Durability of Response to Fecal Microbiota Transplantation After Exposure to Risk Factors for Recurrence in Patients With *Clostridioides difficile* Infection

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Background. Fecal microbiota transplantation (FMT) is highly effective for preventing recurrent *Clostridioides difficile* infection (CDI). Durability (no recurrence despite additional risk factor exposure) of FMT protection is largely unknown. We studied the durability of FMT in patients with recurrent CDI.

Methods. We conducted a retrospective study of adults undergoing FMT for recurrent CDI. Data collected included demographics, CDI risk factors (comorbidities, healthcare exposure, non-CDI antibiotic use, acid suppressant medications), and future CDI episodes. Durable response to FMT was defined as lack of CDI episodes within 1 year post-FMT despite risk factor exposure.

Results. Overall, 460 patients were included (median age, 57 years [18–94]; 65.2% female). Comorbidities included chronic liver disease, 12.8% (n = 59); cancer, 11.7% (n = 54); chronic kidney disease, 3.9% (n = 18); and inflammatory bowel disease, 21.9% (n = 101). Overall, 31.3% (n = 144) received antibiotics, 21.7% (n = 100) received acid suppressants, and 76.8% (n = 350) had healthcare exposure after FMT. Of 374 patients with risk factor exposure, 78.1% (95% confidence interval [CI], 72.7%–84.0%) had durable response to FMT at 1 year. On multivariable analysis, antibiotic use was independently associated with decreased durability of FMT (hazard ratio, 0.27; 95% CI, .15–.49; *P* < .001).

Conclusions. The majority of patients had a durable response to FMT despite exposure to CDI risk factors. Antibiotic exposure after FMT independently predicted loss of durability of FMT. Larger studies are needed to define predictors of durable response in patients with and without exposure to antibiotics.

Keywords. microbiome; outcome; antibiotic; diarrhea; recurrence.

Fecal microbiota transplantation (FMT) is highly effective for treating recurrent *Clostridioides difficile* infection (CDI), with cure rates of up to 90% in observational studies but lower rates in controlled clinical trials [1, 2]. One proposed mechanism of FMT's benefit is restoration of a diverse microbial milieu to abate the risk of future CDI [3]. Patients with multiple recurrent CDI often have risk factors that predispose them to future recurrences, with systemic antibiotic exposure being the strongest risk factor [4]. An important clinical question is the assessment of risk of recurrent CDI in patients exposed to systemic antibiotics after FMT. There are 2 important concepts when assessing the response to FMT: failure and durability.

There are no widely accepted definitions of FMT failure and durability. Previous studies have variably defined FMT failure as either persistent or recurrent symptoms of CDI with a positive stool assay within 8 or 12 weeks of FMT [5–9]. Factors associated with failure of FMT have included severe CDI, inpatient FMT, previous hospitalization, inadequate bowel preparation, and post-FMT antibiotic use [5–7]. Durability was defined in one study as absence of CDI after FMT [10]. Another study looked at CDI recurrence beyond 8 weeks post-FMT and found antibiotic exposure to increase risk of CDI episodes [11]. In both studies, outcomes were defined variably between 2 and 51 months. These definitions are arbitrary, extrapolated from studies on patients with CDI treated with antibiotics.

We conceptualize FMT failure and durability as distinct entities with distinct mechanisms. FMT failure is the primary failure of FMT to treat CDI, which would manifest as persistent symptoms without interim symptom resolution (when FMT is done for refractory CDI) or recurrent CDI after FMT without additional risk factor exposure (Figure 1). This would indicate that the FMT was unsuccessful in restoring the microbiota, hence leading to CDI recurrence despite lack of further

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Figure 1. The process of FMT and the concept of FMT durability and failure. Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.

exposure to risk factors. Durability of FMT refers to the ability to sustain the primary response to FMT despite ongoing or repeated exposure to CDI risk factors. This would be characterized by a lack of recurrent CDI after an initial favorable response to FMT (Figure 1). At the mechanistic level, it would indicate that the restored microbial milieu was resistant to further insults.

There is a paucity of data on the durability of FMT. Hence, we conducted this single-center, retrospective study, looking at durability of response to FMT in patients with ongoing exposure to CDI risk factors, particularly antibiotics.

METHODS

This was a retrospective cohort study in which patients undergoing FMT (via colonoscopy) for recurrent CDI at Mayo Clinic, Rochester, Minnesota, from September 2012 to January 2018 were included. Recurrent CDI was defined as 3 or more definite CDI episodes, diagnosed by typical CDI symptoms (3 or more watery stools in 24 hours) and a positive stool assay, either toxin enzyme immunoassay or polymerase chain reaction (PCR). Patients were screened for eligibility to receive FMT. A detailed history was taken to establish baseline bowel habits. Using a combination of history,

clinical examination, serologic testing, stool testing, and endoscopy, the presence of definite CDI episodes was confirmed and competing causes of symptoms were ruled out. Testing included, but was not limited to, stool gastrointestinal pathogen panel, stool culture, fecal calprotectin, and endoscopy (as clinically indicated). In case patients received standard antibiotic therapy for CDI without clinical improvement, alternative diagnoses were considered, and these patients were not offered FMT. In patients with conditions such as inflammatory bowel disease (IBD) or irritable bowel syndrome, clinical judgment was made regarding whether CDI was superimposed on their baseline disease. In such cases, patients were eligible for FMT if they were deemed to have CDI based on significant improvement of symptoms with antibiotic treatment of CDI.

Our donor screening protocol and patient screening process have been previously published [12, 13]. Briefly, we use a standardized protocol to screen donors for several infectious and noninfectious conditions. FMT product is derived from a single donor; 50 g of stool is used to prepare the product in a final volume of 250 mL of 90% normal saline and 10% glycerol. The freeze-thawed product is instilled via a colonoscope into the cecum.

Follow-up

Patients were followed up for up to 1 year after FMT. Patients were contacted via an online patient portal or via telephone regularly post-FMT to monitor their clinical status (at 1 week, 1 month, 6 months, and 1 year). This information was supplemented by data from each patient's medical records. The date of last contact (either as part of the scheduled follow-up or as in the medical record, whichever was greater) was considered as the last follow-up.

Data regarding demographics and exposure to CDI risk factors (comorbidities [cancer, dialysis-dependent kidney disease, chronic liver disease, IBD], systemic non-CDI antibiotics, acid suppressant medications, healthcare exposure) were collected by reviewing medical records. Healthcare exposure was defined as any outpatient visit, emergency room visit, or hospital contact. All diagnoses were as recorded by physicians in the medical records. Patients were grouped into 2 cohorts: the "risk factor–exposed" cohort consisted of patients who were exposed to 1 or more CDI risk factors after FMT and the "risk factor–nonexposed" cohort consisted of patients who were not exposed to CDI risk factors after FMT (Figure 1). Patients who had persistent diarrhea with a positive *C. difficile* test following FMT without a symptom-free period were categorized as "initial nonresponders."

Occurrence of future episodes of definite CDI within 1 year post-FMT was recorded. Patients who received more than 1 FMT due to further CDI episodes were also included, and the outcomes were recorded with respect to timing of their first FMT. Ethical approval for the study was obtained from the institutional review board. Data were abstracted from the medical records, collected and managed using the REDCap electronic data capture tool hosted at Mayo Clinic [14].

Outcomes Assessed

The primary outcome was the proportion of patients with "durable" response to FMT, defined as no CDI episodes within 1 year post-FMT. The key secondary outcome was identifying which factors affected durability, including if combinations of risk factors affected durability.

Durability was assessed only in the subset of patients with 1 or more CDI risk factors (the risk factor–exposed cohort). Risk factors included comorbidities (IBD, chronic liver disease, dialysis-dependent kidney disease, cancer), healthcare exposure, and use of systemic antibiotics or acid suppressant medications. We also reported the proportion of patients with FMT failure (defined as future CDI episodes within 8 weeks of FMT among patients in the risk factor–nonexposed cohort; see Figure 1). Patients within the nonexposed cohort with CDI episodes beyond 8 weeks of FMT were considered "delayed FMT failures."

Statistical Analyses

Descriptive statistics were used to summarize baseline characteristics and risk factors for CDI in patients. Kaplan-Meier

survival analysis was used to calculate the proportion of patients with durable response up to 1 year after FMT. Patients who did not have a CDI event were censored at last follow-up or 1 year post-FMT, whichever came first. To assess the effect of baseline characteristics and CDI risk factors on durability of FMT, univariate and multivariable Cox proportional hazards models were used. A multivariable model was built using score selection to find the best model with 5 variables (1 variable for approximately 10 patients with future CDI episodes). Different combinations of covariates were modeled as interaction terms to determine whether specific covariates together affect durability. Antibiotic exposure, acid suppressant medications, and healthcare exposure were modeled as time-varying covariates for these analyses. A 2-tailed *P* value < .05 was considered statistically significant. Analyses were done using JMP 14.0 and SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 460 consecutive patients were included in the study; median age was 57 years (18–94), and 65.2% (300) were female. The baseline characteristics and exposure to CDI risk factors are noted in Table 1. Overall, 98.5% of patients (453) received FMT from a standard donor, while 1.5% [7] had a known donor.

In the entire cohort, 374 were exposed to 1 or more risk factors (risk factor–exposed cohort), while 80 patients were not exposed to any CDI risk factors up to 1 year post-FMT (risk factor–nonexposed cohort). Overall, 6/460 patients (1.3%) were initial nonresponders. Among the risk factor–nonexposed cohort, 2 had a future CDI episode within 8 weeks of FMT, while 2 had CDI episodes beyond 8 weeks. Thus, FMT failure occurred in 5% of patients (4/80; early failure in 2.5% [2/80] and delayed failure in 2.5% [2/80]). FMT was successful in 95% of patients (76/80).

Durability was assessed in the 374 patients in the risk factor–exposed cohort. These patients were followed for a median of 224 days (range, 7–365) after their FMT. Within this cohort, 38.2% (*n* = 143) received systemic non-CDI antibiotics within 1 year of FMT. The median number of antibiotic courses received after FMT was 2 (range, 1–7). Considering all patients in the risk factor–exposed cohort, 21.9% (*n* = 53) had a CDI episode within 1 year. Among patients who received antibiotics, 23.3% (*n* = 33) had future CDI episodes; among those without antibiotic exposure, 8.7% (*n* = 20) had future CDI episodes. Using Kaplan-Meier survival analysis, the proportion of patients with durable response at 1 year was 78.1% (95% confidence interval, 72.7%–84.0%; Figure 2). The median time to the first CDI episode was 119 days (range, 7–338) after FMT.

On univariate analysis, exposure to antibiotics was the only risk factor that significantly affected durability of FMT (hazard ratio, 0.27 [0.15–0.48]; *P* < .001; Table 2). On multivariable

Table 1. Baseline Characteristics and *Clostridioides difficile* Infection Risk Factors in Included Patients

Characteristic	Overall (n = 460)	Within the Durability Cohort (n = 374)	
		Without Antibiotic Exposure (n = 231)	With Antibiotic Exposure (n = 143)
Age, y	57 (18–94)	57 (18–89)	59 (22–94)
Sex female	65.2 (300)	61.9 (143)	63.6 (91)
Race (white)	96.7 (445)	95.7 (221)	97.9 (140)
Acid suppressant medications	21.7 (100)	17.8 (41)	41.3 (59)
Healthcare exposure	76.8 (350)	89.0 (203)	100.0 (141)
Chronic liver disease	12.8 (59)	12.6 (29)	20.3 (29)
Cancer	11.7 (54)	13.4 (31)	16.1 (23)
Dialysis	3.9 (18)	3.0 (7)	7.7 (11)
IBD	21.9 (101)	29.9 (69)	21.0 (30)
IBD subtype			
Ulcerative colitis	58.4 (59)	60.9 (42)	53.3 (16)
Crohn's disease	39.6 (40)	37.7 (26)	43.3 (13)
Indeterminate	1.9 (2)	1.4 (1)	3.3 (1)
Donor type (standard donor)	98.5 (453)	98.7 (228)	98.6 (141)

Continuous data are presented as median (range). Categorical data are presented as % (n).

Abbreviation: IBD, inflammatory bowel disease.

analysis, antibiotic exposure remained associated with decreased durability of FMT (Table 2). To explore the effect of different risk factor combinations on durability, these were modeled as interaction terms in a multivariate model. The combination of antibiotic exposure and healthcare exposure significantly affected durability (Table 3). The greatest impact on durability was of antibiotics without healthcare exposure, followed by antibiotics combined with healthcare exposure (Table 4).

Figure 2. Kaplan-Meier survival curve showing proportion of patients with durable response to FMT. Day 0 = date of FMT. Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.

DISCUSSION

FMT is highly effective for treating recurrent CDI, with limited data on durability of response beyond the immediate post-treatment period [2]. In our large, single-center study, the majority of patients exposed to 1 or more CDI-related risk factors had a durable response to FMT, with more than three-fourths of patients not having a recurrence after these exposures. After controlling for other factors, antibiotic exposure independently predicted the durability of FMT. When looking at different combinations of risk factors, antibiotic exposure with and without healthcare exposure significantly predicted durability. In contrast, only 1 in 20 patients without risk factor exposure experienced an FMT failure.

Antibiotics are frequently required in patients for various reasons. In 2016 alone, 270 million antibiotic prescriptions were written in the United States, amounting to 836 prescriptions for every 1000 people [15]. In the outpatient setting, 12.6% of physician visits are associated with antibiotic prescriptions, which increases to more than 50% in the hospital setting [16, 17]. In patients with CDI, antibiotic exposure is fraught with the risk of recurrence. Our results indicate that FMT successfully prevents future CDI in the majority of patients exposed to risk factors post-FMT, including antibiotics.

Data on the long-term durability of FMT are limited. Randomized clinical trials have reported efficacy data for FMT with a follow-up of up to 10–12 weeks [18–20]. In the extension phase of the MODIFY II trial, 18.8% and 27.6% of the actoxumab + bezlotoxumab and the bezlotoxumab-treated patients, respectively, had further CDI episodes up to 1 year after achieving clinical cure [21]. This is comparable to the response seen in our study.

Table 2. Factors Affecting Durability of Response to Fecal Microbiota Transplantation

Factor	Univariate Model ^a		Multivariable Model ^a	
	Hazard Ratio	P Value	Hazard Ratio ^b	P Value
Age (per 10 years)	1.02 (0.89, 1.18)	.74	...	
Sex female	1.25 (0.72, 2.13)	.43	...	
Chronic liver disease	0.61 (0.33, 1.11)	.10	0.63 (0.34–1.16)	.14
Cancer	2.44 (0.88, 6.67)	.085	2.78 (0.99–7.69)	.052
Dialysis	0.56 (0.22, 1.39)	.21	0.71 (0.27–1.85)	.49
Inflammatory bowel disease	0.70 (0.40, 1.23)	.23	0.70 (0.40–1.23)	.22
Exposure to antibiotics	0.27 (0.15, 0.48)	<.001	0.27 (0.15–0.49)	<.001
Exposure to acid suppressant medication	0.84 (0.41, 1.69)	.63	...	
Exposure to healthcare	0.83 (0.40, 1.75)	.63	...	

^aHazard ratios >1 mean more likely to have durable response to fecal microbiota transplantation.

^bThis model contains 5 variables selected using the score method.

Few observational studies have evaluated long-term response to FMT, though none of these have explicitly assessed durability as defined in our study [10, 11, 22]. In a single-center study (n = 137; FMT via nasogastric or colonoscopic route), 82% did not experience recurrent CDI up to a median follow-up time of 22 months [10]. In this study [10], approximately 30% of patients with antibiotic exposure had recurrent CDI compared with approximately 8% without antibiotics. The high risk of recurrence with antibiotic use remained after controlling for use of proton pump inhibitors and probiotics [10]. These results are similar to what we observed.

In a multicenter retrospective study with 404 patients and a mean follow-up of 18 ± 12 months, 8% of patients had recurrent CDI after FMT [11]. When stratified by antibiotic exposure, 16% of patients with antibiotics vs 5% without antibiotics had recurrences [11]. Older age was associated with a lower risk of recurrence. In another retrospective study (n = 134), approximately 37% of patients had recurrent CDI at 6 months of follow-up [22]. In this study, proton pump inhibitor use, severe CDI at the time of FMT, and systemic hypertension were associated with increased risk of recurrence. The presence of IBD did not increase the risk of recurrence. These studies did not explicitly differentiate durability from failure after FMT. The inclusion of severe CDI and the high percentage of inpatient FMTs performed (likely an indicator of worse clinical status) could account for the high recurrence rate observed. In a previous study, CDI patients with concomitant IBD had lower donor stool engraftment, which affected long-term response but not initial response to FMT [23]. We did not find the presence of IBD to affect durability of FMT.

Interestingly, in our study, acid blocker therapy did not affect durability of FMT. This is in contrast to previous studies in which acid suppression was associated with recurrent CDI in patients receiving either antibiotics or FMT for CDI [22, 24]. Thus, acid blocker therapy may be safe post-FMT, without incurring additional risk for recurrent CDI. We also found that patients with cancer tended to have more durable response,

with a trend toward statistical significance. This is an interesting observation, especially because patients with cancer are more likely to be exposed to CDI risk factors (eg, antibiotics, immunosuppressant medications, frequent healthcare contact). Our findings should be confirmed in future studies, and factors that affect the response to FMT in this cohort of patients should be elucidated.

Another noteworthy observation in our study was that 95% of patients did not experience another CDI episode if not exposed to risk factors; this proportion decreased to 75% in patients with additional risk factor exposure. This suggests that FMT is highly effective for preventing future CDI, though its efficacy was lower when patients were exposed to risk factors.

The occurrence of CDI episodes after FMT depends on risk factors for CDI but may also depend on persistent gut colonization with *C. difficile*. In a retrospective analysis of the MODIFY II trial, 16%–32% of patients had colonization with *C. difficile* up to 12 months after treatment [21]. In another study, 45% of patients had persistent colonization postantibiotics, though this did not predict recurrence [25]. To the best of our knowledge, no such data exist for FMT. We did not explore the effect of *C. difficile* colonization post-FMT and its effect on durability. This should be explored in future studies.

In this large, retrospective cohort study, we attempted to redefine the terms “FMT durability” and “FMT failure” based on an intuitive concept of what constitutes a successful and a durable response to FMT. The strengths of our study include a large number of patients from a single center with a standardized FMT follow-up protocol and inclusion of several common CDI risk factors. However, our study has several limitations. The definition of durability takes into account CDI risk factors. We studied several, but not all, risk factors for CDI (eg, immunosuppressant medications). Therefore, it is possible that some patients may have been misclassified as having no risk factors. However, considering the low rates of CDI in the “no risk factor” subset, it is likely that this would not have significantly affected our estimates. Our concept of durability also

Table 3. Interaction of Different Factors and Their Effect on Durability of Fecal Microbiota Transplantation

Interaction	PValue
With age	
Sex	.73
Chronic liver disease	.20
Cancer	.23
Dialysis	.50
IBD	.51
Exposure to antibiotics	.46
Exposure to PPI	.41
Exposure to healthcare	.84
With Sex	
Chronic liver disease	.82
Cancer	.50
Dialysis	.75
IBD	.16
Exposure to antibiotics	.40
Exposure to PPI	.46
Exposure to healthcare	.31
With liver disease	
Cancer	.33
Dialysis	.26
IBD	.38
Exposure to antibiotics	.27
Exposure to PPI	.70
Exposure to healthcare	.98
With cancer	
Dialysis	.39
IBD	.77
Exposure to antibiotics	.89
Exposure to PPI	.75
Exposure to healthcare	.98
With dialysis	
IBD	.59
Exposure to antibiotics	.25
Exposure to PPI	.21
Exposure to healthcare	.22
With IBD	
Exposure to antibiotics	.15
Exposure to PPI	.90
Exposure to healthcare	.31
With antibiotics	
Exposure to PPI	.88
Exposure to healthcare	.050
With PPI	
Exposure to healthcare	.99

Abbreviations: IBD, inflammatory bowel disease; PPI, proton pump inhibitor.

hinges on the premise that a successful FMT will restore the gut microbiota and additional risk factors would perturb it, causing susceptibility to future CDI. In this study, we did not perform stool microbial analysis and could not provide such information. CDI at our center is largely diagnosed using PCR; hence, some patients with persistent *C. difficile* colonization and diarrhea due to another cause could have been falsely diagnosed as

Table 4. Interaction of Antibiotic Exposure and Healthcare Exposure and Their Effect on Durability of Fecal Microbiota Transplantation

Grouping	Hazard Ratio (95% Confidence Interval)	PValue
No antibiotic or healthcare	Reference	
Antibiotic, no healthcare	0.08 (.02, .27)	<.001
Healthcare, no antibiotic	0.70 (.28, 1.79)	.46
Antibiotic and healthcare	0.23 (.09, .63)	.004

having CDI. Finally, as this was a retrospective study, residual confounding cannot be excluded.

CONCLUSIONS

In patients with recurrent CDI, response to FMT is durable in the majority of patients despite exposure to CDI risk factors. Future studies to explore the determinants of durable response in antibiotic-exposed and antibiotic-nonexposed patients are warranted.

Notes

Author contributions. S. S.: study design, data collection, analysis, interpretation, drafting, and revision of the manuscript. K. M.: statistical analysis and interpretation, drafting, and revision of the manuscript. D. S. P.: study design, data interpretation, drafting, and revision of the manuscript. S. K.: study design, data interpretation, drafting, and revision of the manuscript.

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