 56% of our patients were on probiotics. There was no statistical difference for the percent of patients in the outpatient vs. inpatient setting regarding this protective factor. See Table 1.

Description of FMT Success

Eight (53%) of the 15 patients receiving outpatient FMTs and 17 (89%) of the 19 patients receiving inpatient FMTs were successful at clearing the CDI ($P=0.018$). Of the 15 outpatient FMTs, 11 had some type of physician involvement in their treatment. Seven (64%) of these 11 FMTs were successful at clearing CDI with no recurrence within 12 weeks following FMT.

Logistic Regression Analyses for FMT Failure

Simple logistic regression analyses were conducted using patient characteristics and risk and protective factors as predictors of FMT failure. G-tubes were used as the mode of delivery 100% of the time when they were present. We therefore restricted our simple logistic regression analyses to exclude presence of a G-tube, and instead focused on use of a G-tube as a mode of FMT delivery. We did not compare FMT delivery through colonoscopy with other forms of stool delivery since there were only three FMTs delivered solely through colonoscopy.

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The only significant predictors of FMT failure were the use of a G-tube vs. an NG tube as the stool transfer delivery mode ($P = 0.034$) and conducting the FMT in the outpatient vs. inpatient setting ($P=0.027$). Details are given in Table 2.

Adverse Events and Charges Associated with FMTs

Adverse events were collected for one month after the FMT. Four of the 19 patients from the hospital setting (21%) and four of the 15 patients from the outpatient setting (27%) reported adverse events ($P = 0.421$). These included acute events of abdominal pain, bloating, diarrhea not related to *C. diff.*, and emesis during the FMT delivery. No serious adverse events were reported.

The charges for inpatient and outpatient FMTs were highly variable because of the diverse methods that were used to deliver the transplant. The range of charges in the inpatient setting, which includes charges only for the days during which an FMT was performed, was $2,698 to $9,309. The range for outpatient charges was between $0 for those done exclusively at home using an existing G-tube or enemas and $1,800 for those done using outpatient colonoscopies.

DISCUSSION

It is unclear if an earlier FMT might impact the success or failure of a later FMT. To control for potential biases that might be introduced by subsequent FMTs, the study data set was restricted to patients' first FMT only. For the 19 inpatient FMTs performed, 17 resulted in clearance of CDI, equating to a success rate of 89%. This success rate is similar to that reported in the adult literature.[9-11] Although published data for the pediatric population are limited, outpatient case series and studies have found similar success rates with the use of FMT to treat CDI in pediatric patients.[5,6-8,12] These studies typically involved FMT administration into the lower GI tract by a physician during a colonoscopy.[5,6-8,12] Our study showed a similar success rate of FMT success compared to the published data despite delivering the FMT to the upper GI tract.

In our study, FMTs in the outpatient setting were not as successful at clearing CDI as those conducted in the inpatient setting. The success rate of outpatient FMTs overall was only 53%. However, we also found a significant association between delivery mode and setting. Specifically, G-tubes were used more frequently in the outpatient setting, while NG tubes were used more frequently in the inpatient setting. This study's findings support previous literature that identified a lower FMT success rate with G-tube use.[12] It is possible that our higher failure rates with G-tubes can be explained by the fact that this mode of delivery was typically used by parents administering the FMT. Our study is unable to distinguish if the outpatient failure rate is secondary to the G-tube itself, is due to the medical complexity of patients with G-tubes or is because parents may be less precise than physicians in FMT administration.

Four of the outpatient FMTs were done exclusively at home under the supervision of parents and an additional six FMTs involved the physician conducting one day of the FMT transfer followed by two days of stool transfer by the parents. It is unclear what technique parents employed when preparing and transferring the stool as well as the consistency with which it was used. This may account for the relatively poor success rate in our outpatient setting. When including only patients having an outpatient FMT with some level of physician involvement, outpatient transplants were successful 64% of the time. This is lower than the success rate of inpatient FMTs but higher than the overall success rate of all outpatient FMTs.

Short-term adverse effects associated with FMT and reported in the literature have been minimal and include bloating, abdominal cramping, and diarrhea.5-7,12,13 We likewise found few recorded adverse events among our patients, and those that did occur were consistent with what has been reported in the literature.

Little is known about the long-term effects of FMT on the pediatric gut microbiome.5,12,13 This was not assessed in our study as there are no suggestions for expected effects, how to evaluate them, and the timeframe for such an evaluation.

There are several limitations to our study. First, we had a small sample size of 34 patients. However, this sample size is larger than many of those in previously published case series and is

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one of the largest single-center pediatric studies to date. Studies with a more robust sample size are needed to confirm findings.

A second limitation was the large number of patients who were diagnosed initially with stool PCR (79%), which, while sensitive, may have picked up children with past CDI or colonization.[1,2,13,14] In 2018 the Infectious Disease Society of America published updated guidelines for CDI, including recommending use of the stool toxin for diagnosis.[14] This test was not commonly used in our hospital or the surrounding clinics until after these guidelines were released, accounting for the limited number of patients who were diagnosed by toxin positive stool.

A third limitation was that the study involved a chart review and was confined to information noted in the chart. It is likely that treating physicians had limited information from parents regarding how well and how consistently they performed the FMTs over the course of two or three days. Future studies are needed for FMT use in pediatric patients to determine a successful protocol. In our study, FMTs typically involved three consecutive days of stool transfer. Additional studies with different treatment protocols would help illuminate if the success rate among FMTs delivered for one day is similar to the success rate of FMTs delivered daily for three days. If similar, this would minimize the days of admission, consequently lowering the charges associated with inpatient stays.

Additionally, secondary factors that might impact FMT success should also be studied. These include all concomitant medications at the time of FMT delivery. Because there is no accepted standard protocol for FMT, centers tend to use site-specific protocols for prescribed medications such as loperamide, acid suppression, or antibiotics with varying start and end times around the FMT in order to increase the transplant's likelihood of success.[12,13] Additional studies are needed to determine if these various medications should be included in a pediatric protocol for FMT.

Our data suggest that physician involvement in the FMT, whether administered in the outpatient or inpatient setting, may impact the success of the FMT in clearing the CDI. However, because of our small sample size, more studies need to be conducted to evaluate this conclusion and to identify the best approach to pediatric FMTs. Although the adverse events identified in our study were comparable between the inpatient and outpatient settings, the charge difference between the two settings is large enough to warrant efforts to develop an outpatient protocol. Such a protocol would provide a cost-effective approach to treat recurrent CDI in pediatric patients. ■

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