Title: Fecal Microbiota Transplantation is Safe and Effective in Patients with *Clostridioides difficile* Infection and Cirrhosis

Short Title: FMT for CDI is safe and effective in cirrhosis

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Grant Support:
DK and KW are supported by Alberta Health Services and University of Alberta Hospital Foundation. Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number K23AI144036 to MHW. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

List of Abbreviations: AE, adverse event; CLD, chronic liver disease; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IQR, interquartile range; MELD, model for end-stage liver disease; SAE, severe adverse events; SFCDI, severe or fulminant CDI.

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Conflict of Interest Disclosures: JRA consults for and has research support from Finch Therapeutics. MF serves as consultant for Finch Therapeutics Group and DSMB member for Rebiotix. CSK is on the scientific advisory board for Bio-Rad Laboratories. The remaining authors have no conflicts to disclose.

This is the author's manuscript of the article published in final edited form as:

Cheng, Y.-W., Alhaffar, D., Saha, S., Khanna, S., Bohm, M., Phelps, E., Ghabril, M., Orman, E., Sashidhar, S., Rogers, N., Xu, H., Khoruts, A., Vaughn, B., Kao, D., Wong, K., Cammarota, G., Ianiro, G., Dhere, T., Kraft, C. S., … Fischer, M. (2020). Fecal Microbiota Transplantation is Safe and Effective in Patients with Clostridioides difficile Infection and Cirrhosis. Clinical Gastroenterology and Hepatology. https://doi.org/10.1016/j.cgh.2020.06.051

Writing Assistance: None
Authorship Contributions: YC: study concept and design, data acquisition, analysis, and interpretation of data, drafting of the manuscript, manuscript review; HX: study design, data analysis, interpretation of data, drafting of manuscript, manuscript review; MF: study concept and design, data acquisition, analysis, and interpretation of the data, drafting of the manuscript, manuscript review. DA, SS, SK, MB, EP, MG, EO, SS, NR, AK, BV, DK, KW, GC, GI, TD, CK, NM, MHW, JRA, LN, JM, NE: Data acquisition, study conception, and manuscript review. All authors approved the final version of the article, including the authorship list.

Abstract:

Background & Aims: *Clostridioides difficile* infection (CDI) harms a large proportion of patients with cirrhosis. Fecal microbiota transplantation (FMT) is recommended for recurrent CDI, but its effects in patients with cirrhosis have not been established. We performed a multicenter, observational study to evaluate efficacy and safety of FMT for CDI in patients with cirrhosis.

Methods: We performed a retrospective study of 63 adults with cirrhosis (median model for end-stage liver disease score, 14.5; 24 patients with decompensated cirrhosis) who underwent FMT for CDI from January 2012 through November 2018 at 8 academic centers in the United States, Canada, and Italy. We collected data on patient demographics and characteristics of cirrhosis, CDI, and FMT from medical records and compared differences among patients with different severities of cirrhosis, and FMT successes vs failures at 8 weeks follow up. We also obtained data on adverse events (AE) and severe AEs (SAE) within 12 weeks of FMT.

Results: Patients underwent FMT for recurrent CDI (55/63; 87.3%), severe CDI (6/63; 9.5%), or fulminant CDI (2/63; 3.2%) primarily via colonoscopy (59/63; 93.7%) as outpatients (47/63; 76.8%). FMT success was achieved for 54 patients (85.7%). Among FMT failures, a higher proportion used non-CDI antibiotics at time of FMT (44.4% vs 5.6%; $P<.001$), had Child-Pugh scores of B or C (100% vs 37.7%; $P<.001$), used probiotics (77.8% vs 24.1%, $P=.003$), had pseudomembranes (22.2% vs 0; $P=.018$), and underwent FMT as inpatients (45.5% vs 19%; $P=.039$), compared with FMT successes. In multivariable analysis, use of non-CDI antibiotics at time of FMT (odds ratio, 17.43; 95% CI, 2.00–152.03; $P=.01$) and use of probiotics (odds ratio, 11.9; 95% CI, 1.81–78.3; $P=.01$) were associated with greater risk of FMT failure. FMT-related AEs occurred in 33.3% of patients (21/63)—most were self-limited abdominal cramps or diarrhea. There were only 5 SAEs that were possibly related to FMT; none involved infection or death.

Conclusions: In a retrospective study, we found FMT to be safe and effective for treatment of CDI in patients with cirrhosis.

Key Words: intestinal microbiota, infectious diarrhea, MELD, bacterial infection

KEY WORDS:

Need to Know

Background: Studies are needed to determine outcomes of fecal microbiota transplantation (FMT) for *Clostridioides difficile* infection (CDI) in patients with cirrhosis.

Findings: This retrospective analysis of data from 63 patients with cirrhosis who underwent FMT at 8 centers in 3 countries found that 85.7% were cured of CDI after a single FMT. Severe adverse events related to FMT were rare, and none involved infection or death.

Implications for Patient Care: FMT is a safe and effective therapy for patients with cirrhosis and CDI.

INTRODUCTION

Clostridioides difficile infection (CDI) accounts for nearly 1% of annual hospitalizations nationally.[1] Patients with cirrhosis are at high risk of CDI due to dysbiosis, functional immunosuppression, and frequent antibiotic therapies.[2,3] Hospitalized patients with cirrhosis have double the incidence of CDI and higher rates of CDI-related complications including mortality and length of stay compared to patients without cirrhosis.[4,5]

Fecal microbiota transplantation (FMT) is a recommended treatment option for recurrent CDI (RCDI),[6] while emerging evidence suggests that FMT is also effective in patients with severe and fulminant CDI.[7,8] Unfortunately, the FMT Working Group has recommended against FMT use in patients with decompensated cirrhosis due to a possible increased risk for adverse events (AEs) based on limited evidence.[9] Recently, reports of two immunocompromised patients who developed extended spectrum beta-lactamase (ESBL) E. coli bacteremia traced to a single donor warned of potential harm associated with FMT.[10] Overall, rates of adverse events after FMT are low in multiple studies involving immunocompromised patients[11,12] and patients with cirrhosis who received FMT for hepatic encephalopathy (HE).[13,14] Unfortunately, even in large studies of FMT for CDI, patients with cirrhosis comprise only a small fraction of the study population, limiting the ability to delineate outcomes based on liver disease severity or complications, and liver disease-specific medications.[15]

The aim of our study was to investigate the rate of CDI cure and safety of FMT in a large, international, multi-center cohort of patients with liver cirrhosis.

PATIENTS AND METHODS

Patients

This is a retrospective observational study involving 8 academic centers in the United States, Canada, and Italy. We identified adult patients (age ≥18 years) with cirrhosis who were treated with FMT for CDI between January 2012 and November 2018. We excluded patients with <12 weeks follow-up (n=1) and those with a history of liver transplantation. The study protocol was approved by the institutional review board at each participating center.

Patient demographics and characteristics of cirrhosis, CDI, and FMT were extracted from each site's FMT database and medical record. Patient characteristics included age, gender, race, Charlson comorbidity score,[16] and history of inflammatory bowel disease (IBD). Cirrhosis was characterized by etiology, presence of decompensated disease (ascites, HE, hepatorenal syndrome and/or variceal hemorrhage), history of cirrhosis-related complications (including ascites, hepatic encephalopathy, varices, and variceal hemorrhage), Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, pertinent laboratory values at time of FMT (serum sodium concentration, INR, total bilirubin, platelet count, white blood cell count, serum creatinine concentration), and use of cirrhosis-related medications (lactulose, rifaximin, proton pump inhibitors, prophylactic antibiotics for spontaneous bacterial peritonitis (SBP)).

Characteristics of CDI included its severity, number of CDI episodes prior to FMT, history of and number of CDI-related hospitalizations prior to FMT, non-CDI antibiotic at the time of FMT and within 8 weeks after FMT (which excluded rifaximin and antibiotics used for SBP prophylaxis), probiotic use at time of FMT, and colectomy due to CDI after index FMT. We characterized FMT based on setting of delivery (inpatient versus outpatient), donor type (patient directed versus undirected donor), stool type (fresh, frozen, lyophilized), delivery method (capsule, colonoscopy, percutaneous gastric tube), and presence of pseudomembranous colitis at index FMT.

Adverse events and severe adverse events (SAE) were documented within 12 weeks of FMT. Each academic site proactively followed up with patients via in-person clinic visit and/or telephone call.

Definitions

We classified CDI as recurrent, severe, and/or fulminant as previously described.[6] The diagnosis of CDI was made based on the appropriate clinical symptoms along with a positive CDI test. Four of our sites (accounting for 76.2% of patients) used PCR-based testing for detection of *Clostridioides difficile,* while the other four utilized PCR or glutamate dehydrogenase combined with toxin enzyme immunoassay. FMT success was defined as complete resolution of diarrhea and/or negative stool *C. difficile* toxin or PCR without further need for anti-CDI therapy 8 weeks after a single FMT.[17] FMT failure was defined as persistent or recurrent diarrhea after a single FMT in conjunction with a positive stool test for *C. difficile* by toxin EIA or PCR within 8 weeks of FMT. FMT-related diarrhea was defined as self-limited diarrhea following administration of FMT, typically resolving within 48-72 hours, without other suspected etiologies and without concurrent laboratory evidence of CDI. Immunosuppression was identified in any patient with HIV, AIDS-defining illness, inherited or primary immune disorders, treatment with anti-neoplastic agents, or immunosuppressant medications (including monoclonal antibodies, anti-tumor necrosis factor inhibitors, and antimetabolites).

AEs were defined as any detrimental medical occurrence in a patient who received FMT, including clinically significant changes from the patient's baseline physical exam, laboratory values, or pre-existing conditions. SAEs included any unplanned hospitalizations, life-threatening events, or death. These AEs and SAEs were further classified as related or unrelated by the site investigator(s), and by the first author (YWC).

Statistical Analysis

The baseline patient, cirrhosis, CDI, and FMT characteristics were described using proportions for categorical variables, median and interquartile ranges (IQR) for skewed continuous variables, and mean and standard deviation for normally distributed continuous variables. Comparisons of baseline patient, cirrhosis, CDI, and FMT characteristics for patients with and without FMT failure at 8 weeks were performed using Fisher's exact test for categorical variables, two-sample t-test for normally distributed continuous variables, and Wilcoxon rank sum test for skewed continuous variables.

To determine patient risk factors associated with FMT failure, all baseline characteristics with a p-value < 0.25 were placed in a forward stepwise selection model using logistic regression. Due to the small sample size, Firth's penalized logistic regression was used. Final risk factors included those that were significant at the 0.05 level. All statistical analysis was performed with SAS version 9.4 (SAS, Cary, NC).

RESULTS

Patient and CDI characteristics at baseline

Baseline patient and cirrhosis characteristics of the 63 patients included in our analysis are shown in **Table 1**. The mean age was 62.3 ± 13.2 years, 54% were female and 7.9% were non-Caucasian. The median MELD score was 14.5 (IQR 8.0 – 20.0), and the most common etiologies of cirrhosis were non-alcoholic steatohepatitis (33.3%), alcoholic liver disease (22.2%), hepatitis C (14.3%), and primary sclerosing cholangitis (11.1%). Twenty-four subjects presented with decompensated cirrhosis; among these patients, 36.5% had ascites, 38.1% varices, 11.1% had history of variceal hemorrhage, and 20.6% HE. Some patient were prescribed cirrhosis-related medications at the time of FMT, which included lactulose (15.9%), rifaximin (23.8%) for HE, and antibiotics for SBP prophylaxis (9.5%).

The majority of patients had non-severe CDI and RCDI was the primary indication for FMT (87.3%). Only a fraction of patients had severe CDI (9.5%) or fulminant CDI (3.2%). Complications due to CDI were rare: ileus (3.2%), toxic megacolon (1.6%), and colectomy (1.6%). The median number of prior CDI episodes was 3.0 (IQR 3.0 – 5.0) and the median number of CDI-related hospitalizations prior to FMT was 1.0 (0.0 – 2.0), with 55.6% of patients previously admitted due to CDI.

FMT characteristics

FMT-related characteristics are shown in **Table 2**. The majority of FMTs were performed as outpatient (76.8%), were delivered via colonoscopy (93.7%), used frozen stool (81%), and mainly derived from undirected donor material (39.7% stool bank, 55.6% center-based universal donor program, 4.8% patient-directed donor).

FMT cure rates

The overall rate of FMT success for CDI treatment was 85.7% (54/63) (**Figure 1**), 87.3% (48/55) for recurrent CDI and 75% (6/8) for severe or fulminant CDI. Among the 9 patients who failed the first FMT, five experienced early FMT failure (<4 weeks from FMT), 4/5 were inpatients, and 2/5 had severe CDI. All four of the late FMT failures (>4 weeks from FMT) had RCDI and were treated outpatient. Eight of these nine patients (88.9%) of these patients achieved cure with subsequent FMT(s). Therefore, overall cure was 98.4% (62/63). A single patient with severe CDI and decompensated cirrhosis (MELD 18, Child-Pugh C) received 3 FMTs and was receiving a course of oral vancomycin for RCDI 8 weeks after index FMT.

Upon comparison of FMT success to FMT failures, there were no significant differences in most baseline characteristics, with some notable exceptions including Child Pugh scores, pseudomembranous colitis, use of non-CDI antibiotics, use of probiotics at time of FMT, and inpatient status. Specifically, 37.7% (20/54) of FMT successes and 100% (9/9) of FMT failures had Child-Pugh B/C cirrhosis ($p<0.001$). Pseudomembranous colitis at time of index FMT was observed in 0 patients who had FMT success and in 22.2%(2/9) of FMT failures ($p= 0.018$). Non-CDI antibiotic use at time of FMT was present in 5.6% (3/54) of FMT successes and in 44.4% (4/9) of FMT failures ($p<0.001$), and probiotic had been administered in 24.1% (13/54) of FMT successes and in 77.8% (7/9) of FMT failures ($p= 0.003$). Finally, FMT successes were less likely to receive FMT as inpatients than FMT failures (19.0% vs 45.5%, $p= 0.039$).

Patient characteristics associated with FMT failure

Based on the forward stepwise selection model, two patient characteristics were associated with FMT failure at 8 weeks. The odds of FMT failure for patients who used non-CDI antibiotics at time of FMT was 17.43 times the odds for those who did not use non-CDI antibiotics (95% CI: 2.00-152.03; P =

0.01). The use of probiotics immediately prior to FMT was associated with an approximately 12-fold greater odds of FMT failure (OR=11.9, 95% CI: 1.81-78.3; P=0.01).

Adverse events

Thirty (47.6%) patients had at least one non-severe adverse event (Table 3). AEs related or possibly related to FMT occurred in 30.2% (19/63) of patients, and consisted of abdominal pain/cramping or diarrhea after FMT. An additional 17.5% (11/63) of patients had an AE unrelated to FMT.

The overall rate of SAEs was 17.4% (11/63). Five of these (7.9%) were classified as possibly related to FMT. These included hospitalizations related to a Crohn's flare, fecal urgency, and dehydration with acute kidney injury. The other two events represented hepatic decompensation possibly related to FMT; one patient experienced worsening HE 2 months after FMT while another patient with known PHG was admitted for melena and anemia found related to PHG based on esophagogastroduodenoscopy. The remaining six observed SAEs (9.5%) were not related to FMT.

DISCUSSION

To our knowledge, this is the largest study of cirrhosis patients treated with FMT. In this cohort, FMT had a similar success rate for RCDI and therapy-refractory severe CDI as previously reported in systematic reviews and meta-analyses of non-cirrhotic CDI patients.[15,18,19] Specifically, 87.3% of patients were cured of RCDI, and 75% of severe/fulminant CDI after a single FMT. Among nine patients who failed a single FMT, eight were successfully treated with subsequent FMT(s) ± anti-CDI antibiotic therapy. Our results are similar to a previously reported cure rate of 87% in 14 patients with cirrhosis, however, FMT success in that study was defined as resolution of diarrheal symptoms within 7 days of FMT.[20]

In this series, use of non-CDI antibiotics (which excludes rifaximin and antibiotics for SBP prophylaxis) at time of FMT was associated with FMT failure on multivariable analysis, a finding previously demonstrated in patients without cirrhosis.[15,19,21] SBP prophylaxis did not impact FMT outcome, though the agent used and frequency of administration differed between patients and across sites. Further studies on use of antibiotics for SBP prophylaxis at time of FMT (including class, dosage, and frequency) are needed.

Probiotic use was also implicated as an association to FMT failure in our study. Recent animal and human studies suggested that probiotics may impede spontaneous recovery of the microbiome following antibiotic-induced perturbation and that the ability for probiotic-derived organisms to colonize the colon is highly variable between individuals.[22,23] Moreover, a multi-center study demonstrated that use of probiotics after successful FMT was associated with CDI recurrence.[24] These studies, along with the IDSA guideline's statement that there is insufficient evidence to recommend probiotics for primary prevention of CDI, suggests that probiotics should be avoided in patients with cirrhosis.

On univariate analysis, significantly higher rates of FMT failure were noted in the presence of pseudomembranes on index FMT endoscopy and in patients with a higher Child-Pugh score. The proportion of patients with decompensated cirrhosis in the FMT failure group was also twice that of the FMT success group, though this did not reach significance. Pseudomembranous colitis is a known

surrogate for severe CDI,[25] and has been associated with higher rates of failure after a single FMT.[15] FMT failure was associated with advanced stages of cirrhosis in a study by Pringle and colleagues,[26] in which patients who required more FMT capsules for CDI cure had a higher median MELD score than cirrhotic patients only requiring a single FMT.

The use of FMT in patients with cirrhosis has been controversial given the limited safety data in this population.[9] Patients with cirrhosis frequently have dysbiosis[27] and are at increased risk for translocation of bacteria leading to SBP, HE, and systemic infections.[28-30] Previous studies of FMT for CDI have only included a handful of patients with cirrhosis, therefore specific conclusions about AEs could not be drawn. In a series of four patients with liver cirrhosis, one patient developed E. coli bacteremia 3 days after FMT, while another developed cholangitis and died within 7 days of FMT.[31] The latter patient had a history of recurrent cholangitis and also received FMT via nasogastric tube. In another series, of which 9 patients had cirrhosis, there was no significant worsening of Child-Pugh scores after FMT, though specific data about adverse events was not tabulated.[32] Specific AE data were collected by Bajaj and colleagues in a phase 1, randomized, placebo-controlled trial of FMT for HE.[33] In this study, SAEs (defined as hospitalizations and emergency room visits) occurred in 6/10 patients who received placebo, and only 1/10 patients who received FMT. In a separate study comparing treatment of HE with FMT versus standard of care (SOC; lactulose and add-on rifaximin), long term follow up (>12 months) revealed SAES occurred in 8/8 patients in the SOC arm and 1/9 patients in the FMT arm.[14]

Our study had higher rates of AEs (47.6% vs 26.0%) and SAEs (17.4% vs 9.2%) unrelated to FMT, possibly due to our study's sicker population of patients with underlying cirrhosis. However, rates of FMT-related AEs and SAEs were low in our cohort of cirrhosis patients, including no infections (including SBP) attributed to FMT. The rate of FMT-related AEs was similar in our study (30.2%; 19/63) compared to a previous systematic review consisting of all-comers (28.5%; 310/1089).[34] Notably, there were two SAEs representing hepatic decompensation (bleeding portal hypertensive gastropathy 23 days post-FMT and HE 56 days post-FMT) that were possibly related to FMT. While rates of FMT-related SAEs were comparable among patients with compensated cirrhosis (7.7%; 3/39) and those with

decompensated cirrhosis (8.3%; 2/24), clinicians will need to rigorously weigh the risks and benefits of utilizing FMT in those with severely decompensated cirrhosis. The ability to extrapolate safety results to severely decompensated cirrhotics may be limited as our study contained primarily patients with compensated disease, while the maximum MELD score in our cohort was 31.

There has been significant interest in utilizing FMT to restore both functional and compositional aspects of the gut microbiome to reduce immune dysfunction that may underlie various liver-related diseases and complications.[35] FMT has been effective in improving cognition and dysbiosis in patients with cirrhosis and recurrent hepatic encephalopathy (HE).[13,36] The effects of FMT were also sustained >12 months, with significantly fewer episodes of HE and hospitalizations compared to a group of patients who were not given FMT.[14] With the high rate of infection by multi-drug resistant organisms (MDRO) among patients with cirrhosis,[37,38] and the known potential of microbial transplant to reduce bloodstream infections in patients with CDI,[39] FMT's potential to decrease MDRO colonization and subsequent infection is worth further exploration.[40,41] The low frequency of SAEs observed in this retrospective series supports the safety of the future study of FMT in cirrhotic patients with multiple conditions that are potentially modifiable by FMT.

Our study has a number of limitations. While all of our patients had liver cirrhosis, the etiology of liver disease and associated complications were heterogenous. As a retrospective study, no control group consisting of non-cirrhotic patients was present to assess baseline risk of FMT efficacy and adverse events. The multi-center format of this study also introduced patient-level and institution-level differences in the source of donor stool, technical proficiency of endoscopists, protocol for follow-up after FMT, and subsequent treatment approach after an initial failed FMT. The vast majority of FMTs were administered via colonoscopy, therefore this study is not able to determine safety of FMT via upper GI routes in patients with cirrhosis. Finally, our multivariable analysis to identify patient characteristics associated with FMT failure was limited by our small sample size and even smaller number of patients with FMT failure. It is possible that due to this limitation, factors associated with FMT failure were not identified by our study due to lack of power. We also acknowledge that as a retrospective study, selection bias could

have been introduced while evaluating patients for FMT candidacy due to uncertainty about the role of FMT in those with decompensated cirrhosis. A larger study focusing specifically on those with decompensated cirrhosis is necessary to further analyze this.

Further investigation is needed to determine the optimal route of FMT delivery in patients with cirrhosis. Colonoscopic delivery of FMT was performed in 93.7% of our cohort. Previous experimental studies have demonstrated that bacteria preferentially translocates across the small bowel rather than the colon.[42] Therefore, an upper GI route of FMT delivery could potentially increase the risk of bacterial translocation and associated AEs. Nevertheless, a recent prospective study utilized FMT capsules prepared from a single donor to treat recurrent HE, showed lower hospitalization and mortality rates in the FMT arm without significant safety issues.[33] Rates of FMT cure in a larger cohort of liver cirrhosis patients with severe or fulminant CDI need to be examined. Finally, the long-term effects of FMT on liver-related indices including fibrosis, hepatic decompensation, infections, mortality, and liver transplant candidacy need to be explored.

In conclusion, a single FMT appears effective in the treatment of CDI in patients with cirrhosis. On multivariable analysis, non-CDI antibiotic and probiotic use at time of FMT was associated with FMT failure. Adverse event rates due to FMT in this series were low.

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Table 1. Patient and Cirrhosis Characteristics by FMT Outcome

	Total (n = 63)	FMT outcome at 8 weeks		P Value
		Success (N = 54)	Failure (N = 9)	
Age, mean (sd)	62.3 (13.2)	61.2 (12.7)	69.0 (15.1)	0.1
Female gender	34 (54.0%)	29 (53.7%)	5 (55.6%)	1
Non-Caucasian race	5 (7.9%)	5 (9.3%)	0 (0%)	1
Charlson comorbidity score, mean (sd)	6.7 (2.9)	6.6 (3.0)	7.2 (2.4)	0.54
IBD	10 (15.9%)	10 (18.5%)	0 (0%)	0.33
Chronic dialysis	5 (7.9%)	5 (9.3%)	0 (0%)	1
Immunosuppression	17 (27.0%)	16 (29.6%)	1 (11.1%)	0.42
Etiology of Liver Cirrhosis				0.27
ETOH	14 (22.2%)	13 (24.1%)	1 (11.1%)	
Hepatitis C	9 (14.3%)	9 (16.7%)	0 (0%)	
NASH	21 (33.3%)	16 (29.6%)	5 (55.6%)	
PSC	7 (11.1%)	7 (13.0%)	0 (0%)	
Other	12 (19.0%)	9 (16.7%)	3 (33.3%)	
Decompensated cirrhosis	24 (38.1%)	18 (33.3%)	6 (66.7%)	0.073
History of cirrhosis-related complications				
Ascites	23 (36.5%)	18 (33.3%)	5 (55.6%)	0.27
Hepatic encephalopathy	13 (20.6%)	10 (18.5%)	3 (33.3%)	0.38
Varices	24 (38.1%)	20 (37.0%)	4 (44.4%)	0.72
Variceal hemorrhage	7 (11.1%)	5 (9.3%)	2 (22.2%)	0.26
Child-Pugh Score				<0.001
A	33 (53.2%)	33 (62.3%)	0 (0%)	
B/C	29 (46.8%)	20 (37.7%)	9 (100%)	
MELD Score, median (IQR)	14.5 (8.0 - 20.0)	13.0 (8.0 - 20.0)	18.0 (14.0 - 20.0)	0.17
Serum sodium, median (IQR)	138.0 (135.0 - 140.0)	138.0 (135.0 - 140.0)	138.0 (134.0 - 140.0)	0.64
Serum creatinine, median (IQR)	0.9 (0.7 - 1.6)	0.9 (0.7 - 1.5)	1.5 (0.5 - 3.0)	0.75
White blood count, median (IQR)	5.2 (3.9 - 8.7)	5.0 (4.0 - 7.6)	6.1 (3.4 - 10.0)	0.87
INR, median (IQR)	1.2 (1.1 - 1.4)	1.2 (1.1 - 1.4)	1.3 (1.2 - 1.4)	0.58
Serum total bilirubin (mg/dL), median (IQR)	0.7 (0.5 - 1.0)	0.7 (0.5 - 1.0)	1.0 (0.7 - 2.8)	0.11
Platelet Count, median (IQR)	139.5 (91.0 - 213.0)	138.0 (85.0 - 215.0)	158.0 (126.0 - 172.0)	0.91
Use of cirrhosis-related medications				
Lactulose	10 (15.9%)	8 (14.8%)	2 (22.2%)	0.63
Rifaximin	15 (23.8%)	12 (22.2%)	3 (33.3%)	0.43
SBP prophylaxis	6 (9.5%)	4 (7.4%)	2 (22.2%)	0.2
Indication for FMT				0.42
Recurrent CDI	55 (87.3%)	48 (88.9%)	7 (77.8%)	
Severe CDI	6 (9.5%)	4 (7.4%)	2 (22.2%)	
Fulminant CDI	2 (3.2%)	2 (3.7%)	0 (0%)	
Hypotension	7 (11.1%)	6 (11.1%)	1 (11.1%)	1
Ileus	2 (3.2%)	2 (3.7%)	0 (0%)	1

Toxic megacolon	1 (1.6%)	1 (1.9%)	0 (0%)	1
Colectomy due to CDI	1 (1.6%)	1 (1.9%)	0 (0%)	1
Number of CDI episodes prior to FMT, median (IQR)	3.0 (3.0 - 5.0)	3.0 (3.0 - 5.0)	4.0 (3.0 - 6.0)	0.45
Number of CDI-related hospitalizations prior to FMT, median (IQR)	1.0 (0.0 - 2.0)	1.0 (0.0 - 1.0)	2.0 (1.0 - 2.0)	0.11
CDIFF related hospitalizations prior to FMT	35 (55.6%)	28 (51.9%)	7 (77.8%)	0.28

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IQR, interquartile range; NASH, non-alcoholic steatohepatitis; MELD, model for end-stage liver disease; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; SD, standard deviation.

Table 2. *Clostridioides difficile* Infection and Fecal Microbiota Transplantation Characteristics by FMT Outcome

	Total (n = 63)	FMT outcome at 8 weeks		P Value
		Success (N = 54)	Failure (N = 9)	
Inpatient FMT	16 (23.2%)	11 (19.0%)	5 (45.5%)	0.039
Presence of pseudomembranes at first FMT	2 (3.2%)	0 (0%)	2 (22.2%)	0.018
Donor type				0.67
Patient selected	3 (4.8%)	3 (5.6%)	0 (0%)	
Universal donor	35 (55.6%)	31 (57.4%)	4 (44.4%)	
Stool bank	25 (39.7%)	20 (37.0%)	5 (55.6%)	
Stool type				1
Fresh	11 (17.5%)	10 (18.5%)	1 (11.1%)	
Frozen	51 (81.0%)	43 (79.6%)	8 (88.9%)	
Lyophylized	1 (1.6%)	1 (1.9%)	0 (0%)	
FMT delivery method				0.47
Capsule	3 (4.8%)	2 (3.7%)	1 (11.1%)	
Colonoscopy	59 (93.7%)	51 (94.4%)	8 (88.9%)	
PEG	1 (1.6%)	1 (1.9%)	0 (0%)	
Probiotic use prior to FMT	20 (31.7%)	13 (24.1%)	7 (77.8%)	0.003
Non-CDI antibiotics use at time of FMT	7 (11.1%)	3 (5.6%)	4 (44.4%)	<0.001
CDI antibiotics use in 7 days prior to FMT	44 (69.8%)	38 (70.4%)	6 (66.7%)	1
Non-CDI antibiotics use in 8 weeks post FMT	11 (17.5%)	10 (18.5%)	1 (11.1%)	1

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy.

Table 3. Adverse Events Related and Unrelated to FMT During 12-Week Follow-Up.

	#of patients (N = 63)
AE related to FMT	
No	**44**
Yes (abdominal pain/cramping, N = 10; FMT-related diarrhea (N = 9)	**19**
AE unrelated to FMT	
No	**52**
Yes (chronic diarrhea despite negative CDI testing, N = 4; diarrhea due to underlying Crohn's disease, N = 1; abdominal pain; back pain; cellulitis; fever/chills; anemia; fatigue)	**11**
Serious AE related to FMT	
No	**58**
Yes (hospitalizations for Crohn's disease flare, fecal urgency, AKI/dehydration post-procedure, hepatic encephalopathy, portal hypertensive bleed).	**5**
Serious AE unrelated to FMT	
No	**57**
Yes (transition to hospice; hospitalizations for pneumonia (N = 2), sepsis due to leg cellulitis, recurrent CDI, hyperglycemia).	**6**

Abbreviations: AE, adverse event; AKI, acute kidney injury; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplant; GI, gastrointestinal.