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Small intestinal bacterial overgrowth: Should screening be included in the Pre-Fecal Microbiota Transplantation evaluation?

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Abstract

Background: Fecal microbiota transplantation (FMT) is safe and effective for recurrent *Clostridium difficile* infection (rCDI) and often involves terminal ileal (TI) stool infusion. Patients report gastrointestinal (GI) symptoms post-FMT despite rCDI resolution. Small intestinal bacterial overgrowth (SIBO) screening is not routinely performed pre-FMT. The effect of donor/recipient SIBO status on FMT outcomes and post-FMT GI symptoms is unclear. We aim to evaluate the value of pre-FMT SIBO screening on post-FMT outcomes and symptoms.

Methods: This was a prospective pilot study of consecutive adults with rCDI undergoing FMT by colonoscopy at a tertiary center. Routine pre-FMT screening and baseline lactulose breath tests (LBT) were performed for donors and recipients. Positive LBT required a rise >20ppm in breath hydrogen or any methane level >10ppm within 90 minutes. Presence of GI symptoms and CDI resolution were assessed 8 weeks post-FMT. Fisher's exact/student's t-tests were performed for statistical analyses.

Results: Twenty recipients (58.3 years, 85% women) enrolled in the study. Fourteen (70%) FMTs involved TI stool infusion. Four (20%) recipients and 6 (30%) donors had positive LBT pre-FMT. At 8 weeks post-FMT, 17 (85%) recipients had CDI resolution and 5 (25%) reported GI symptoms. Pre-FMT LBT result was not associated with post-FMT CDI resolution or GI

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symptoms. There was a trend towards increased GI symptoms among recipients receiving stool from LBT-positive donors (50% vs 14.2%, $p=0.09$).

Conclusions: FMT is effective and well-tolerated for rCDI. Positive LBT in asymptomatic donors may have an effect on post-FMT GI symptoms. Larger studies are needed.

Keywords

Clostridium difficile; fecal microbiota transplantation; small intestinal bacterial overgrowth; lactulose breath test; diarrhea

INTRODUCTION

Clostridium difficile is a spore-forming, potentially pathogenic organism that colonizes the human gut and causes symptoms ranging from self-limited diarrhea to fulminant colitis. *C. difficile* is the most common healthcare-associated infection and recurrent disease complicates 20–30% of cases. [1–3] *C. difficile*, like other gastrointestinal (GI) infections, can lead to post-infectious irritable bowel syndrome (IBS) in up to 25% of people. [4] In fact, post-infectious IBS has been reported in up to a third of patients after an episode of *C. difficile* infection (CDI). [5]

Fecal microbiota transplantation (FMT) has emerged as a safe and effective treatment for recurrent or refractory CDI. [6] Donor stool for this procedure can either be patient-directed (e.g. spouse) or from a universal stool bank. [7] Regardless of the source, donors must undergo a screening evaluation that involves a comprehensive medical history for infectious risk factors and microbiome-mediated diseases, as well as blood and stool testing. [8–10] Donor material can be delivered to the recipients by retention enema, nasoenteric tube, oral capsules, or most commonly by colonoscopy. [11–15] Patients have reported bloating or loose stool post-FMT despite resolution of CDI. [6] Specifically, the most common symptoms reported post-FMT by lower GI delivery are transient diarrhea (70%), abdominal cramps (10%), or nausea (<5%) during the 24 hours post-FMT, as well as constipation (20%) and excess flatulence (25%) during the follow-up period. These symptoms are traditionally mild-moderate in severity and self-limiting; although the etiology is often unclear. [16] Broadly, they have been hypothesized to represent standard post-infectious IBS, recurrence of pre-existing GI conditions of the recipient, or *de novo* changes acquired from the donor, such as small intestinal bacterial overgrowth (SIBO). Additionally, there may be small bowel exposure to donor fecal material, and it remains unclear if this can lead to a new diagnosis of SIBO in the recipient caused by the FMT, given limited data [17].

Screening of both the patient and donor must occur prior to performing an FMT. Recipient screening is often done to ensure appropriateness and rule out contraindicating factors. However, screening for pre-existing gastrointestinal conditions such as IBS or SIBO are not routinely conducted. Additionally, donor screening pre-FMT involves testing for infectious and microbiome-mediated diseases as well as blood-borne and intestinal infections. Assessment for SIBO among donors, whether through breath testing or small bowel aspirates is also not traditionally performed.

In this study, we aimed to determine the role of SIBO testing in pre-FMT screening by evaluating the relationship between the pre-FMT SIBO status of both recipients and donors on lactulose breath testing (LBT) and post-FMT gastrointestinal symptoms.

MATERIALS AND METHODS

This was a prospective pilot study of consecutive adult patients from an academic medical center who underwent FMT for recurrent CDI by colonoscopy with a patient selected donor (e.g spouse). In addition to routine pre-FMT screening to ensure eligibility, all potential FMT recipients underwent LBT for SIBO prior to FMT. For patients, this was performed while they were still completing chronic vancomycin therapy for CDI. Donor selection, screening for relevant communicable diseases, and stool processing were performed by standards suggested by the Fecal Microbiota Transplantation Working Group. [8] Donors were also screened with LBT for SIBO prior to FMT. All patients undergoing lactulose breath testing were instructed to avoid medications that may affect motility, such as laxatives, for a least 1 week prior to breath testing. They were also asked to avoid high-fiber food and caffeinated beverages on the day before the test, and no food for twelve hours prior to the study. On the day of the test, a 10 g dose of lactulose was administered. Breath samples were obtained at baseline, 5 minutes, 10 minutes, 15 minutes, and every 15 minutes after for a total of 120 minutes for analysis. All breath tests results were reviewed by an expert reviewer. Positive LBT required a rise >20 ppm in breath hydrogen or any breath methane level >10 ppm within 90 minutes per consensus guidelines. [18] All patients discontinued anti-CDI therapy 24–48 hours prior to FMT and those who underwent colonoscopy took a standard bowel preparation.

All patients were assessed at 8 weeks after FMT for both the presence of GI symptoms (abdominal discomfort, bloating, loose stools, constipation) and signs of CDI recurrence as per standard of care. GI Symptoms were assessed using a standard clinic intake form at both baseline and week 8. Additionally, CDI recurrence was defined by the presence of diarrhea together with a positive stool test for *C. difficile*, either by enzyme immunoassay tests (EIA) for *C. difficile* toxins A and B, or polymerase chain reaction (PCR) for toxin B genes. Data collected included patient demographics, CDI characteristics, concurrent diagnosis of inflammatory bowel disease (IBD) and IBD characteristics, post-FMT outcomes, and adverse events (AEs). Patients without at least 8 weeks of post-FMT follow-up data were excluded from analysis.

Fisher's exact test for binary variables and student's t-test for continuous variables were performed for univariate analyses. Predictors for post-FMT irregular bowel movements were assessed by univariate logistic regression. All statistical analyses were performed using the SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Twenty subjects undergoing FMT for recurrent CDI were enrolled in the study, each selecting his/her own related donor. The mean age of the recipients was 58.3 years, with 85% women (Table 1). Fourteen (70%) of the FMTs performed involved donor stool

infusion directly into the terminal ileum. Four (20%) recipients and 6 (30%) asymptomatic donors had positive LBT pre-FMT. With regard to the recipients all were hydrogen positive and methane negative. With regard to donors all 6 were hydrogen positive and methane negative. The main outcomes of interest were post-FMT GI symptoms (abdominal discomfort, bloating, loose stools or constipation) at the 8-week follow-up visit, as well as recurrence of CDI at 8 weeks post FMT. Among the 20 FMTs performed, 3 patients (15%) were confirmed to have CDI recurrence, while 5 (25%) experienced at least one GI symptom post-FMT after CDI recurrence was ruled out. Recipient pre-FMT LBT results were not associated with post-FMT CDI resolution or GI symptoms (Table 2). There was a trend towards increased GI symptoms among recipients receiving stool from LBT-positive donors (50% vs 14.2%, $p=0.09$), with a number needed to harm of 2 (attributable Risk 40%) (Figure 1).

DISCUSSION

Post-infectious IBS is an established consequence of CDI with reports of up to 25% of patients experiencing GI symptoms. FMT is a promising therapy for recurrent CDI and generally well tolerated. However, there have been reports of symptoms such as bloating, loose stools and abdominal pain after FMT despite successful clearance of CDI, and the etiology of those post-FMT symptoms remain unclear.

In this data set, we found that recipients who had a positive pre-FMT LBT did not have worse post-FMT outcomes, including CDI recurrence or GI symptoms, compared to those with normal LBT. It is interesting to note that all positive tests among recipients were achieved while on chronic vancomycin therapy. These results may be dependent on host factors such as intestinal motility. Intestinal dysmotility, most notably rapid transit, is common among patients with GI tract infections such as CDI. The positive LBT observed in this population may have resulted from rapid intestinal transit and early delivery of the ingested lactulose to the colon. However, vancomycin is not active against methanogens and may not be active against all hydrogen producing bacteria. Hence, it is still possible that patients on vancomycin to have true SIBO. Based on our results and the well-documented limitations of LBT, routine pre-FMT LBT in recipients does not appear to be indicated and at this point should not be recommended.

Although a statistically significant relationship was not found between donors' positive LBT testing and post-FMT outcomes, a trend towards more post-FMT GI symptoms, such as bloating, diarrhea, and constipation, was observed among patients who received FMT from LBT positive donors. Studies have shown that a substantial proportion of healthy, asymptomatic controls may get a positive result on LBT. [19] When compared to patients with IBS, controls undergoing LBT have been found to produce similar levels of breath hydrogen after lactulose ingestion and show similar oral-cecal transit times. [20] Thus, LBT may not adequately discriminate IBS patients from healthy, asymptomatic controls. [21] It should be noted however, that these studies used less strict criteria to define positive results and may not be applicable to this study, which used strict cut-offs. As previously discussed, results of LBT may be affected by various host factors such as anatomical differences, history of surgery, baseline intestinal microbiome, or intestinal motility.

The clinical significance of positive LBT among asymptomatic donors, therefore, remains unclear. It may represent an overgrowth of microorganisms that may not lead to symptoms in the donor host environment, but result in bacterial overgrowth and/or symptoms when transferred to the recipients. In this scenario, pre-FMT screening of donors for SIBO with LBT and exclusion of those who test positive may appear to be reasonable in reducing potential post-FMT symptoms; however, further evidence is required before such a recommendation. There has been a case study recently published describing a FMT recipient who developed significant post-FMT symptoms and was found to have elevated methane levels. Her donor was subsequently test and was also found to have elevated methane levels, though he was asymptomatic. [17] Albeit this case report does not present a baseline test on recipient, it certainly raises the concern that these methane or certain hydrogen-producing organisms may be transferable.

The strength of our study is the standardized manner with which all donors and recipients were evaluated pre-FMT and followed post-FMT, thereby significantly reducing potential confounding factors. Our institution is also a large referral center for FMT, with an experienced, dedicated staff, thereby reducing potential inter-provider variability in FMT quality. Limitations of our study include the small size of the study, precluding the ability to perform further sub-group analyses. We were only able to enroll 20 patients as shortly after our hospital converted to a universal donor model and could no longer screen donors. However, given the relative novelty of the treatment modality, our study size is still within the range of most other published literature on FMT. In addition, as stated above, LBT may not accurately capture true, clinically significant SIBO or intestinal dysbiosis, given the suboptimal sensitivity and specificity of the test. Small bowel aspirate, obtained endoscopically, remains the gold standard in the diagnosis of SIBO, although its clinical use is limited by the invasiveness of the test and cost. Therefore, LBT remains the most widely-used testing modality for SIBO and the most appropriate option potentially as a part of routine pre-FMT assessment.

Overall, given the small sample size of this study we were not adequately powered to detect a statistically significant association between pre-FMT LBT positivity in donors and post-FMT recipient symptoms, although this data suggests worse outcomes may occur. Given our results and the limitations of the LBT discussed, currently we do have enough data to support routine use of LBT as part of pre-FMT screening of donors and further larger studies are clearly needed. Regardless, we would recommend FMT stool donors be thoroughly screened not only current but prior history of GI symptoms which, if present, could lead to worse patient post-FMT outcomes

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Figure 1. Recipients with positive and negative pre-FMT LBT experienced similar post-FMT GI symptoms. There was a trend towards increased post-FMT symptoms in those performed with LBT positive donor stools, although statistical significance was not reached.

Table 1.

Baseline characteristics of FMT recipients and donors.

	Recipients N=20		Donors N=20	
	Pre-LBT Positive N=4	Pre-LBT Negative N=16	LBT Positive N=6	LBT Negative N=14
Female	4 (100.0)	13 (81.2)	3 (50)	7 (50)
TI	3 (75.0)	11 (68.7)	-	-
Age	66.7 +/- 18.7	56.2 +/- 19.0	43 +/- 19.1	43.6 +/- 11.1
IBD	1 (25.0)	3 (18.7)	0 (0)	0 (0)
Recurrence	3.7 +/- .5	3.9 +/- 1.1	-	-
BMI	22.2 +/- 20.1	26.1 +/- 23.9	29.8 +/- 4.7	30.1 +/- 7.1
Outpatient	4 (100)	16 (100)	-	-

Table 2.

Prevalence of LBT positivity and clinical predictors with and without post-FMT GI symptoms.

	Post-FMT GI symptoms N=5	No Post-FMT GI symptoms N=15	<i>p</i> -value
Pre-breath test Positive	1 (20.0)	3 (20.0)	1.0
Donor Breath test Positive	3 (60.0)	3 (20.0)	0.09
Female	4 (80.0)	13 (76.4)	0.71
TI	3 (60.0)	11 (73.3)	0.57
Age	59 +/- 19.4	58.1 +/- 20.9	0.91
Number of <i>C difficile</i> recurrence	3.6 +/- 1.1	4 +/- 1.0	0.56