Risk Factors for Gastrointestinal Symptoms Following Successful Eradication of *Clostridium difficile* by Fecal Microbiota Transplantation (FMT)

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Background: Fecal microbiota transplantation (FMT) is a promising therapy for recurrent *Clostridioides difficile* infection (CDI). Many patients report altered bowel habits including constipation, bloating, gas and loose stool post-FMT despite resolution of CDI, and the etiology remains unclear.

Methods: This was a prospective cohort study of adult patients with recurrent CDI who underwent FMT (1) via colonoscopy with patient-selected donor stool, (2) via colonoscopy from a universal stool bank donor, or (3) via capsules from a universal stool bank. Reassessment occurred 8 weeks post-FMT. Those cured were assessed for gastrointestinal symptoms (bloating, loose stools, constipation). Multivariate logistic regression was performed to assess predictors of post-FMT gastrointestinal symptoms.

Results: A total of 150 subjects underwent FMT for recurrent CDI, of which 68.7% (103) were female, mean age was 61.5 years ± 18.1 and 31 patients (20.7%) had preexisting irritable bowel syndrome. Thirty-six had FMT via colonoscopy with a patient-selected donor, 67 via colonoscopy with stool bank donors, and 47 via FMT capsules from stool bank donors. Among those cured, 41 (31.2%) had gastrointestinal symptoms post-FMT. The factors associated with symptoms included younger age (57.2 vs. 64.1 y, $P = 0.03$), a baseline history of irritable bowel syndrome (36.6% vs. 13.3%, $P = 0.002$) and preexisting inflammatory bowel disease (31.7% vs. 10%, $P = 0.002$). Small bowel exposure to donor stool was not related to symptoms (63.4% vs. 62.2%, $P = 0.89$).

Conclusions: Altered bowel habits are a consequence of CDI and are common after FMT. This study suggests that donor type and FMT delivery modality are not related to the presence of irregular gastrointestinal symptoms after FMT.

Key Words: *Clostridium difficile*, fecal microbiota transplantation, irritable bowel syndrome

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BACKGROUND

Clostridium (now *Clostridioides*) *difficile* is a spore-forming organism that colonizes in the human gut. Under the right conditions spore will germinate, release toxin and lead to clinical infection. After an initial infection recurrent disease complicates 20% to 30% of cases.[1,2] Fecal microbiota transplantation (FMT), using either a patient-selected donor or universal stool bank, has emerged as a safe and effective treatment for recurrent *Clostridioides difficile* infection (CDI).[3,4] During FMT, donor material can be delivered in several different ways, most commonly via colonoscopy.[5] However, capsule formulations have emerged as an effective delivery modality as well.[6]

Many patients report gastrointestinal symptoms post-FMT despite resolution of CDI.[4] These symptoms may occur acutely post-FMT or during follow-up, and may include diarrhea, abdominal cramps, constipation, bloating, and excess flatulence.[7] The etiology of these post-FMT symptoms remains unclear. CDI, like other gastrointestinal infections, can lead to postinfectious irritable bowel syndrome (IBS) in up to one-third of patients.[8] Postinfectious IBS, therefore, may account for the post-FMT gastrointestinal symptoms. Other possible causes may include small intestinal bacterial overgrowth, especially when modalities involving small bowel exposure to donor stools such as capsules are used, recurrence or exacerbation of preexisting conditions such as underlying IBS or inflammatory bowel disease (IBD), or development of a new motility or functional gastrointestinal disorder as a result of the FMT.

Pre-FMT factors that may predict development of post-FMT gastrointestinal symptoms are currently unknown. Routine screening of either donors or recipients for any potential risks for post-FMT gastrointestinal symptoms, such as history of IBS or testing for small intestinal bacterial overgrowth, is not routinely performed. Moreover, whether any FMT-related factors, such as donor stool types or delivery modality, predisposes to post-FMT symptoms is also not clear. A better understanding of risk factors for post-FMT gastrointestinal symptoms may help improve management of these patients. In this study, we aimed to evaluate the risk factors associated with development of post-FMT gastrointestinal symptoms, by assessing the relationship between the presence of post-FMT symptoms and (1) FMT characteristics including delivery modality, (2) donor type, and (3) recipient clinical features.

METHODS

This was a prospective cohort study of consecutive adult patients from an academic medical center with recurrent CDI who underwent FMT administered by 1 of 3 modalities: (1) via colonoscopy with patient-selected donor, (2) via colonoscopy from a universal stool bank donor, or (3) via capsules from a

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Z.K. is employed at OpenBiome, a nonprofit stool bank that provides clinicians with preparations for fecal microbiota transplantation and supports research into the human microbiome. The remaining authors declare that they have nothing to disclose.
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universal stool bank. All included subjects completed routine pre-FMT screening to ensure clinical eligibility for FMT. In addition, detailed pre-CDI health and symptom history were obtained for all FMT candidates, including pre-CDI bowel habits and stool characteristics, as measured by Bristol stool scale, as well as conditions such as IBD. Patients felt to be having significant IBD flares were excluded. The presence of baseline IBS was assessed using Rome III criteria. Donor selection, screening for relevant communicable diseases, and stool processing were performed according to standards suggested by the Fecal Microbiota Transplantation Working Group[9] for both patient-selected donors and samples from universal stool bank. The choice of donor type and modality are based mainly on patient preference or hospital policy and practices. All patients discontinued anti-CDI therapy at least 24 to 48 hours before FMT. Subjects undergoing colonoscopy for administering of donor stools also took a standard bowel preparation preprocedure.

All patients were assessed at 8 weeks after FMT for signs of CDI recurrence or FMT failure, which was defined as the presence of diarrhea together with a positive CDI test. Stool enzyme immunoassay tests for *C. difficile* toxins A and B, and polymerase chain reaction for toxin B genes were used for CDI testing in a 2-step approach.[10] The presence of any gastrointestinal symptoms (abdominal pain, bloating, flatulence, loose stools, and constipation) at the time of follow-up was also assessed using a standard intake form. Other data collected for the study included patient demographics, CDI characteristics, and any adverse events.

Statistical Analyses

Univariate analyses were performed using Fisher's exact test for binary variables and student's *t* test for continuous variables. Multivariate logistic regression was performed to identify predictors of post-FMT gastrointestinal symptoms, controlling for potential confounders. All statistical analyses were completed using SAS 9.4 (SAS Institute Inc., Cary, NC). The protocol was approved by the Institutional Review Board (IRB) at Brigham and Women's Hospital.

RESULTS

Overall, 150 subjects underwent FMT for recurrent CDI during the study period (January 2015 to December 2017). Among the cohort, 68.7% (103) were female with a mean age of 61.5 ± 18.1 years. In addition, 36 (24%) patients completed FMT via colonoscopy using patient-selected donor, whereas 67 (45%) underwent colonoscopy with universal stool bank donor and 47 (31%) used FMT capsules from universal stool bank (Table 1). Thirty-one patients (20.7%) had preexisting IBS by Rome III criteria, while 26 (17.3%) had a history of IBD (46% Crohn's and 54% ulcerative colitis). Across all modalities, 19 patients (13.8%) did not achieve cure with one FMT. No serious adverse events were noted in any patients. At the time of testing for CDI eradication, all patients with a history of IBD also provided samples for fecal calprotectin and serum C-reactive protein (CRP), which were all negative.

Among the 131 patients whose CDI was eradicated after 1 FMT, 41(31.3%) noted symptoms of irregular bowel habits at follow-up, including 11 reporting constipation and 27 reporting loose stools. In addition, 21(16%) patients described bloating or increased gas during follow-up visit. On univariate analyses, younger age (57.2 vs. 64.1 y, $P = 0.03$), a baseline history of IBS (36.6% vs. 13.3%, $P = 0.002$) and preexisting IBD (31.7% vs. 10%, $P = 0.002$) were associated with post-FMT gastrointestinal symptoms. For all patients with IBD, CRP and fecal calprotectin were also checked to confirmed that symptoms were not due to an IBD flare. Specifically, donor stool type and administration modality were not associated with post-FMT symptoms, nor did small bowel exposure to donor stool (63.4% vs. 62.2%, $P = 0.89$) (Table 2).

TABLE 1. Patient Characteristics by Donor Type

Patients Characteristics	Patient-directed Donor (N = 36)	Stool Bank Donor (N = 67)	Capsules (N = 47)
Female [n (%)]	28 (80)	43 (64.2)	31 (6.9)
Age (mean ± SD) (y)	55.3 ± 19.5	61.2 ± 17.2	67.4 ± 16.4
IBD [n (%)]	10 (28.6)	16 (23.8)	0 (0)
No. recurrences (mean ± SD)	3.6 ± 1.24	3.07 ± 1.18	3.4 ± 0.77
IBS [n (%)]	8 (22.8)	16 (23.8)	7 (14.8)
FMT failure [n (%)]	3 (8.6)	9 (13.4)	7 (14.9)
BMI (mean ± SD)	25.5 ± 4.8	27.1 ± 8.4	25.8 ± 4.2
Inpatient [n (%)]	3 (8.5)	10 (14.9)	0 (0)
Pre-CDI Bristol (mean ± SD)	4.5 ± 1.09	4.58 ± 1.39	3.85 ± 0.86

BMI indicates body mass index; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

On multivariate analysis, covariates entered into the model were determined a priori with possible risk factors for post-FMT symptoms (Table 3). After adjusting for age, gender, donor type, and small bowel exposure to donor stool, preexisting IBS (odds ratio: 3.95, 95% confidence interval: 1.47-10.6, $P = 0.006$) and history of IBD (odds ratio: 5.37, 95% confidence interval: 1.54-18.6, $P = 0.008$) remained independent predictors for post-FMT gastrointestinal symptoms.

DISCUSSION

FMT is a safe, well-tolerated, and effective therapy for recurrent CDI. However, gastrointestinal symptoms such as

TABLE 2. Clinical Factors Associated With GI Symptoms Post-FMT

Clinical Factors Assessed	GI Symptoms Post-FMT (N = 41)	No Post-GI Symptoms Post-FMT (N = 90)	*P*
Female [n (%)]	26 (63.4)	65 (72.2)	0.31
Age (mean ± SD) (y)	57 .2 ± 16.3	64.1 ± 18.5	0.03
No. recurrences (mean ± SD)	3.1 ± 0.89	3.3 ± 1.02	0.21
IBS [n (%)]	15 (36.6)	12 (13.3)	0.002
IBD [n (%)]	13 (31.7)	9 (10)	0.002
BMI (mean ± SD)	26.3 ± 6.1	25.9 ± 6.2	0.77
Inpatient [n (%)]	1 (2.44)	6 (6.67)	
Capsules [n (%)]	10 (24.4)	30 (33.3)	0.30
Patients directed [n (%)]	11 (26.8)	21 (23.3)	0.66
Stool Bank [n (%)]	20 (48.8)	38 (42.2)	0.48
Pre-CDI Bristol (mean ± SD)	4.3 ± 1.3	4.2 ± 1.2	0.89
TI [n (%)]	26 (63.4)	56 (62.2)	0.89

BMI indicates body mass index; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

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TABLE 3. Multivariate Analysis of Clinical Factors Associated with GI Symptoms Post-FMT

Clinical Factors	Odds Ratio	95% CI	*P*
Female	0.46	0.19-1.12	0.08
Age (y)	0.98	0.96-1.01	0.34
IBS	3.95	1.47-10.6	0.006
IBD	5.37	1.54-18.6	0.008
Donor type	0.94	0.52-1.71	0.83
TI	1	0.36-2.78	0.99
Pre-CDI Bristol	0.73	0.50-1.06	0.76

CDI indicates *Clostridioides difficile* infection; CI, confidence interval; FMT, fecal microbiota transplantation; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

abdominal pain, bloating, and irregular bowel movements have been reported after FMT despite successful eradication of CDI. The etiology and risk factors for development of these post-FMT symptoms remain unclear, although a few possible causes have been speculated, including new-onset or preexisting gastrointestinal disorders such as IBS or IBD, and small bowel exposure to donor stools depending on the FMT technique or modality used.

In our study, almost one-third of patients who underwent FMT for recurrent CDI reported at least 1 gastrointestinal symptom during follow-up despite successful clearance of CDI. Furthermore, we found that patients with preexisting IBS or IBD were at significantly higher risks for development of post-FMT gastrointestinal symptoms, even after controlling for baseline demographics and potential confounders. Specifically, no FMT-related factors, including donor stool type and method of administration, were associated with post-FMT symptoms. The development of these post-FMT symptoms, therefore, appear to depend more on clinical history and characteristics of the recipient, rather than the donor or the administration of the FMT itself, so long as donor selection and stool processing are performed as per currently accepted guidelines.

Prior studies have shown that up to 25% of patients with CDI may develop postinfection IBS,[8] defined by symptoms such as abdominal pain and diarrhea, after clearance of their CDI. The post-FMT symptoms observed in our study may, therefore, at least partly represent postinfection IBS, specifically among those without symptoms or a diagnosis of IBS before FMT (N = 26). Our data also suggest that those already with a history of IBS at baseline are at higher risk of these post-FMT symptoms than those without prior IBS. The post-FMT symptoms in this subgroup of patients likely represent recurrence of their underlying IBS.

Prior studies have demonstrated evidence of altered gut microbiome among IBS patients compared with that in healthy individuals.[11] FMT, therefore, has been suggested as a possible treatment modality for IBS by changing the gut microbiota. However, clinical data on the possible benefit by FMT in treating IBS symptoms remains variable and limited.[12] The largest study published to date by Johnsen et al[13] using a double-blind, randomized, placebo-controlled design in a single center demonstrated a modest benefit by FMT compared with placebo in moderate-to-severe IBS patients (65% vs. 43%, $P = 0.049$) using a validated IBS symptom survey as the primary endpoint. Our data may call into question the potential benefit for FMT in treating IBS, as preexisting IBS was the main, independent risk factor associated with post-FMT gastrointestinal symptoms. However, despite the increase in risk, 15 (55.6%) of the 27 patients with baseline IBS in our cohort developed post-FMT gastrointestinal symptoms, while this is still greater than half not all patients developed symptoms. This suggests that almost half of the preexisting IBS patients were completely asymptomatic from a gastrointestinal standpoint during the 8 weeks following FMT. Although our study was not powered nor designed to assess treatment of preexisting IBS symptoms, our data, which includes one of the largest cohorts of IBS patients published to date, would seem to support a beneficial role for FMT in at least a subset of patients with IBS. Nevertheless, caution should be taken when performing FMT in patients with preexisting IBS with regard to expectations of post-FMT symptom course, as over half of the IBS patients in our cohort did report symptoms during follow-up despite CDI eradication.

Our study also found baseline IBD to be a significant predictor for post-FMT gastrointestinal symptoms. All IBD patients, in the setting of post-FMT symptoms, were ruled out for IBD flare and all included patients had negative inflammatory markers with both fecal calprotectin and serum CRP. Prior studies have found high prevalence of IBS symptoms among IBD patients, including those in biochemical or endoscopic remission.[14] The possible causes of these symptoms in the IBD population remain unclear, with previously proposed contributors including low-level inflammation, changes in epithelial barrier, altered microbiome, psychosocial stress, and dysmotility.[14,15] Interestingly, a recent study by Shutkever et al[16] showed no significant association between fecal microbiome and IBS-type symptoms among patients with IBD in remission. This would suggest that the post-FMT gastrointestinal symptoms observed among IBD patients in our cohort may be more likely due to underlying IBS overlap or postinfection IBS, rather than alteration in microbiome resulting from FMT. Indeed, the increased prevalence of post-FMT symptoms among IBD patients appears to parallel that of the IBS cohort, suggesting possible shared underlying etiology.

Our findings have important clinical implications in the management of FMT patients. Although post-FMT gastrointestinal symptoms are generally benign in nature and controllable pharmacologically, they often pose significant distress to both patients and providers. These post-FMT symptoms not only negatively affect patient quality of life and satisfaction with the FMT, they also often lead to extensive additional tests and procedures. Understanding the factors associated with development of post-FMT gastrointestinal symptoms would help with pre-FMT patient assessment and counseling, as well as development of a logical post-FMT management and monitoring algorithm for these patients.[5] Moreover, the donor stool type and modality of transplant, including small bowel exposure to donor stool, did not seem to affect the development of post-FMT gastrointestinal symptoms. The use of universal donor stools and administration of donor stool capsules orally appear to be both effective and safe, at least from the standpoint of post-FMT symptoms.

There are several limitations to our studies. The selection of FMT modality and donor stool types were nonrandomized, raising possibilities of selection bias. However, no significant effect was observed with regard to methods of FMT and post-FMT symptoms. In addition, post-FMT symptoms were assessed at 8 weeks post-FMT, when eradication of CDI was tested. This did not allow full application of Rome criteria for IBS, as symptoms would have

needed to be present for 3 months with onset at least 6 months before diagnosis for criteria of IBS to be fulfilled. As regards, the presence of symptoms without other identifiable etiologies would strongly suggest a functional cause similar to IBS, especially since preexisting IBS is found to be an independent risk factor. Finally, the severity and control of underlying IBS symptoms or IBD activity before CDI could not be ascertained for all patients, preventing further analysis of the relationship between these underlying conditions and post-FMT symptoms.

In conclusion, FMT is a promising therapy for recurrent CDI. A significant proportion of patients who undergo successful FMT may experience post-FMT gastrointestinal symptoms despite CDI eradication, including abdominal discomfort, bloating, and irregular bowel habits. The etiology of these symptoms remains unclear, but donor stool type and FMT delivery modality do not appear to be related to the presence of symptoms after FMT. Preexisting diagnoses of IBS and IBD are independent predictors of post-FMT symptoms. All patients undergoing FMT should be appropriately evaluated and managed for these conditions in order to provide appropriate counseling post-FMT and to set realistic patient expectations.

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