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Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection

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Abstract

BACKGROUND & AIMS—A significant fraction of patients with recurrent *Clostridium difficile* infections (CDI) have inflammatory bowel disease (IBD). Fecal microbiota transplantation (FMT) can break the cycle of CDI recurrence and can be performed without evaluation of the colon. We evaluated the efficacy of colonoscopic FMT in patients with and without IBD, and whether we could identify IBD in patients during this procedure.

METHODS—We collected clinical meta-data and colonoscopy results from 272 consecutive patients that underwent FMT for recurrent CDI at the University of Minnesota from 2008 through 2015. Patients had at least 2 spontaneous relapses of CDI following their initial episode and did not clear the infection after 1 extended antibiotic regimen. We collected random mucosal biopsies from patients' right colons to identify lymphocytic or collagenous colitis during the FMT procedure. Failure or success in clearing CDI was determined within or at 2 months after the FMT.

RESULTS—Of patients undergoing FMT, 15% had established IBD and 2.6% were found to have IBD during the FMT procedure. A single colonoscopic FMT cleared CDI from 74.4% of patients with IBD and 92.1% of patients without IBD ($P = .0018$). Patients had similar responses to FMT regardless of immunosuppressive therapy. More than one-quarter of patients with IBD (25.6%) had a clinically significant flare of IBD after FMT. Lymphocytic colitis was documented in 7.4% of patients with endoscopically normal colon mucosa; only 3 of these patients (20%) required additional treatment for colitis after clearance of CDI.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.02.018.

Conflicts of interest

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CONCLUSIONS—Based on an analysis of 272 patients, FMT is somewhat less effective in clearing recurrent CDI from patients with IBD, compared with patients without IBD, regardless of immunosuppressive therapy. More than 25% of patients with IBD have a disease flare following FMT. Lymphocytic colitis did not affect the outcome of FMT, but a small fraction of these patients required pharmacologic treatment after the procedure.

Keywords

Clostridium Difficile; Complication; Crohn's Disease; Ulcerative Colitis

Fecal microbiota transplantation (FMT) has emerged over the past decade as a highly effective rescue therapy in treatment of recurrent *Clostridium difficile* infection (RCDI) syndrome.[1] Unlike standard antibiotic treatments, which exacerbate and perpetuate gut dysbiosis that leads to *C difficile* infection (CDI) in the first place, FMT restores the normal microbial community structure and function in the gut.[2–4]

An important subpopulation of patients with RCDI has underlying inflammatory bowel diseases (IBD), which can independently contribute to gut dysbiosis.[5] Patients with Crohn's disease (CD) and ulcerative colitis (UC) have increased incidence of CDI, and presence of CDI commonly complicates the course of these underlying diseases.[6] Less is known about the interplay between CDI and microscopic colitis, but both conditions disproportionately target older women.[7,8] Therefore, prevalence of different IBDs is likely increased in the RCDI patient population. However, only limited information exists on the relevance of these diagnoses with respect to the outcomes of FMT, including success rate in clearing the infection and the effects of the procedure on the activity of the underlying IBD.

Our program has offered FMT to patients with RCDI since 2008, until recently exclusively via colonoscopy, which served as both a diagnostic procedure and a means of introducing the microbiota suspension. A significant minority of patients had underlying IBD and we compared the outcomes of colonoscopic FMT in these patients with those in the non-IBD population.

Methods

Study Design

All potential participants for FMT underwent a standardized screening process that included information about initial CDI trigger, concurrent medical and surgical history, medications, and previous therapies tried. This clinical metadata, results of the colonoscopies, and clinical outcomes at 2 months following the procedure were prospectively collected. Additional clinical data beyond 2 months were extracted from retrospective chart review. The patients were treated at a single medical center, the University of Minnesota. The study was approved by the University of Minnesota Institutional Review Board.

Patient Population

Patients were offered FMT in our program if they satisfied the following inclusion criteria: (1) informed consent, (2) documentation of at least 2 spontaneous relapses of CDI following

the initial episode of the infection, (3) failure of at least 1 extended antibiotic regimen to clear the infection, (4) documentation of CDI by stool testing within 2 months of FMT. Spontaneous relapse of CDI was defined as recurrence within 3 months of discontinuation of anti-CDI antibiotic treatment in conjunction with diarrheal symptoms and absence of exposure to another antibiotic given for a non-CDI indication. Extended antibiotic regimens were defined as treatment given over a period of 6 weeks or longer. The most common such regimen was vancomycin pulse/taper. Other extended regimens included sequential combinations of vancomycin, rifaximin, and fidaxomicin. Exceptions to the requirement for multiple spontaneous recurrences and an extended antibiotic course could be made if the patient was admitted to the intensive care unit for both the initial episode and first spontaneous recurrence because of complications of CDI. Exclusion criteria included anticipation of non-CDI antibiotic treatment within 3 months of FMT; and life expectancy of less than 2 years if the patient was able to tolerate suppressive therapy with vancomycin, 125 mg daily. This cohort does not include patients that received FMT for acute, severe, and complicated CDI, refractory to antibiotic therapy.

Patients treated in our center came primarily from the Minneapolis and St. Paul metropolitan area, greater Minnesota, and nearby Midwestern states. Most patients were referred by community infectious disease or gastroenterology specialists. A smaller fraction of patients was self-referred.

Fecal Microbiota Transplantation Procedure

Patients were treated with vancomycin (125 mg orally, 4 times daily) or fidaxomicin (200 mg orally, twice daily) for at least 10 days leading up to the FMT and discontinued 2 days before the procedure. All patients took their colonoscopy purgative preparation the day before the procedure. Fecal microbiota was delivered as a liquid suspension via the biopsy channel of the colonoscope into the terminal ileum or cecum. Freshly prepared material was used in the early phases of our program, which was then switched exclusively to use of frozen/thawed, standardized material as described previously.[9] Random mucosal biopsies were performed routinely in the right colon to evaluate for possible underlying lymphocytic or collagenous colitis during the FMT colonoscopy.

Clinical Outcomes

Patients were seen in follow-up at 2 months following the FMT. In the interim period they were instructed to contact the clinic via telephone or e-mail with any questions or concerns. The patients were also encouraged to contact the clinic with any concerns indefinitely after the 2-month follow-up, especially when antibiotics were being prescribed for any indication. The relapse of CDI, or FMT failure, was defined as diarrhea (>3 loose bowel movements over a 24-hour period) and laboratory confirmation of *C difficile* in stool within the 2-month period. Stool testing was not done within the first week following FMT regardless of symptoms.

Statistical Analysis

Noncategorical data were compared using unpaired Student *t* test. Categorical data were compared using Fisher exact test. GraphPad Prism software (La Jolla, CA) was used to

calculate 2-tailed and 2-sided *P* values with each test, respectively. Multiple logistic regression was used to explore for predictors of CDI relapse following FMT. First-order interactions were assessed for and included in the model if the interaction was significant. Reverse stepwise regression was used to determine the optimal model, with age and gender being included in the final model a priori. All regression was performed using R (version 3.2.1).

Results

Patient Population

We treated 272 patients for refractory RCDI syndrome using colonoscopic FMT (Table 1). The patients in this cohort had minimal chances of breaking the cycle of CDI recurrence with any antibiotic used in clinical practice today given the strict inclusion and exclusion criteria maintained in our program. The mean duration of RCDI treatment since the initial episode was close to 1 year, and we approximate 5 spontaneous relapses in an average patient in this cohort based on the number of CDI therapies prescribed by referring physicians. Almost a third of our patients were hospitalized at least once for treatment of a CDI episode. Intercurrent antibiotics given for non-CDI indications added to the total antibiotic burden in one-quarter of patients. A routine question about fecal incontinence during the course of RCDI was introduced over the last 18 months of data collection for this cohort, and 76% admitted to history of “accidents,” wearing diapers or pads, and carrying spare underwear.

Presence of Inflammatory Bowel Disease at the Time of Fecal Microbiota Transplantation

CD or UC were noted in 43 patients, of which 6 were de novo diagnoses (Table 2). Notably, 3 out of 6 newly diagnosed patients had prior recent negative colonoscopic evaluations, which failed to examine the terminal ileum. The specific diagnosis of pre-existing CD disease versus UC was changed in 6 patients based on the FMT colonoscopy and no evidence of either disease was found in 4 patients who carried a diagnosis of IBD at the time of their initial clinical evaluation. Most patients (4 of 6) with newly diagnosed CD or UC received IBD-specific therapy after clearing CDI in long-term follow-up, including mesalamine, corticosteroids, and azathioprine.

Random mucosal biopsies were performed in 204 of 229 patients with normal mucosa by endoscopic criteria (Table 2); the main reason for omitting biopsies in some patients was concurrent anticoagulation therapy. Mild, nonspecific abnormalities were noted in 29 of 204 patients; the findings included mild architectural distortion of the epithelium, mild lymphocytic infiltration in the lamina propria, and focal increase in intraepithelial lymphocytes. These findings most likely represent mucosal healing responses from relatively recent CDI; by protocol the patients have completed a minimum of a 10-day course of antibiotic therapy before FMT. However, 15 patients (7.4%) were found to have lymphocytic colitis, newly diagnosed in 14 of 15; 3 of these patients received treatment specifically for lymphocytic colitis with budesonide after clearing CDI. Interestingly, most patients with lymphocytic colitis did not require additional medical therapy and normalized their bowel function after a single FMT. One patient with lymphocytic failed to clear CDI

after 3 FMTs, but remains under excellent symptomatic control with suppressive 125-mg daily dose of vancomycin.

Clinical Characteristics of Patients With Inflammatory Bowel Disease Versus Without Inflammatory Bowel Disease With Recurrent Clostridium Difficile Infection

Patients with underlying IBD were significantly younger than the other patients in the cohort (Table 3). Interestingly, although female sex was more common in patients without IBD, the sex ratio was approximately equal in the IBD population. Gastrointestinal symptoms did not easily distinguish patients with and without IBD, because both populations had diarrheal symptoms during evaluation conducted while the patients were taking antibiotics that suppressed CDI. Both patient groups reported increased frequency and looser consistency of stools compared with their baseline or normal, although the symptoms were generally more profound in patients with IBD. Absence of a clear history of antibiotic exposure that could be linked to the initial CDI episode was more common in patients with IBD, but the difference did not reach statistical significance. Both groups admitted to remarkably high incidence of fecal incontinence since the initial CDI diagnosis, 85% and 74% for IBD and non-IBD groups, respectively.

Outcome of Fecal Microbiota Transplantation in Patients With Underlying Inflammatory Bowel Disease

FMT was ultimately largely successful in clearing CDI in both IBD and non-IBD patient populations. However, clearance of CDI was somewhat less effective with a single FMT in patients with underlying IBD compared with those without IBD (74.4% vs 92.1%; $P = .0018$). The type of IBD (CD vs UC), severity, or the degree of immunosuppression did not correlate with success or failure of FMT (Supplementary Table 1). The success rate in clearing CDI with 2 or more FMTs increased to 82.9% in patients with IBD, and 98.7% in patients without IBD. Notably, 3 patients with IBD technically counted as successes in clearing CDI within the initial 2 months of FMT, but had later spontaneous relapse of CDI without any antibiotic provocation within 6 months of further follow-up. Immunosuppression by itself was an unlikely reason for the inability to sustain the benefit of FMT in patients with CD and UC because our cohort also included 8 solid organ recipients, only 1 of whom failed to clear CDI with 1 FMT. In addition, 30 patients in the non-IBD cohort were receiving significant immunosuppression with biologics (anti-tumor necrosis factor drugs, rituximab), immunomodulators (methotrexate and purine analogs), and corticosteroids for various forms of autoimmunity, and all cleared CDI with just 1 FMT. In contrast, 6 of 11 (54.5%) of patients with IBD who failed to clear CDI with their first FMT were taking no immunosuppressive drugs at all or mesalamine only. Other clinical factors, such as age, sex, use of proton pump inhibitors, or history of hospitalization for CDI, also did not correlate with CDI recurrence following FMT on univariate analysis (Supplementary Table 1). After multiple logistic regression, IBD remained the only significant predictor in the final model (Table 4).

Another problem unique to the IBD population treated with FMT is the possibility of a flare of IBD activity despite clearing CDI. In our cohort an FMT-related flare was diagnosed in 11 of 43 (25.6%) patients (Supplementary Table 2), and 13 of 43 patients received treatment

with prednisone after FMT; the severity of underlying IBD noted during the FMT colonoscopy was the indication for prednisone in 2 patients. IBD pancolitis was present in 7 of 11 (63.6%) patients who suffered an FMT-related flare of IBD activity; 4 of 11 (36.4%) flare patients had left-sided active colitis at the time of the FMT colonoscopy. Two patients were hospitalized with IBD flare within 2 months of FMT. Clearance of CDI by FMT generally was associated with improved control of IBD over the long-term. However, 6 patients continued to struggle with IBD despite optimization of their immunosuppressive therapies, and 3 of these patients underwent colectomies. It is possible that these patients were merely colonized with *C difficile*, and its presence was not the main driver of their IBD activity.

Discussion

Presence of underlying IBD is an important consideration in treatment of patients with RCDI, including their care following FMT. We determined that IBD is a significant risk factor for failure of FMT, although repeat FMT can still be successful. Additionally, colonoscopic FMT provided valuable diagnostic information in some patients with RCDI. Colonoscopy with mucosal biopsies is a single most sensitive and specific test for presence of IBD, including CD, UC, and microscopic colitis. Colonoscopy can also serve as a means of introducing donor microbiota during FMT, and this was the exclusive route of administration for the cohort described here. We found a nontrivial rate (7.4%) of lymphocytic colitis in patients with endoscopically normal colon mucosa. De novo diagnosis of CD or UC was made in 2.6% of patients with RCDI at the time of FMT. Young age of the patient, onset of CDI without a likely antibiotic trigger, and persistently severe symptoms while taking anti-CDI antibiotics should raise the suspicion for underlying IBD. Although there are no absolute criteria to distinguish patients with and without IBD, failure of FMT should raise the suspicion of IBD and prompt appropriate evaluation. Patients commonly have diarrheal symptoms while on CDI therapy related to antibiotics or post-infectious irritable bowel syndrome. Loss of secondary bile acid metabolism may be one reason for the antibiotic-associated diarrhea in these cases, although additional mechanisms may be involved given profound dysbiosis found in these patients.[10] Regardless, patients are unlikely to be able to distinguish diarrhea from CDI versus a non-CDI etiology. Therefore, our experience supports the need for careful evaluation of patients with RCDI syndrome being considered for FMT for potential underlying coexistent intestinal disorder.

Our results clarify the risks and benefits associated with FMT in patients with IBD, which need to be discussed during the consent process. First, although still generally successful in most cases in clearing CDI, the procedure is more likely to fail in patients with underlying CD or UC. Second, FMT has a significant risk of precipitating a flare of IBD activity, especially in cases with extensive colon involvement. In most cases such a flare can be treated with a course of prednisone. A physician may consider increasing anti-inflammatory therapy immediately following infusion of donor microbiota if significant active IBD colitis is noted at the time of FMT. This practice was increasingly adapted in our program, which may have lowered the overall incidence of such flares. Third, although most patients with IBD seem to benefit from clearing CDI and some show remarkable improvements in their

IBD over the longer term of follow-up, a significant minority of patients may continue to struggle with their underlying disease and may not see an improvement in their symptoms.

The reasons for the higher failure rate in the presence of underlying IBD may include instability of engraftment of critical bacterial taxa caused by IBD-related host factors and a deficiency in host immune defenses, such as antimicrobial peptides that may be associated with IBD.[11,12] Given the importance of the immune system in imposing constraints on the composition and structure of gut microbial communities, these mechanistic possibilities are not mutually exclusive. Moreover, hypotheses addressing these possible mechanisms may be testable by careful examination of microbiota composition over time after FMT and measurements of host mucosal gene expression. Our data did not suggest that the severity of underlying IBD or specific immunosuppressive regimens correlated with higher failure rates, although a significantly higher number of patients with IBD is needed to tease out such risk factors. A robust national registry of FMT patients with relevant metadata and outcomes, if developed, could become a valuable resource to facilitate better mechanistic understanding of IBD-associated CDI.

Experience of a single center is an obvious limitation of our study. However, the patient cohort is likely very representative of patients with refractory RCDI because it accumulated from a broad referral base of community infectious disease and general gastroenterology physicians in a large metropolitan area. Nevertheless, a significant minority (15.8%) of patients had underlying IBD, which has a known association with greater CDI burden.[6,13] We have not examined noninvasive diagnostics to further risk stratify patients (eg, measurements of serum C-reactive protein or fecal calprotectin). Strengths of the study include the large size of this cohort, which captured the full spectrum of the patients with RCDI. This population is intrinsically highly complex medically and multitude of underlying medical problems are the rule rather than exception. Most of these patients probably would have been excluded from early phase, controlled, explanatory clinical trials.[14,15] This experience is pragmatic with its consequent intrinsic strengths and weaknesses.[15]

Arguably the most important diagnostic consideration in patients with RCDI is the possibility of underlying CD or UC. Our data suggest that this diagnostic possibility should be considered especially in younger patients. We currently insist on a diagnostic evaluation in all patients with RCDI ≤40 years of age that includes a colonoscopic examination with visualization of the terminal ileum within a year of FMT, including patients that choose to receive an oral encapsulated FMT preparation in our program. Importantly, endoscopic examination at the time of FMT offers not only a possibility of new diagnosis, but also staging of the disease that can impact additional clinical management. For example, a physician may elect to initiate corticosteroids in a patient with extensive IBD colitis to mitigate the high likelihood of a flare. This is one of the reasons for steering patients with RCDI with known IBD for colonoscopic FMT at this time. Underlying lymphocytic colitis is another important consideration in all patients with RCDI. However, we were reassured so far in our experience that these patients generally responded well to FMT and only a minority required additional treatment after the procedure.

The current Food and Drug Administration guidance allows performance of FMTs in treatment of CDI failing standard antibiotic therapies, but requires provision of an informed consent. However, the range of risks and benefits remains poorly defined because the published FMT experience remains limited. Several host factors likely play significant roles in the pathophysiology of RCDI and can affect risks and benefits of FMT and clinical care of patients after the procedure. As more options for FMT emerge, patients will likely opt for less invasive mechanisms, such as oral delivery capsules. However, underlying gastrointestinal pathology should be considered in patients with refractory RCDI and colonoscopic evaluation may provide valuable diagnostic information. Our experience should help practitioners determine the relative risks and benefits of diagnostic evaluation in patients with RCDI and inform the appropriate mechanism for FMT administration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

CD	Crohn’s disease
CDI	Clostridium difficile infection
FMT	fecal microbiota transplantation
IBD	inflammatory bowel diseases
RCDI	recurrent Clostridium difficile infection
UC	ulcerative colitis

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Table 1

Clinical Characteristics of the Total FMT Patient Cohort

All patients, N	272
Age, *y*	
Mean ± SD	57.2 ± 19.2
Median (range)	59.0 (16–100)
Sex, n (*%*)	
Female	189 (69.5)
Male	83 (35.5)
Time from initial CDI diagnosis (*mo*)	
Mean ± SD	11.26 ± 10.34
Median (range)	7.00 (2–60)
History of hospitalization for CDI, n (*%*)	100 (30.8)
Dialysis, n (*%*)	10 (3.68%)
Antibiotics used to treat CDI, n (*%*)	
Metronidazole	206 (75.7)
Vancomycin	270 (99.3)
Fidaxomin	69 (25.4)
Rifaximin	71 (26.1)
Intercurrent non-CDI antibiotics, n (*%*)	70 (25.7)
Probiotics, n (*%*)	104 (38.2)
Additional medication, n (*%*)	
Proton pump inhibitors	86 (31.6)
HMG-CoA reductase inhibitor	82 (31.1)

Table 2

Endoscopic and Histopathologic Findings on FMT Colonoscopies

Presence of IBD (newly diagnosed or confirmed), n	
CD	22
UC	21
Lymphocytic colitis	15
New diagnosis of IBD, n	
CD	5
UC	1
Lymphocytic colitis	14
Reclassified IBD, n	
UC to CD	4
CD to UC	3
No evidence for prior diagnosis of CD or UC, n	4
No evidence for prior diagnosis of lymphocytic colitis, n	2
Other findings, n	
Diverticulosis	88
Adenomatous polyps	23
Colon cancer	2
Nonspecific mucosal inflammation and regenerative changes	29
Eosinophilic colitis	4
Radiation colitis	1

NOTE. Results of colonoscopies in 272 patients with RCDI performed at the time of FMT. Biopsies were not taken in 25 patients without suspicion for Crohn’s disease or ulcerative colitis.

Table 3

Clinical Characteristics of Patients With and Without IBD

	IBD	Non-IBD	*P* value
Age, *y*			
Mean ± SD	38.8 ± 17.9	60.8 ± 17.3	<.0001
Median (range)	32.0 (16–84)	61.5 (16–100)	
Female sex (*%*)	22 of 43 (51.2)	167 of 229 (72.9)	.0065
Number of bowel movements over 24 hours			
Mean ± SD	8.3 ± 7.2	5.2 ± 4.6	.0044
Median (range)	5.5 (1–30)	4.0 (1–30)	
Median stool consistency, Bristol stool scale (range)	6.0 (4–7)	5.0 (1–7)	.0116
Absence of antibiotic trigger for initial CDI (*%*)	10 of 43 (23.3)	30 of 229 (13.1)	.1001

SD, standard deviation.

Table 4

Multivariate Analysis for Clinical Factors Associated With Failure of Initial FMT to Clear CDI

Variable	aOR (95% CI)	*P* value
Age	1.01 (0.99–1.04)	.2
Gender	0.9 (0.4–2.1)	.8
Immunosuppression	0.4 (0.1–1.2)	.08
IBD	8.7 (2.4–30.8)	.0008

aOR, adjusted odds ratio; CI, confidence interval.