Characteristics of Fecal Microbiota Transplantation Use in Inflammatory Bowel Disease Cohort

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Background: There is a growing interest in the role of gut bacteria in a number of diseases and an emerging hypothesis that inflammatory bowel disease (IBD) is triggered by microbial dysbiosis in genetically susceptible individuals. Currently, fecal microbiota transplantation (FMT) is utilized for the treatment of *C*lostridium *difficile* colitis. Data on the efficacy of FMT for IBD are mixed, but patients are interested in its use for the treatment of IBD. We sought to describe the use of FMT (self or medical professional administered) in individuals with IBD using IBD Partners, an Internet-based cohort.

Methods: Patients enrolled in the IBD Partners cohort were offered the opportunity to complete an optional survey on the use of FMT between January 2017 to September 2018 (n = 5430). A cross-sectional analysis was performed within patients who completed the survey and did not have a pouch or ostomy. Patients' demographic characteristics, disease activity and phenotype, mode of FMT delivery, and patient-reported efficacy were compared.

Results: Among 3274 eligible patients, 51 (1.6%) responded that they had an FMT in the past. Of patients undergoing FMT, 22 patients had the FMT for *C. difficile* while 29 reported that the FMT was for another indication. Most patients receiving FMT for an indication other than *C. difficile* had ulcerative colitis/indeterminate colitis (25, 86.2%). Colonoscopy (68.2%) and nasogastric tube (18.2%) were the most common routes of administration for patients receiving FMT for *C. difficile* colitis. Self-administration (72.4%) and enemas (17.2%) were the most common routes of administration in patients receiving FMT for an alternate indication. Patients reporting FMT for an indication other than *C. difficile* were less likely to have a physician directing their FMT treatment (20.6%) as compared to patients receiving FMT for *C. difficile* (86.3%). Patient-reported efficacy was lower for FMT given for a non-*C. difficile* indication.

Conclusions: Patients undergoing FMT for an indication other than *C. difficile* infection were more likely to have ulcerative colitis, self-administer FMT, and were less likely to be receiving FMT under the guidance of a medical professional. FMT was not as effective for symptoms when given for a non-*C. difficile* indication. Patients should be counseled on potential harms and lack of proven benefit associated with FMT for IBD indications to try to discourage self-administered FMT without proper medical oversite.

Lay Summary

In a survey-based study of 3247 patients with inflammatory bowel disease, 51 reported having a fecal transplant in the past. Patients were more likely to self-administer the transplant and reported lower response rates if done for an indication other than *C. difficile*.

Key Words: Crohn's disease, ulcerative colitis, inflammatory bowel disease, fecal microbiota transplant

INTRODUCTION

There are over 10^{14} bacterial cells in the human body, most of which are located in the gut. Currently, there is a growing interest in the role of gut bacteria in a variety of diseases. Although the precise etiology of inflammatory bowel disease (IBD) remains unknown, there is an increasing belief that IBD is triggered by the inappropriate activation of the immune system by the intestinal microbiota in genetically susceptible individuals.[1] Microbial dysbiosis is thought to lead to a dysregulation of the balance between beneficial and injurious commensals.[2] Patients with IBD have previously been found to have an abundance of *Enterobacteriaceae* and a paucity of *Faecalibacterium*[3] as well as a significant reduction in the biodiversity of their microbiome. IBD patients were more likely to have been prescribed antibiotics before their diagnosis.[4] This evidence raises the possibility that restoring a balanced microbiome may be of benefit in IBD.

Received for publications November 9, 2019; Editorial Decision January 15, 2020.

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Funding: This research was supported, in part, by grants from the National Institutes of Health (P30 DK034987) and the Crohn's and Colitis Foundation.

Disclosures: C.M.B., R.S.S., and X.Z.: none; M.D.L.: consulting AbbVie, Pfizer, UCB, Salix, Valeant, Takeda, Prometheus, Janssen, and Target PharmaSolutions. Research support: Takeda and Pfizer.

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doi: 10.1093/crocol/otaa024
Published online 18 April 2020

Fecal microbiota transplant (FMT) is the process of administering fecal bacteria from the donor or commercial stool sources to restore microbial diversity. Studies have used various routes of administration including nasoduodenal tube, colonoscopy, enema, and combination of colonoscopy plus enema at various frequencies. FMT was initially developed and studied in *C*lostridium *difficile* infection nonresponsive to antibiotics and has demonstrated efficacy rates of more than 90%.[5] FMT is currently recommended in updated infectious disease and gastroenterology guidelines for refractory *C. difficile*.[6, 7] Given the proposed role of microbial dysbiosis in the pathogenesis of IBD, FMT has also been investigated as a potential treatment for Crohn's disease (CD) and ulcerative colitis (UC).

Despite a paucity of high-quality evidence to support FMT in IBD and a potential for harm, a survey of patients with UC showed that the majority were interested in or willing to consider FMT.[8] Interest in FMT was thought to reflect the perception that FMT was a "natural" treatment for UC. Little is known, however, on the current state of FMT use (including both self and medical professional administered FMT) more broadly in IBD populations. There are unanswered questions regarding types of FMT delivery, stool dosage per infusion, preparation of inoculum, frequency of FMT, indication for FMT (whether for refractory *C. difficile* infection or other uses), FMT donor source, and whether FMT is being done as part of a research study or off-label.

To learn more about the current use of FMT, we used a large online cohort of IBD patients to investigate the use of FMT, mode of administration, and perceived response.

METHODS

Study Design

We performed a cross-sectional analysis of a subset of patients within the Crohn's and Colitis Foundation IBD Partners cohort.

Study Population

IBD Partners is a longitudinal Internet-based cohort of adult patients with IBD established in 2011. Development of this cohort has been previously described in detail.[9] Briefly, patients were recruited to participate in this online cohort registry via email, social media, and Crohn's and Colitis Foundation educational events. More than 15,000 patients with self-reported IBD have enrolled in the cohort since 2011. Participants are given a baseline survey at the time of entry into the study and are invited to complete follow-up surveys every 6 months. Data on demographics, disease subtype, medication use, patient-reported disease activity, and other patient-reported outcomes are collected. In January 2017 an optional, 13-question survey of fecal microbiota transplant was added to baseline and follow-up surveys. Patients were included in the study if they completed the survey. Patients were excluded from the study if they were younger than 18 years of age at the time of the survey. Patients with an ileoanal pouch or ostomy were also excluded from the analysis due to the potential heterogeneity in this group. As dates of FMT were not collected it could not be determined if patients had an FMT before or after pouch or ostomy creation. These patients may have received FMT after surgery for treatment of pouchitis and not IBD, making the data less interpretable.

Study Variables

Demographic data including age, gender, race, and ethnicity were collected. Clinical data included BMI, smoking status, disease phenotype, medication use, and prior hospitalization. Disease activity was assessed using 2 validated patient-reported instruments including the short Crohn's disease activity index (sCDAI) for CD[10] and the simple clinical colitis activity index (sCCAI) for UC.[11]

Statistical Analysis

Bivariate analyses were used to compare demographics, disease activity, medication use, and quality of life between FMT recipients and non-FMT recipients. FMT characteristics and efficacy were compared between FMT recipients for *C.difficile* and FMT recipients for other indication. Categorical variables were compared using chi-square statistics or Fisher's test as appropriate. Continuous variables were compared using *t* tests or Wilcoxon rank-sum test as appropriate. Statistical significance was defined as a *P*-value less than 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Ethical Considerations

The study protocol was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

RESULTS

Among 5430 participants offered the survey between January 2017 and September 2018, 3647 participants completed the survey (67.2% response rate). Excluding patients with an ileoanal pouch or ostomy, 3274 patients were eligible for the analysis. Clinical characteristics of patients completing the FMT survey are summarized in Table 1. There were 51 people who reported a prior FMT. The average age of FMT recipients was 41.7 years old and 74.5% were women; similar to the overall Partners cohort (72% women). There were 31 (60.8%) FMT recipients with UC or indeterminate colitis (IC) versus 36.6% UC/IC in the non-FMT cohort. The average duration of disease was 13.7 years in patients reporting prior FMT. Patient-reported disease activity, as measured by the sCCAI and the sCDAI, was similar between FMT and non-FMT patients.

TABLE 1. Descriptive Statistics of CCFA Partners Who Completed FMT Survey

	Prior FMT (N = 51) n (%)	No FMT (N = 3223) n (%)	*P*
Patient Characteristics			
Age, mean (SD)	41.7 (13.9)	46.1 (15.0)	0.036
Female	38 (74.5)	2319 (72.0)	0.686
Race			
White	47 (92.2)	2882 (89.4)	
Black	0 (0.0)	35 (1.1)	
Other/unknown	4 (7.8)	306 (9.5)	
Ethnicity			
Hispanic	2 (4.1)	77 (2.5)	0.478
BMI kg/m^2, mean (SD)	23.0 (4.3)	25.9 (6.2)	0.001
Current smoker	0 (0)	132 (4.5)	0.149
Clinical Characteristics			
CD	20 (39.2)	2004 (63.4)	<0.001
UC/IC	31 (60.8)	1179 (36.3)	<0.001
Family history of IBD	1 (2.0)	236 (7.4)	0.147
Years of disease, mean (SD)	13.7 (10.7)	16.8 (12.4)	0.068
Prior bowel surgery	36 (70.6)	1901 (59.0)	0.094
IBD hospitalizations	7 (13.7)	1099 (34.1)	0.002
Disease activity, mean (SD)			
sCDAI	161.3 (120.1)	135.5 (88.5)	0.197
SCCAI	3.3 (2.3)	3.0 (2.6)	0.501

FMT recipients were more likely to use rectal steroids (7.4% vs 2.6%, $P = 0.022$), budesonide (11.8% vs 3.6%, $P = 0.002$), and systemic steroids (13.7% vs 5.4%) as compared to non-FMT patients. FMT recipients also reported more current use of probiotics (56.9% vs 29.0%) and lifetime use of probiotics (96.1% vs 65.8%) as compared to non-FMT patients. Use of 5-ASA, immunomodulators, and biologics was not significantly different in FMT recipients (Table 2).

Of patients receiving FMT, 22 reported that the FMT was for *C. difficile* and 29 reported FMT for another indication (Table 3). Most patients receiving FMT for an indication other than *C. difficile* had UC/IC (25, 86.2%). The majority of patients (41, 80.4%) reported that their FMT was more than 1 year before completing the survey. Route of FMT delivery was significantly different in patients receiving FMT for *C. difficile* versus those receiving FMT for an alternate indication. Colonoscopy (68.2%) and nasogastric tube (18.2%) were the most common routes of administration for patients receiving FMT for *C. difficile* colitis. Self-administration (72.4%) and enemas (17.2%) were the most common routes of administration in patients receiving FMT for an alternate indication. Patients reporting FMT for an indication other than *C. difficile* were less likely to have a physician directing their FMT treatment (20.6%) as compared to patients receiving FMT for

TABLE 2. Use of IBD Medications

	IBD Medications Current			IBD Medications Ever		
	Prior FMT (N = 51) n (%)	No FMT (N = 3223) n (%)	*P*	Prior FMT (N = 51) n (%)	No FMT (N = 3223) n (%)	*P*
Rectal steroids	4 (7.8)	89 (2.6)	0.022	28 (54.9)	1194 (37.1)	0.009
Oral/IV steroids	7 (13.7)	173 (5.4)	0.009	47 (92.2)	2700 (83.9)	0.109
Budesonide	6 (11.8)	117 (3.6)	0.002	26 (51.0)	1415 (43.9)	0.315
Antibiotics	1 (2.0)	77 (2.4)	0.841	40 (78.4)	2069 (64.3)	0.036
5-ASA	22 (43.1)	1119 (34.8)	0.213	48 (94.1)	2916 (90.6)	0.390
Immunomodulator	16 (31.4)	831 (25.8)	0.372	37 (72.5)	2093 (65.0)	0.263
Biologic	23 (45.1)	1580	0.568	32 (62.7)	2067 (64.2)	0.831
Probiotic	29 (56.9)	932 (29.0)	<0.001	49 (96.1)	2117 (65.8)	<0.001

TABLE 3. Characteristics of FMT Given in IBD Patients

	FMT for *C. difficile* (N = 22) n (%)	FMT for Other Indication (N = 29) n (%)	*P*
Number of antibiotic courses for *C. difficile* before FMT		—	0.691
2	7 (31.8)		
3–4	9 (40.9)		
≥5	6 (27.3)		
Duration since last FMT			0.685
Within 1 year	5 (22.7)	5 (17.2)	
More than 1 year ago	17 (77.3)	24 (82.8)	
Route of FMT			<0.001
Nasogastric tube	4 (18.2)	0 (0)	
Colonoscopy	15 (68.2)	2 (6.9)	
Enema	0 (0)	5 (17.2)	
Pill/capsule	2 (9.1)	1 (3.4)	
Self-administration	1 (4.5)	21 (72.4)	
Source of FMT	12 (54.5)	25 (86.2)	0.017
Known donor/family member	4 (18.2)	0 (0)	
Commercial source	6 (27.3)	4 (13.8)	
Hospital or clinic source			
FMT as part of a research study	4 (18.2)	3 (10.3)	0.032
Provider directing FMT treatment			<0.001
Primary care provider	1 (4.5)	1 (3.4)	
Gastroenterologist	11 (50.0)	2 (6.9)	
Other physician	7 (31.8)	3 (10.3)	
Other health care provider	1 (4.5)	3 (10.3)	
Self	1 (4.5)	20 (69.0)	
Other		0 (0.0)	

C. difficile (86.3%). Only 7 (13.7%) of all FMTs were done as part of a research study. FMT for an alternative indication was less effective in relieving symptoms as compared to FMT for *C. difficile* infection (Figure 1). Fourteen patients (63.6%) receiving FMT for *C. difficile* infection reported complete relief of symptoms versus 3 patients (10.3%) who reported complete relief of symptoms after FMT for another indication.

DISCUSSION

Here we present a large survey of FMT in a cohort of patients with UC and CD with a 67.2% response rate. Survery nonresponders were 6 years older, had the disease for about 5 more years, and had approximately 5% more hospitalizations and IBD surgery. These differences are likely of little clinical significance and represent a slightly older population with more time to have IBD and complications rather than a sicker population. Overall FMT was rare: only 51 patients (1.6%) reported having a prior FMT at the time of the survey. Patients receiving FMT were more likely to have UC as compared to the general IBD Partners cohort. While this may be explained by the higher rate of *C. difficile* in UC patients compared to CD patients,[12] even the patients having an FMT for a non-*C. difficile* indication were much more likely to have UC (86.2%). This likely reflects the more promising outcomes of FMT for primary UC treatment as compared to CD. Despite similar disease activity indices between FMT recipients and the general cohort, FMT recipients were less likely to report prior IBD hospitalization (13.7% vs 34.1%, $P = 0.002$). FMT recipients were also more likely to use probiotics both currently and in the past. The lack of hospitalization and higher rates of probiotic use may reflect a greater interest in alternative or natural therapies which could be associated with a greater acceptance of fecal microbiota transplantation as a treatment in general.

There have been several prior studies of FMT for IBD, but data have been mixed and studies are often small. To date, there have been 4 randomized controlled trials (RCTs) investigating FMT in UC. Most recently Costello et al[13] investigated steroid-free remission of UC in 73 patients with mild to moderate UC. Pooled donor FMT or autologous FMT was delivered via colonoscopy followed by 2 enemas over 7 days. At 8 weeks, overall steroid-free remission was achieved in 32% of the pooled donor FMT versus 9% in the autologous FMT (odds ratio 5.0, 95% confidence interval 1.2–20.1, $P = 0.03$) and 42% maintained remission at 12 months. However, prior RCTs showed mixed results in UC specifically with nasoduodenal administration.[13–16] Furthermore, while Moayyedi et al[14] showed remission in 24% of patients administered FMT, it was found that 7 of the 9 patients who achieved remission received fecal material from the same donor. Paramsothy et al[17] found that among UC patients, an increased number of infusions (>10) was associated with a higher rate of clinical remission (49% vs 27% in patients receiving ≤10 infusions). Also, lower infusion (colonoscopy or enema) was more effective than upper administrations.

There are currently no RCTs in CD. A recent meta-analysis and systematic review[17] identified 53 studies (41 in UC, 11 in CD, and 4 in pouchitis) of FMT in IBD, most were cohort studies with the exception of the 4 RCTs conducted in UC. Overall remission rates were 36% in UC, 50.5% in CD, and 21.5% in pouchitis patients. Posttransplant microbiota analysis was performed in 24 studies with many identifying increased diversity and a shift toward donor microbiota profile. In addition to low remission rates in IBD, FMT also carries the potential for harm. A recent study of patients receiving FMT for CD was halted early after 2 of the 10 patients had significant decompensations requiring an escalation of IBD therapy.[18]

Patients undergoing FMT for an indication other than *C. difficile* were mostly self-administering their treatment without the oversite of a medical practitioner. One prior study of patient perceptions around FMT for the treatment of UC showed that a majority of patients were willing to consider FMT despite good disease control on conventional therapy.

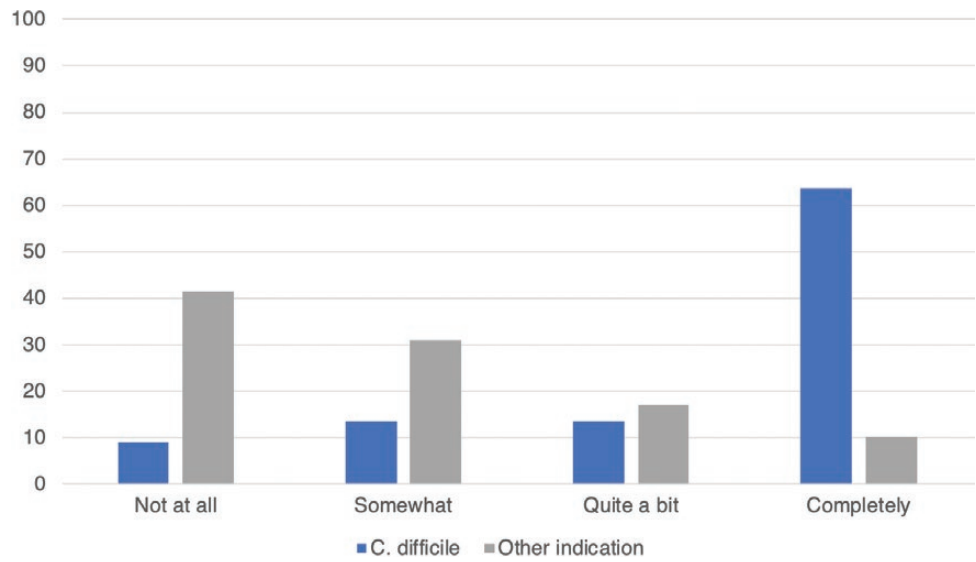

FIGURE 1. Patient-reported effectiveness of FMT on IBD symptoms. Fourteen patients (63.6%) receiving FMT for *C. difficile* infection reported complete relief of symptoms versus 3 patients (10.3%) who reported complete relief of symptoms after FMT for another indication.

This willingness existed in the absence of safety or efficacy data for FMT.[8] Our study confirms that patients are not only willing to consider FMT for treatment but are also engaged in self-directed FMT without the supervision of a clinician. However, patient-perceived efficacy rates for FMT were significantly lower than in those undergoing FMT for *C. difficile*. These findings are particularly concerning in light of a recent FDA-issued safety alert for FMT after 2 episodes of invasive infections by extended-spectrum beta-lactamase-producing *Escherichia coli* and 1 death. These serious adverse events coupled with the potential for IBD flare after FMT should make physicians take pause before recommending FMT as a benign treatment. Furthermore, physicians should warn their patients of these potential harms and discourage patients from performing self-administered FMT without the guidance of a medical professional.

A strength of our study is the large sample size and diverse geographic enrollment in IBD Partners. Additionally, the majority of patients in IBD Partners are treated in a community setting. Therefore, we are able to describe practice patterns outside academic centers. Limitations of the study include the self-reported nature of our survey that may bias efficacy claims or recall of disease severity. However, a prior validation study revealed a 97% accuracy rate of self-reported IBD status and disease subtype within the CCFA Partners cohort.[19] Another limitation of the study is that there were a larger number of women enrolled in the Partners cohort and responding to the FMT survey (74.5%). This may limit the external validity of the study and may not be generalizable due to the self-selection of survey respondents. Additionally, our validated measures of disease activity were not at the time of FMT, we therefore relied on patient perception of efficacy at that time as our endpoint.

CONCLUSIONS

In this cross-sectional study of patients with IBD, there were only 51 (1.6%) who reported having prior FMT. Twenty-two patients underwent FMT for *C. difficile* infection while the remaining underwent FMT of another indication. Patients undergoing FMT for an indication other than *C. difficile* infection were more likely to have UC, self-administer FMT, and were less likely to be receiving FMT under the guidance of a medical professional. FMT was not as effective for symptoms when given for a non-*C. difficile* indication. Although FMT in IBD patients is rare, there is increasing interest in the role of the microbiome and the use of FMT for several chronic diseases. FMT is also increasingly reported in the media. Patients should be warned of potential risks (including death) and lack of proven efficacy associated with FMT for IBD to try to discourage self-administered FMT without proper medical oversite.

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