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Fecal microbiota transplantation for the treatment of recurrent and severe *Clostridium difficile* infection in solid organ transplant recipients: A multicenter experience

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Disclosure

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Abstract

Fecal microbiota transplant (FMT) is recommended for *Clostridium difficile* infection (CDI) treatment, however use in solid organ transplantation (SOT) patients has theoretical safety concerns. This multicenter, retrospective study evaluated FMT safety, effectiveness, and risk factors for failure in SOT patients. Primary cure and overall cure were defined as resolution of diarrhea or negative *C. difficile* stool test after a single FMT or after subsequent FMT(s) ± anti-CDI antibiotics, respectively. 94 SOT patients underwent FMT, 78% for recurrent CDI and 22% for severe or fulminant CDI. FMT-related adverse events (AE) occurred in 22.3% of cases, mainly comprised of self-limiting conditions including nausea, abdominal pain, and FMT-related diarrhea. Severe AEs occurred in 3.2% of cases, with no FMT-related bacteremia. After FMT, 25% of patients with underlying IBD had worsening disease activity, while 14% of CMV seropositive patients had reactivation. At 3 months, primary cure was 58.7%, while overall cure was 91.3% Predictors of failing a single FMT included inpatient status, severe and fulminant CDI, presence of pseudomembranous colitis, and use of non-CDI antibiotics at the time of FMT. These data suggest FMT is safe in SOT patients. However, repeated FMT(s) or additional antibiotics may be needed to optimize rates of cure with FMT.

1. Introduction

The incidence of *Clostridium difficile* infection (CDI) has increased over the past two decades,[1,2] afflicting over 1% of hospitalized patients.[3,4] In patients with a history of solid organ transplantation (SOT), the impact is even more pronounced due to exposure to multiple CDI risk factors including hospitalization, profound immunosuppression, and frequent antibiotic exposure.[5–8] CDI is the most frequent cause of infectious diarrhea in SOT patients, accounting for 11.8% of hospital-onset diarrhea cases.[9] Reported rates are 3–19% in liver, [5,6,10,11] 3.5–16% in kidney,[10–12] 1.5–7.8% in kidney-pancreas,[5,12,13] 9% in small bowel,[10,11] 8–15% in heart,[5,14] and 7–31% in lung transplant recipients,[5,15] with median

onset of CDI at 31.5 days after transplantation.[16] SOT recipients also appear to be at higher risk for recurrent CDI (RCDI), with studies in heart and lung transplant recipients showing 28.6%–33.0% had one or more recurrences.[17] Progression to severe and fulminant CDI afflicts 13.8%–15.8% of SOT patients[7,18] versus 8% of the general population.[19] There is also a higher rate of CDI-related complications in these patients, including 23.1% colectomy, 53.8% mortality, and 30.8% graft loss.[7]

While anti-CDI antibiotics are recommended first line therapy, there are some specific concerns relating to their use in SOT individuals. Metronidazole is no longer recommended by the IDSA/SHEA for CDI treatment due to high rates of failure. Vancomycin resistant enterococcus (VRE) has been commonly documented in immunocompromised patients.[20] Fidaxomicin may be preferred in SOT patients where data demonstrate decreases in recurrent CDI and avoidance of VRE colonization, but its use may be prohibitive in many clinical settings due to cost and availability.[21] Among patients who fail medical management, CDI-related mortality approaches 70–80%,[22,23] and it only improves marginally following colectomy at approximately 50%.[22,24] Immunosuppressive therapy may impair wound healing, thus SOT patients may face additional surgical complications when undergoing colectomy.[25,26] Moreover, surgery often is not even an option for the critically ill patients.[27]

The American College of Gastroenterology (ACG) and the Infectious Disease Society of America (IDSA) both suggest that fecal microbiota transplantation (FMT) for recurrent CDI should be considered following three or more episodes of CDI.[28,29] FMT is superior to traditional anti-CDI therapy at inducing lasting cure. The rate of recurrence in these patients is between 35–65% following a 10-day vancomycin course,[30] 25% after a 10-day treatment with fidaxomicin,[31] while only 5–15% recur after FMT.[32,33] Recent evidence demonstrated that FMT is efficacious in severe and fulminant CDI both for cure[34] and improvement of patient outcomes such as mortality and colectomy rates.[35]

Despite FMT's proven efficacy in treating CDI and promising results from a handful of case-reports,[36–38] the transplant community has been hesitant to embrace FMT in immune compromised patients. Practice guidelines released in 2013 by the American Society of Transplantation,[39] which are now under revision, recommended avoidance of probiotics in SOT patients due to concern for superinfection from such formulations.[40,41] The guidelines also discourage use of FMT in SOT patients given the theoretical risk of translocation of transplanted microbes across gut mucosa, thereby causing bacteremia. A subsequent study of FMT for the treatment of CDI in immunocompromised patients (including 19 SOT patients) revealed no increase in infectious complications or risk of adverse events.[8] Studies of patients with underlying inflammatory bowel disease (IBD), who are also frequently immunosuppressed and have disrupted gut mucosal barrier, have yielded favorable safety outcomes as well.[42] However, up to 25% of patients developed an IBD flare or worsening disease course following gut microbiota transplant.[43]

We aimed to assess safety and efficacy of FMT for the treatment of CDI in patients with SOT and to determine factors predictive of early (in 1 month) and late FMT failure (between 1–3 months) in this population.

2. Materials and Methods

2.1 Study Cohort and Definitions

This multicenter, retrospective study included adult patients (age ≥18 years) with a history of SOT and FMT for the treatment of CDI between May 2012 and February 2017 in 10 academic centers in the US and Canada. Eligible patients were identified through the institutional FMT databases at each site, and data were collected by a standardized 36-item questionnaire distributed to each site. Patient characteristics included age, gender, presence of underlying inflammatory bowel disease (IBD), Charlson comorbidity index,[44] diabetes, renal disease, number of immunosuppressive medications at time of FMT, and history of cytomegalovirus (CMV) infection (a positive CMV IgG). Variables describing SOT included the type of organ transplanted (liver, kidney, heart, lung, pancreas, intestine, stomach, spleen, multi-organ), history of organ re-transplantation, and history of antithymocyte globulin (ATG) exposure.

Clostridium difficile infection was characterized by severity and CDI-related complications in accordance with the 2013 ACG guidelines and 2018 IDSA/SHEA guidelines (definition of fulminant colitis),[28,29] pseudomembranous colitis, number of previous CDI episodes and CDI-related hospitalizations. FMT related data captured time elapsed between SOT and FMT, inpatient status at time of administration, route of administration, type of stool utilized (fresh, frozen, lyophilized), use of non-CDI antibiotics before, after, and during FMT administration.

Adverse events (AE) were defined as any untoward medical occurrence in a patient who received FMT. Any clinically significant changes from the patient's baseline physical exam or laboratory values, complications related to FMT administration, and new events or worsening of pre-existing conditions within 3 months post-FMT were recorded and considered to be AEs. Severe adverse events (SAEs) were defined as death, life threatening events, unplanned hospitalizations, or other important medical events within 3 months of FMT. AEs and SAEs were reviewed and classified as related or unrelated to FMT by the site investigator(s), and by the first (YWC), second (EP) and last author (MF) of the manuscript. Follow-up to determine adverse events after FMT was variable between sites. All sites maintained an FMT database populated by post-FMT nursing phone calls and/or clinic visits at pre-determined intervals per site protocol.

FMT success was defined as complete resolution of diarrhea and/or negative stool *C. difficile* toxin or PCR testing without need for further anti-CDI therapy. Primary cure was defined as achieving FMT success after a single FMT, while overall cure was defined as requiring more than one FMT with or without additional anti-CDI antibiotics (e.g. metronidazole, vancomycin, and fidaxomicin). FMT failure was defined as persistent or recurrent diarrhea after FMT in conjunction with a positive stool test of *C. difficile* by toxin EIA or PCR. FMT failure was sub-classified by time since FMT as early failure (FMT failure within 1 month) and late failure (initial response followed by recurrence of diarrhea between 1–3 months).[45] Self-limited diarrhea following administration of FMT without other suspected underlying etiologies and concurrent laboratory evidence of CDI was considered FMT-related diarrhea.

This study was approved by the Indiana University Institutional Review Board (IRB). The study protocol and data collection form were made available to all participating institutions for institution-specific IRB approval.

2.2 Statistical Analysis

Baseline patient, SOT, CDI, and FMT characteristics were summarized using proportions for categorical variables, median and interquartile ranges (IQR) for skewed continuous variables, and mean and standard deviations (SD) for normally distributed continuous variables. Differences between patients who had FMT success versus FMT failure at 1 and 3 months post-FMT were determined using Fisher's exact test for categorical variables and nonparametric Wilcoxon rank sum for continuous variables.

Risk factors associated with FMT failure to achieve primary cure were identified using multivariable logistic regression. All potential risk factors were included into the model utilizing a forward stepwise selection method to determine the final predictors associated with FMT failure. The cutoff p value of 0.05 was used in the stepwise variable selection procedure to determine when to stop selecting more factors into the model. Because inpatient FMT was correlated with a significant number of variables (including severe CDI, presence of pseudomembranes, presence of prior CDI-related hospitalization, number of prior CDI-related hospitalizations, use of non-CDI antibiotics at FMT, IBD, and diabetes), a secondary analysis was performed with inpatient status excluded from the model. All statistical analyses were performed using SAS version 9.4 (SAS, CARY, NC).

3. Results

3.1 Patient baseline Characteristics

A total of 94 patients were included in the analysis for FMT failure at 1-month, and 92 patients at 3-months after two patients were excluded due to loss of follow up. Patient demographics, clinical variables, and transplant characteristics were not significantly different between patients who had FMT success versus failure outcome at 1 and 3 months. The only exception was mean number of immunosuppressive medications at time of FMT, which was on average higher in the FMT failure group versus FMT success group at both 1 and 3 months (Table 1). Rate of re-transplantation of SOT prior to FMT was marginally higher but not statistically significant in the FMT failure group compared to FMT success at 1 month (11.7% FMT success vs 26.5% FMT failure, p=0.09).

3.2 Characteristics of CDI and FMT

FMT was administered for RCDI in 78% (73/94), while the remaining 22% of patients received FMT for the treatment of severe (15%; 14/94) or fulminant CDI (7%; 7/94) refractory to standard antimicrobial therapy. Among patients with severe or fulminant CDI at the time of FMT, 42.9% (9/21) also met criteria for RCDI (Table 2). The median length of time between SOT and FMT was 21.5 (range 9–95) months, with an average number of four CDI episodes prior to FMT. Almost 60% (53/94) had a prior CDI-related hospitalization. Colonoscopy was the most common route of FMT administration (81.9%, N=77) followed by enema (17%, N=16), while capsule, sigmoidoscopy, and nasojejunal/nasoduodenal

accounted for the remaining methods of FMT delivery. Fourty-one percent (N=38) of FMTs utilized fresh stool, among these 16% (N=15) had a patient-directed donor, while the rest received frozen stool from a stool bank (universal donor).

3.3 FMT Safety

Adverse events possibly related to FMT occurred in 22.3% (21/94) of patients and most frequently consisted of nausea, abdominal pain, abdominal cramping, and/or loose stools (Table 3). In most cases, these events were rated as mild and occurred within the first week of FMT and were self-limited, however there were 3 cases of CMV reactivation after FMT. Among these patients, one developed oral and colonic ulcers after FMT along with a positive CMV viral load 62 days after FMT, however colonic biopsies were more consistent with mycophenolate toxicity. Another patient had persistent diarrhea and fevers post-FMT and was later found to have a positive CMV PCR within 4 weeks of FMT. A third patient who was CMV PCR negative, but IgG positive 4 days prior to FMT also had reactivation within 2 months of receiving FMT. Severe adverse events (SAE) possibly related to FMT occurred in 3.2% (3/94) of patients, and included severe diarrhea requiring hospitalization, acute kidney injury, and/or fever. There were 4 cases of worsening IBD activity (among 16 patients with underlying IBD) after FMT, 2 of which required hospitalization. There were no instances of bacteremia due to FMT.

AE classified as unrelated to FMT occurred in 12.8% (12/94). Severe AEs classified as unrelated to FMT occurred in 27.7% (26/94), including two deaths from multi-organ failure due to persistent CDI despite FMT(s), and a third death from acute respiratory failure after an aspiration event.

3.4 FMT Cure Rates

The primary cure rate following a single FMT was 63.8% (60/94) at 1 month and 58.7% (54/92) at 3 months (Figure 1). Overall cure at 3 months was 91.3% (84/92). For patients that failed a single FMT, 17 had a second FMT, five had a third FMT, and four patients received 4 or more FMTs before cure was achieved. Two patients were lost to follow up after 1 month. Of the eight patients who did not achieve overall cure, two had refractory CDI and was placed on long-term suppressive vancomycin therapy, two underwent colectomy, three died for reasons unrelated to CDI (respiratory failure, multi-system organ failure, septicemia, and hospice referral for bronchiolitis obliterans), and one died of refractory CDI despite three FMTs and additional anti-CDI antibiotics.

Notably, there was a low rate of primary cure at 1 and 3 months for severe and fulminant CDI, with a significant improvement in overall cure after repeat FMT and/or anti-CDI antibiotics (Figure 2).

The majority of FMT failures (89%, N=34/38) occurred early within 1 month of FMT: among these 41% (14/34) did not respond at all or had recurrent diarrhea within 1 week and 56% (19/34) had recurrent symptoms associated with positive stool test between 1 week and 1 month. Only 11% (4/34) had late failure between 1–3 months post procedure.

Patients who failed FMT had higher rates of severe and fulminant CDI, pseudomembranes, stool transplant performed in the inpatient setting, and use of non-CDI antibiotics within 8 weeks post FMT. FMT delivery via colonoscopy was associated with a higher rate of success at 3-month follow-up relative to other delivery methods (91% vs 74%, p=0.04). The median number of CDI-related hospitalizations prior to FMT was significantly higher in patients who had FMT failure at both 1 and 3 months follow-up.

3.5 Predictors of FMT failure

There were multiple risk factors associated with greater risk for FMT failure, including FMT performed in the hospital setting (OR 16.32, 95% CI: 4.32–61.58, p<0.001 at 1 month; OR 12.96, 95% CI: 3.71–45.29, p<0.001 at 3 months), and use of non-CDI antibiotics at time of FMT (OR 4.13, 95% CI: 1.19–14.31, p=0.026 at 1 month; OR 3.5, 95% CI: 1.05–11.66, p=0.041). Compared to frozen stool sourced from a universal donor, FMTs performed with fresh stool from a patient-directed donor were also associated with FMT failure (OR 7.47, 95% CI: 1.53–36.41, p=0.013 at 1 month; OR 6.94, 95% CI: 1.57–30.6, p=0.011 at 3 months).

Further multivariable logistic regression was performed after removing inpatient FMT status due to its correlation with multiple variables. In the secondary analysis, that excluded inpatient status, higher odds of FMT failure was associated with severe or fulminant CDI (OR 4.69, 95% CI: 1.28–17.24, p=0.02 at 1 month; OR 4.97, 95% CI: 1.36–18.17, p=0.015 at 3 months), presence of pseudomembranes at time of FMT (OR 6.76, 95% CI: 1.39–32.82, p=0.018 at 1 month; OR 8.53, 95%CI: 1.56–46.78, p=0.014 at 3 months), and the use of non-CDI antibiotics at time of FMT (OR 3.34, 95% CI: 1.07–10.38, p=0.037 at 1 month). Patients receiving fresh stool FMTs from a patient-directed donor had higher rates of failure compared to FMTs utilizing frozen stool from a universal donor (OR 4.12, 95% CI: 1.15–14.76, p=0.03 at 3 months).

4. Discussion

This multicenter, retrospective, observational study describes safety outcomes, effectiveness, and predictors of failure associated with FMT for the treatment of CDI in SOT recipients. The rate of AEs was low, generally described as self-limiting conditions such as abdominal pain or diarrhea. There were no cases of infectious AEs attributed to FMT. Our data support a 63.8% cure rate at 1 month after first FMT and overall cure rate of 91.3% when including additional FMT(s) and CDI antibiotic treatments. We found that risk factors for FMT failure were similar to studies of non-SOT patients, including inpatient FMT administration, use of non-CDI antibiotics at the time of FMT, severe and fulminant disease, and presence of pseudomembranes.

We found that FMT is a safe option in the SOT population. Both non-serious AEs and SAEs occurred at comparable rates reported in immunocompetent population.[46] Importantly, no infectious complications including bacteremia related to the fecal transplant material were reported. Post-FMT diarrhea was noted in 13.8% (13/94) of cases; 6 were self-limited cases attributed to the FMT itself, while another 7 were due to recurrent CDI. Of the 16 patients with underlying IBD, 4 (25%) had a flare shortly after FMT. Two of these cases required

hospitalization, with a change from adalimumab to infliximab in one patient and escalation from mesalamine to vedolizumab in another. Of the two patients with IBD flare who were not hospitalized, only one required a change in IBD management, going from low-dose prednisone to infliximab initiation. Interestingly, all three cases that resulted in a change in IBD management were Crohn's disease patients, while the IBD flare without hospitalization was UC. Rates of worsening IBD activity after FMT have been reported as high as 25%,[43] though in a recent meta-analysis the rate was only 4.6% when analysis was restricted to randomized controlled trials.[47]

While immediate adverse events were accounted for in this study, late-onset adverse events related to FMT may not have been identified due to the limited follow up. These include transmission of organisms that are not recommended as standard testing for donors by the FMT Working Group, such as CMV, JC virus, and human papillomavirus.[48] The American Gastroenterological Association and the National Institute of Health have announced a joint venture FMT registry to determine long-term safety outcomes,[49] but results of these efforts are not anticipated to be published in the near future. Elevated cancer risk is a well-known complication of SOT,[50] and malignancies related to infections like Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B virus, hepatitis C virus, human herpes virus 8 (HHV8), and *Helicobacter pylori* could potentially be transferred via FMT. Further study of fecal donor screening schema for potential opportunistic infections is needed to optimize safety of FMT for SOT patients.

Transmission of CMV is of particular interest in our population of SOT patients because CMV infection can cause significant infections in SOT patients and induce immunomodulatory effects that can increase the risk of allograft rejection.[51] Twenty-two percent of our study population was CMV IgG seropositive at the time of FMT. Even though none of our study subjects underwent CMV seroconversion within 12 weeks of receiving FMT therapy, the high rate of CMV reactivation among patients who were CMV IgG positive at time of FMT (14%; 3/21) is noteworthy. Alterations in the gut microbiome and the host immune system as a result of FMT could possibly underlie this phenomenon. Decreased levels of CD4 activation have been observed in the jejunum, colon, and rectum of Rhesus macaques 6 weeks post-FMT.[52] CD4 T-cells are needed for the maintenance and promotion of virus-specific CD8 cells that directly suppress CMV and eliminate CMV-infected cells.[53–55] Further studies will be needed to clarify whether routine testing of CMV serostatus and viral load, use of CMV IgG-negative donors, or CMV prophylaxis around the time of FMT should be used where immunocompromised patients are concerned.

The primary cure rate for all SOT patients undergoing FMT for RCDI and severe or fulminant CDI was 63.8% at 1 month and 58.7% at 3 months. These rates of cure are lower in comparison to those reported in immunocompetent patients.[56–58] The primary cure rates for the subgroup of SOT patients undergoing FMT for RCDI were 74% at 1 month, and 69% at 3 months. Only after additional therapy (repeat FMT ± anti-CDI antibiotics) did the RCDI cure rate (94.4%) achieve levels comparable to the 90% success rate in immunocompetent patients.[56,57] SOT patients treated with FMT for severe and fulminant CDI had lower cure rates compared to those treated for RCDI. FMT in severe CDI attained a primary cure rate of 28.6% at 1 month and 3 months, and an overall cure rate of 85.7%, while in fulminant CDI

the primary cure was 28.6% at 1 month and only 14.3% at 3 months, with an overall cure of 71.4%. Recent studies on largely immunocompetent populations of patients with severe and fulminant CDI treated with FMT have suggested cure rates of 66% following a single FMT[59] and overall cure after a sequential FMT protocol of 87%.[34]

The high rate of FMT failure in our study was likely related to increased hospitalization and non-CDI antibiotic use. However, microbiome changes related to immunosuppressive medications in SOT patients likely contribute to CDI and FMT failure as well [60]. Our study demonstrated that compared to the FMT success group, patients with FMT failure had a higher average number of immunosuppressive medications and a higher rate of re-transplantation. More than one FMT may be necessary to correct the profound gut dysbiosis associated with SOT status.[36]

Predictors for FMT failure in SOT patients with CDI found in our study are similar to those in immunocompetent patients. Previous studies reporting on mostly immunocompetent populations found, in agreement with our findings, that inpatient status at time of FMT, presence of pseudomembranes, severe or fulminant CDI, and systemic antibiotic use at the time of FMT were associated with FMT failure.[34,61–63] While pseudomembranous colitis is a marker of severe or fulminant CDI, its presence conferred an additional risk of FMT failure. Among patients with severe or fulminant CDI, FMT failure increased from 60% to 81% in the presence of pseudomembranes. A novel finding is that fresh stool from a patient-directed donor, as opposed to frozen biobanked stool from a universal donor was associated with FMT failure. While this finding contradicts previous publications,[64,65] it is not entirely surprising. It can possibly be explained by the complexities and delays associated with patient-directed donor selection and screening[66] and variable stool preparation methods used at different sites. There may be a theoretical benefit to frozen over fresh stool. Freezing increases the ratio of more beneficial Firmicutes to Bacteroidetes. In a recent metaanalysis, Costello points out that in FMT trials targeting ulcerative colitis, the majority of patients who achieved remission received frozen stool.[67] Timing of FMT failure is similar in SOT patients compared to immunocompetent counterparts. In a previous study of FMT for CDI including 462 patients where 76.5% of the study population was immunocompetent, early FMT failure rate was 18.6% and late failure was 2.7%.[61] Importantly, 89% of failure occurred before 1 month of FMT. The rate of early failure was much higher in our study (36.4%), while late FMT failure was comparable at 4.3%. Nevertheless, vast majority of FMT failures occurred early, during the first month post-FMT. Therefore, we recommend that SOT patients are followed closely in particular within the first month post-procedure and evaluated for FMT failure if symptoms present to allow for prompt rescue therapy.[68]

Overall, a more aggressive approach to treatment of CDI may be warranted in SOT patients. Given the lower primary cure rate in SOT patients, consideration of early and possibly empiric retreatment with FMT ± anti-CDI antimicrobial therapy is advisable particularly in cases of severe or fulminant CDI. A sequential FMT protocol described by Fischer and colleagues[69] has yielded superior cure rates and decreased association with mortality and colectomy in hospitalized patients.[35] In this protocol, presence of pseudomembranes during colonoscopic FMT delivery guides the need for additional therapy after FMT such as re-initiation of vancomycin followed by repeat FMT. SOT patients may need to be evaluated by

alternative criteria because immunosuppressive therapies limit pseudomembrane formation due to suppression of neutrophil cell counts,[70] and decreased capacity for neutrophil extracellular trap (NET) formation.[43]. Thus, reliance on the presence of pseudomembranes to guide the need for further therapy may be less reliable in SOT patients. Optimal timing between repeated FMT treatments for SOT patients will need to be further evaluated.

There are several limitations of this study. While all patients included in our study previously underwent SOT, there was heterogeneity in the type of organ transplanted. This heterogeneity could translate to patient-level and institution-level differences in immunosuppression regimens, frequency of rejection, and time elapsed since SOT. Our multicenter study also allowed for differences between sites in FMT route of delivery, source of stool, and technical proficiency of endoscopists. Further studies will need to focus on efficacy, safety, and patient outcomes after FMT among specific CDI subgroups including patients that have severe CDI, fulminant CDI, and patients who do not respond to FMT-based therapy.

In conclusion, FMT in patients with a history of SOT appears to be a safe and effective treatment for CDI. There were no instances of bacteremia or CMV seroconversion due to FMT observed in our study cohort. However, a significant minority of CMV seropositive patients had reactivation shortly after FMT, a finding that needs further elucidation and should be included in the informed consent process. Rates of cure after a single FMT are much lower for SOT patients with RCDI, severe CDI, and fulminant CDI, but can be improved to levels comparable to immunocompetent patients when additional therapies such as repeat FMT ± anti-CDI antibiotics are subsequently utilized.

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Abbreviations

AE	adverse events
ATG	anti-thymocyte globulin
CDI	*Clostridium difficile* infection
CMV	cytomegalovirus
EBV	Epstein-Barr virus
FMT	fecal microbiota transplantation
HPV	human papillomavirus
IBD	inflammatory bowel disease

IQR	interquartile range
SAE	severe adverse event
SD	standard deviation
SOT	solid organ transplantation
VRE	vancomycin resistant enterococcus

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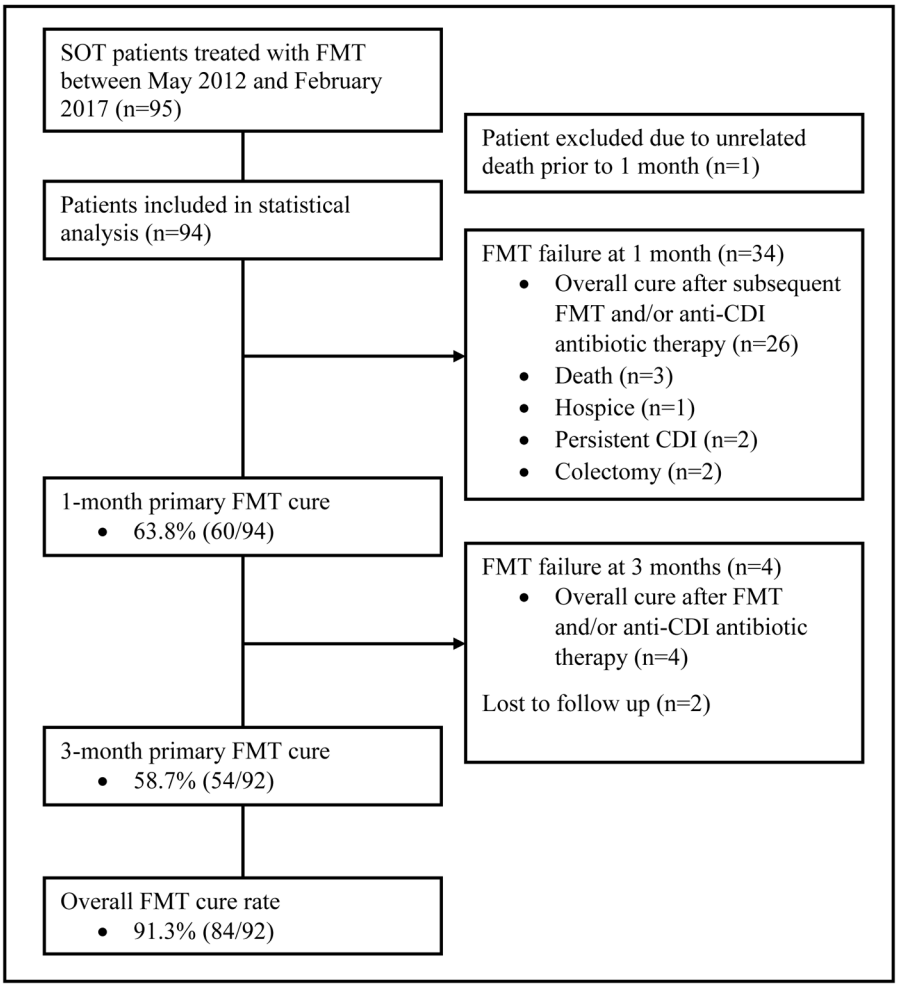

Figure 1.

FMT outcomes at 1 and 3 months follow-up. CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; SOT, solid organ transplantation.

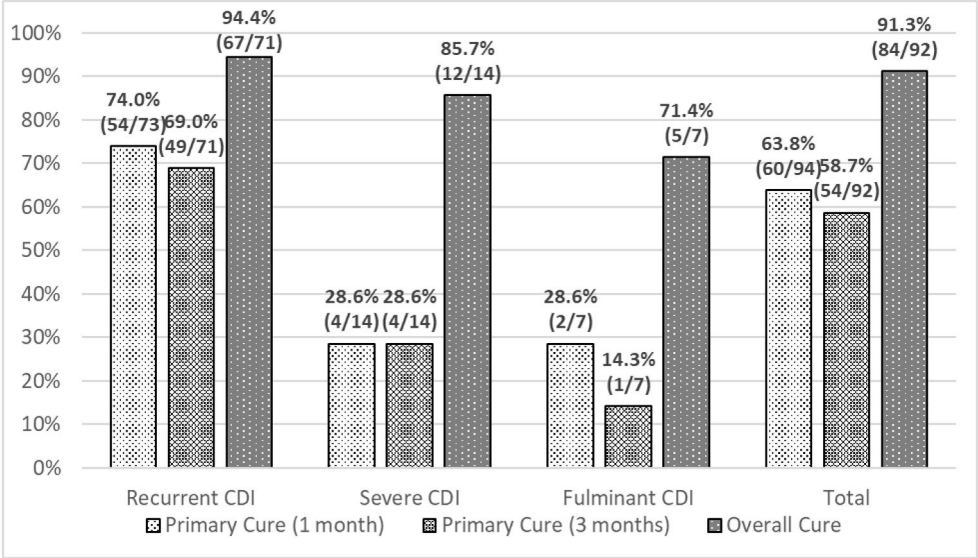

Figure 2.

Primary and Overall Cure Rates for Recurrent, Severe, and Fulminant CDI. CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant.

Table 1

Patient characteristics stratified by 1-month and 3-month FMT outcome.

	FMT outcome at 1 Month				FMT outcome at 3 Months			
	Total (n = 94)	**Success (n = 60)**	**Failure (n = 34)**	**P Value**	**Total (n = 92)**	**Success (n = 54)**	**Failure (n = 38)**	**P Value**
Age, mean (SD)	56.3 (12.2)	56.4 (12.3)	56.3 (12.3)	**0.63**	56.1 (12.2)	56.1 (12.3)	56.2 (12.3)	0.68
Female	47 (50.0%)	29 (48.3%)	18 (52.9%)	0.83	45 (48.9%)	25 (46.3%)	20 (52.6%)	0.67
IBD	16 (17.0%)	12 (20.0%)	4 (11.8%)	0.40	16 (17.4%)	12 (22.2%)	4 (10.5%)	0.17
Charlson comorbidity score, mean (SD)	5.4 (3.0)	5.5 (2.7)	5.2 (3.5)	0.41	5.3 (3)	5.4 (2.7)	5.2 (3.3)	0.7
Diabetes	34 (36.2%)	23 (38.3%)	11 (32.4%)	0.66	33 (35.9%)	18 (33.3%)	15 (39.5%)	0.66
Renal disease	50 (53.2%)	30 (50.0%)	20 (58.8%)	0.52	48 (52.2%)	26 (48.1%)	22 (57.9%)	0.4
CMV infection	21 (22.3%)	11 (18.3%)	10 (29.4%)	0.3	21 (22.8%)	11 (20.4%)	10 (26.3%)	0.62
Antithymocyte globulin	5 (6.0%)	5 (9.1%)	0 (0%)	0.16	5 (6.2%)	5 (10.0%)	0 (0%)	0.15
Multiple organs transplanted	12 (12.8%)	9 (15.0%)	3 (8.8%)	0.53	12 (13.0%)	8 (14.8%)	4 (10.5%)	0.76
Transplanted organs								
Liver	45 (47.9%)	28 (46.7%)	17 (50.0%)	0.83	45 (48.9%)	27 (50.0%)	18 (47.4%)	0.84
Kidney	38 (40.4%)	25 (41.7%)	13 (38.2%)	0.82	36 (39.1%)	21 (38.9%)	15 (39.5%)	1
Heart	8 (8.5%)	7 (11.7%)	1 (2.9%)	0.25	8 (8.7%)	7 (13.0%)	1 (2.6%)	0.13
Lung	9 (9.6%)	4 (6.7%)	5 (14.7%)	0.28	9 (9.8%)	4 (7.4%)	5 (13.2%)	0.48
Pancreas	7 (7.4%)	5 (8.3%)	2 (5.9%)	1	7 (7.6%)	3 (5.6%)	4 (10.5%)	0.44
Intestine	2 (2.1%)	1 (1.7%)	1 (2.9%)	1	2 (2.2%)	1 (1.9%)	1 (2.6%)	1
Stomach	1 (1.1%)	0 (0%)	1 (2.9%)	0.36	1 (1.1%)	0 (0%)	1 (2.6%)	0.41
Spleen	1 (1.1%)	0 (0%)	1 (2.9%)	0.36	1 (1.1%)	0 (0%)	1 (2.6%)	0.41
Re-transplant of solid organ	16 (17.0%)	7 (11.7%)	9 (26.5%)	0.09	16 (17.4%)	7 (13.0%)	9 (23.7%)	0.26
Number of immunosuppressive medications, mean (SD)	2.1 (0.8)	1.9 (0.7)	2.4 (0.9)	0.021	2.1 (0.8)	1.9 (0.7)	2.4 (0.9)	0.005

CMV, cytomegalovirus; IBD, inflammatory bowel disease; SD, standard deviation.

Table 2

Clostridium difficile infection and fecal microbiota transplant characteristics stratified by 1-month and 3-month FMT outcome.

	FMT outcome at 1 Month				FMT outcome at 3 Months			
	Total (n = 94)	**Success (n = 60)**	**Failure (n = 34)**	**P Value**	**Total (n = 92)**	**Success (n = 54)**	**Failure (n = 38)**	**P Value**
Months between SOT and FMT, median (IQR)	21.5 (9 – 95)	18 (11 – 77)	33 (6 – 104)	0.97	19 (9 – 94.5)	16 (10 – 72)	40 (7 – 104)	0.62
Presence of CDI-related hospitalization prior to FMT	53 (60.2%)	30 (53.6%)	23 (71.9%)	0.12	53 (61.6%)	27 (52.9%)	26 (74.3%)	0.07
Number of CDI-related hospitalization prior to FMT, median (IQR)	1 (0 – 2)	1 (0 – 1.5)	1 (0 – 3)	0.041	1 (0 – 2)	1 (0 – 2)	1 (0 – 3)	0.027
Number of CDI episodes prior to FMT, median (IQR)	4 (3 – 5)	4 (3 – 5)	4 (2 – 5)	0.74	4 (3 – 5)	4 (3 – 5)	4 (2 – 5)	0.47
Severe and fulminant CDI	21 (22.3%)	6 (10.0%)	15 (44.1%)	<0.001	21 (22.8%)	5 (9.3%)	16 (42.1%)	<0.001
Presence of pseudomembranes	15 (16.1%)	3 (5.0%)	12 (36.4%)	<0.001	15 (16.5%)	2 (3.7%)	13 (35.1%)	<0.001
Inpatient FMT	29 (31.2%)	10 (16.7%)	19 (57.6%)	<0.001	29 (31.9%)	9 (16.7%)	20 (54.1%)	<0.001
FMT delivered via colonoscopy	77 (81.9%)	51 (85.0%)	26 (76.5%)	0.4	77 (83.7%)	49 (90.7%)	28 (73.7%)	0.044
Use of non-CDI antibiotics at FMT	23 (25.0%)	11 (18.3%)	12 (37.5%)	0.07	23 (25.6%)	10 (18.5%)	13 (36.1%)	0.084
Use of non-CDI antibiotics within 8 weeks post FMT	33 (35.9%)	17 (28.3%)	16 (50.0%)	0.04	33 (36.7%)	14 (25.9%)	19 (52.8%)	0.014
Use of CDI antibiotics in 7 days prior to FMT	88 (94.6%)	55 (93.2%)	33 (97.1%)	0.65	86 (94.5%)	49 (92.5%)	37 (97.4%)	0.4
Donor and stool type				0.47				0.34
Universal donor, frozen stool	55 (59.1%)	38 (63.3%)	17 (51.5%)		55 (60.4%)	36 (66.7%)	19 (51.4%)	
Universal donor, fresh stool	23 (24.7%)	14 (23.3%)	9 (27.3%)		21 (23.1%)	11 (20.4%)	10 (17%)	
Patient directed donor, fresh stool	15 (16.1%)	8 (13.3%)	7 (21.2%)		15 (16.5%)	7 (12.9%)	8 (21.6%)	

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; IQR, interquartile range; SOT, solid organ transplantation.

Table 3

Adverse Events Related and Unrelated to FMT.

	#of patients (N=94)
AE related to FMT	
No	**73**
Yes	**21**
FMT-related diarrhea ± abdominal pain/cramping	9
Abdominal pain/cramping and nausea	6
Miscellaneous (dehydration, fever, rectal prolapse)	3
CMV reactivation	3
AE unrelated to FMT	
No	**82**
Yes	**12**
UTI	3
URI	2
Miscellaneous (diverticulitis, cervical radiculopathy, headaches, failure to thrive requiring TPN, transaminitis, unresolved diarrhea, back pain with myoclonic jerks)	7
Serious AE related to FMT	
No	**91**
Yes	**3**
Hospitalization for Crohn's disease flare	2
Hospitalization for worsening abdominal pain and fever with significant post-hernia surgery seroma hours after FMT	1
Serious AE unrelated to FMT	
No	**68**
Yes	**26**
Hospitalization for non-*C. difficile* infection[a]	7
Hospitalization for RCDI ± AKI	6
Hospitalization for persistent diarrhea and positive *C. difficile*± AKI shortly after FMT	4
Death (2 cases of multi-organ failure from persistent CDI, 1 case of hypoxemic respiratory failure due to aspiration)	3
Organ Rejection	2
Miscellaneous Hospitalizations (Bowel obstruction requiring exploratory laparotomy, bronchiolitis obliterans resulting in hospice enrollment, AKI, and hemiplegia)	4

AE, adverse event; AKI, acute kidney injury; CMV, cytomegalovirus; FMT, fecal microbiota transplant; URI, upper respiratory infection; UTI, urinary tract infection.

[a]Non-*C. difficile* infections included UTI, cholangitis, diverticulitis, liver abscess, pneumonia, unspecified septicemia, and coagulase negative staphylococcus bacteremia.