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ORIGINAL RESEARCH—CLINICAL

Family Stool Donation Predicts Failure of Fecal Microbiota Transplant for *Clostridioides difficile* Infection

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BACKGROUND AND AIMS: Fecal microbiota transplant (FMT) via colonoscopy is highly effective treatment for *Clostridioides difficile* infection (CDI). We aimed to determine baseline patient characteristics that predict failure to respond to colonoscopy-based FMT. **METHODS:** We evaluated adult patients who received FMT for CDI not responding to standard therapies at a single tertiary center between 2014 and 2018 in this retrospective cohort study. We defined clinical success as formed stool or *C difficile*–negative diarrhea at 2 months after FMT. If patients required a second FMT, follow-up was extended 2 months after repeat infusion. We performed multivariate logistic regression and a random forest model to identify variables predictive of response to FMT. **RESULTS:** Clinical success was attained in 87.3% of 103 patients who underwent FMT for CDI. In the multivariate model, the odds of FMT failure for family donation compared with stool bank were odds ratio 4.13 (1.00–7.01 $P = .049$). Diarrhea while taking anti-CDI antibiotics was common (37.8% of patients) and did not predict failure (odds ratio 0.64, 0.19–2.11 $P = .46$) in the univariate model. A machine learning model to predict response using clinical factors only achieved a sensitivity of 70%, specificity of 77%, and negative predictive value of 96%. **CONCLUSION:** Colonoscopy-based FMT was highly effective for CDI, even in a population where immunosuppression and proton pump inhibitor use were common. Family stool donation was associated with FMT failure, compared with the use of a stool bank. The study suggests that the use of a stool bank may not only improve access to FMT but also its efficacy.

Keywords: Fecal Microbiota Transplant; *Clostridium difficile* Infection; Diarrhea; Stool Bank

Introduction

Clostridioides difficile infection (CDI) causes a cytotoxin-mediated diarrhea and disproportionately affects those with reduced immune systems or multiple comorbidities. The burden of disease is great and is rooted in its propensity to recur after antibiotic treatment.[1,2] With each recurrence of CDI, the risk of a future recurrence increases, reaching 65% after a second recurrence.[3,4] The exact mechanism for susceptibility is unknown, but believed to be related to an altered host microbiome that becomes more deranged with each successive course of antibiotics.[5]

Multiple studies, beginning with the landmark study by van Nood et al[6] in 2013, have demonstrated the efficacy of fecal microbiota transplant (FMT) to treat recurrent CDI. The U.S. Food and Drug Administration gives regulatory discretion for clinicians to perform FMT outside of clinical trials for patients with CDI "not responding to standard therapies". In our institution, FMT was performed with stool from friends or family members of the patient until December 2015, at which point we began to use stool prepared by a stool bank from universal donors. The development of vetted volunteer stool banks has allowed the use of FMT to grow considerably. Stool banks can perform more thorough testing on potential pathogens and microbial diversity than can routinely be performed in clinical laboratories.[7]

However, little is known whether this testing could translate to improved patient outcomes. Clinically, there is significant confusion regarding what diarrhea on anti-CDI antibiotics signifies. In fact, many physicians empirically switch antibiotics if symptoms persist after one week, despite the low likelihood of vancomycin resistance and high luminal drug concentration.[8,9] Other clinicians investigate for alternative causes for diarrhea. A single study showed that among patients with a first CDI recurrence, initial response and resolution of diarrhea on vancomycin is high (>90%), but there are few data on response to antibiotics among patients with subsequent (second, third) recurrences.[10]

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Abbreviations used in this paper: **BMI, body mass index; CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplant; OR, odds ratio.**

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FMT is currently recommended by expert opinion after the third episode of CDI, but guidelines on treatment after a first recurrence are a weak recommendation and based on low-quality evidence.[1] As more fecal microbiota–derived therapeutics come to market in the coming years, it is increasingly important to understand which patients respond to FMT.[11] In this study, we aimed to determine predictors of FMT success among preprocedure clinical characteristics of patients receiving FMT.

Methods

Study Design

We performed a retrospective cohort study of all patients receiving colonoscopy-based FMT at the University of North Carolina Hospitals between 2014 and 2018. All patients were at least 18 years old and were treated for recurrent CDI with or without severe disease. We included both inpatients and outpatients and had no exclusion criteria based on clinical characteristics. We collected information from the electronic medical record and excluded from our analysis patients who did not return to the University of North Carolina for a post-FMT follow-up. The University of North Carolina Institutional Review Board approved the study. All authors had access to the study data and reviewed and approved the final article.

Covariates. We collected data via manual chart review. We documented basic demographic information: age, sex, smoking status, BMI (body mass index), and race, history of irritable bowel syndrome and inflammatory bowel disease, use of the proton pump inhibitor, immunosuppressive therapy, antibiotic use, probiotic use, and number of prior courses of anti-CDI antibiotics. Specifics regarding CDI history included time from initial CDI diagnosis to FMT, presence of diarrhea while on anti-CDI antibiotics, disease severity, and diarrhea at time of FMT. We defined diarrhea on anti-CDI antibiotics as self-reported frequent or loose bowel movements. We defined severe disease as white blood cells >15k or serum creatinine greater than or equal to 1.5× baseline renal function, based on the infection just before FMT. We noted if donor stool was procured from a patient's relative or a stool bank.

Fecal Donor Criteria. Each FMT used stool from a single donor, whether from a family donor or the stool bank. The family stool donor exclusion criteria at our center were as follows: no history of high-risk sexual behavior or illicit drugs, no tattoos in the last 6 months, no prior incarceration, no known communicable diseases, no inflammatory bowel disease or history of gastrointestinal malignancy, no metabolic syndrome, and no chemotherapy or antibiotics in the last 3 months. Family donor stool testing included *C diff* toxin, stool ova and parasites, stool bacterial pathogen panel and serum human immunodeficiency virus, rapid plasma reagin, viral hepatitis, liver function tests, and cytomegalovirus/Epstein Barr viral load.

Stool bank donor criteria were much more rigorous; among the extensive exclusions were age >50 years, use of medications or supplements, BMI >30, recurrent gastrointestinal symptoms, atopy, allergies, or asthma, and family history of gastrointestinal cancer or illness. Stool, serologic, and nasal testing was extensive.[12]

Main Outcome: Clinical Cure Determination. Our main outcome was clinical cure after FMT, defined as resolution of diarrhea (formed stools or <3 loose stools daily) or diarrhea that was tested and *C. diff* negative at the first clinical follow-up after FMT. Alternatively, failure was defined by persistent or recurrent diarrhea that was positive for *C. diff* within 2 months or at the first follow-up, if longer than 2 months. The principal investigator determined clinical cure via chart review. For patients who experienced recurrent diarrhea after FMT within 2 months and were treated with a second FMT, the timeline for clinical cure was extended for 2 months.

Statistical Analysis. We performed a multivariable logistic regression to assess factors associated with clinical cure. A priori covariates included gender (categorical), age (continuous), and BMI (continuous). We considered covariates with model-estimated probabilities of 0.10 or below for inclusion in our final model. We considered biological sex to be a conceptual confounder and retained it in the final model despite not meeting inclusion criteria ($P = .015$). We then performed a univariate analysis via chi-square and one-way analysis of variance with post hoc Tukey analysis specifically investigating diarrhea as the dependent variable.

Machine Learning Analysis. As an exploratory aim, we performed a machine learning classification analysis with FMT success as the binary outcome and with feature variables: irritable bowel syndrome history, inflammatory bowel disease history, sex, age, race, BMI, previous FMT, type of prior FMT, antibiotic type, proton pump inhibitor, probiotic, immunosuppressive therapy, antibiotic course number, prior hospitalization for CDI, CDI severity, diarrhea status at FMT, FMT donor type, admit status, and smoking status. We split the data into training and testing sets using 5-fold cross validation. Because of the imbalanced FMT outcomes within the patient population, we used SMOTE or synthetic minority oversampling technique to oversample for FMT failure data points within the training set.[13]

We used a random forest classification technique as a predictive model with a tuning grid to determine the most accurate tree number and number of variables randomly sampled at each split. Based on the random forest algorithm from the training set, we calculated the area under the curve for the test set. We ran the model on the test set with confusion matrices to calculate mean sensitivity, defined as the proportion of FMT successes predicted as such by the learning algorithm, specificity, defined as the proportion of FMT failures as predicted by the algorithm, and positive and negative predictive values. We derived a variable importance feature from the random forest model to determine the most integral variables in the predictive model. Specifically, global variable importance was derived by observing mean decrease in overall out-of-bag accuracy per variable through permutation.

Results

In total, 87.4% (90/103) of patients had clinical cure of CDI after FMT. Sixteen patients required a second FMT after initial failure—45.8% (n = 11/24) of inpatients, including 6

Table 1. FMT Characteristics

FMT characteristics	N (%) or mean (SD)[a]
Prior CDI hospitalization	51 (52%)
Inpatient FMT	24 (23.8%)
Severe CDI	11 (11%)
Mean number of CDI episodes	4.7 ± 1.5
Requirement of the second FMT	16 (16%)
Prior antibiotics	
Vancomycin	99 (99%)
Metronidazole	80 (81.6%)
Fidaxomicin	62 (60.2%)
Donor type	
Family donation	13 (12.6%)
OpenBiome	89 (87.4%)

SD, standard deviation.
[a]Total N = 103.

with severe disease, and 6.3% (n = 5/79) of outpatients—and of those, 14 of 16 patients were cured. All patients with severe disease also had a history of recurrent CDI, and no patients within our cohort received bezlotoxumab or met criteria for fulminant disease as defined by hypotension, shock, ileus, or megacolon.[14] We initially identified 113 patients for eligibility in the study, but excluded 10 patients because of the lack of follow-up.

In the multivariable analysis, family stool donation predicted FMT failure, with an odds ratio (OR) of 4.13 (1.00, 17.01 $P = .049$). A trend toward severe CDI predicting FMT failure was observed with an OR of 3.86 (0.91, 16.25 $P = .065$). FMT characteristics are reported in Table 1. Diarrhea on anti-CDI antibiotics before FMT was common and did not predict FMT failure (OR 0.45, 0.25, 2.79 95% confidence interval, $P = .78$) in the bivariate analysis. Among the 37.8% of patients (n = 39) who reported diarrhea, all reported diarrhea on vancomycin, 35.9% (14/39) reported diarrhea on both vancomycin and fidaxomicin, and 5% reported diarrhea on fidaxomicin alone.

We report baseline patient characteristics in Table 2. The average patient age was 58 years, and 66% of patients were women. Of the patients analyzed, 19% had inflammatory bowel disease, and 44% were on acid suppression medications. Patients averaged 4.7 (standard deviation 1.5) episodes of CDI before FMT, and the average time from the first CDI diagnosis to FMT was 275 days (interquartile range 213, median 214 days). FMT was administered to the terminal ileum or cecum in 95% of patients and to the left colon in 5% of patients.

The random forest model yielded an area under the curve of 60% within the testing set, with an average sensitivity of 70%, specificity of 77%, positive predictive value of 46%, and negative predictive value of 96%. The variable importance based on mean decreased accuracy through permutation is presented in Figure, with the top 4 variables being admit status, stool type on antibiotics, FMT donor status, and sex.

Discussion

Our study found that donor stool from family predicts FMT failure, compared with stool from a stool bank. Most FMT providers have switched to stool banks for reasons of convenience—stool is available on demand—and safety—the rigorous donor testing is far beyond what can be provided by most individual centers. Stool banks analyze diversity of donor stool, weeding out dysbiotic donors, which cannot be performed locally.[15] Microbial diversity has been suggested as a primary driver of FMT success, and the phenomenon of the "super-donor" is increasingly recognized.[16] Given our findings, it is troubling that the dominant stool bank in the United States has communicated its plan to cease operations sometime this year and is currently only supplying most of its partners with stool in emergency conditions. We will see if commercial players with approved products fill the void.

In our study of FMT patients, diarrhea on treatment was surprisingly common but did not predict FMT failure. Over a third of patients had diarrhea while on treatment. Clinical trials studying patients with an initial or first recurrence have reported only rare failure (<10%) while on vancomycin and fidaxomicin.[8,9] Our data suggest that diarrhea on appropriate medical therapy should not be a barrier to FMT and should not necessarily inspire a workup for alternative diagnoses.

Our cohort demonstrated an impressive real-world success rate of FMT at 87% among patients with significant baseline medical comorbidities—over a fifth of patients were immunosuppressed, had inflammatory bowel disease, or both. Severe CDI trended in the direction of a predictor of FMT failure, findings consistent with prior cohorts who identified severe CDI,[14,17] prior CDI-related hospitalization, and inpatient status to be predictive factors for FMT failure.[18] The success of FMT is particularly relevant as the COVID-19 pandemic corresponded with the shutdown of many FMT programs related to concerns of fecal viral transmission.[19]

Of our cohort, about half of hospitalized patients and about 1 in 20 outpatients required a second FMT. Second FMT success was high at 87%, in line with the results of a systematic review from Clinical Infectious Diseases which noted 14 of 16 patients experienced disease resolution with repeat FMT.[20] The Food and Drug Administration recommends that clinicians counsel patients that FMT is an experimental therapy and that transmission of disease and other risks is possible. Our study suggests that practitioners should also consider counseling patients on the potential need for repeat FMT to achieve success. Our single-center cohort study with an 87% FMT success rate is similar to other FMT studies, including a systematic review of 536 patients that demonstrated an 87% cure rate.[17,21–24]

In our study, the mean time from diagnosis to FMT was over 9 months. Given the high efficacy of FMT and the emotional, economic, and physical burden on patients with recurrent CDI, this raises the question whether FMT should

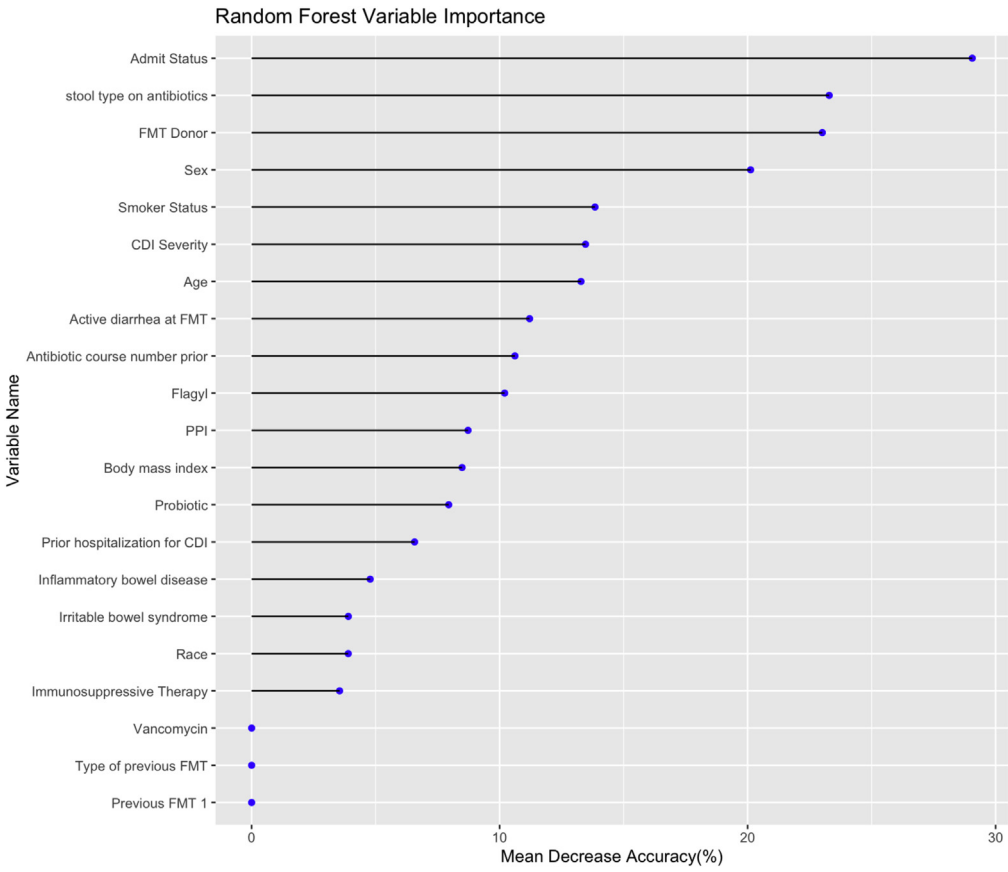

Figure. Variable feature importance on random forest: an estimate of degree of accuracy lost by excluding each variable.

be considered sooner in the disease course. There is no established time frame from the first CDI diagnosis to FMT referral; the expert opinion from the panel was for consideration of FMT after a third infection. This would place referral for FMT at least 3 months after the first diagnosis, assuming recurrences 2 weeks after antibiotic cessation and the use of a 6-week vancomycin taper. Despite its high cost, FMT via colonoscopy for recurrent CDI was cost-effective in a recent analysis.[25] A 2018 pilot study by Juul et al[12] showed promising data for the primary treatment of first CDI with FMT, and a phase III trial evaluating this concept is currently underway. As the clinical and economic efficacy of FMT becomes increasingly apparent, use for primary infection or after the first recurrence may expand. However, recent Infectious Diseases Society of America guidelines advocate fidaxomicin as first-line therapy over vancomycin, and data are needed to see if this practice change will decrease the prevalence of recurrent CDI.[14]

Table 2. Baseline Patient Characteristics

Variable	N (%) or mean (SD)[a]
Age	58.4 (SD 19.1)
Male	34 (33%)
Female	69 (67%)
White	86 (84.3%)
Black	8 (7.8%)
Native American	1 (1%)
Other race/ unknown	5 (4.9%)
BMI	26.7 (SD 6.5)
Active smoker	16 (16.3%)
Inflammatory bowel disease history	20 (19.4%)
Irritable bowel disease history	11 (10.68%)
Medications before FMT	
Acid suppression	42 (40.8%)
Immunosuppressive medications	24 (23.3%)
Probiotics	39 (37.9%)

SD, standard deviation.
[a]N = 103.

Our study found that severe CDI trended in the direction of predicting FMT failure. There is no trial of FMT vs standard of care in this population, and there may never be due to ethical reasons, but historical data strongly suggest that colonoscopy-based FMT saves lives if performed serially and in conjunction with continued antibiotics.[26] Previous retrospective cohorts found that patients with severe CDI only had a 30% FMT cure rate after single FMT, whereas 90% of these were cured with a second infusion,[27] similar to the 90% cure rate in severe-fulminant inpatients treated with serial FMT in addition to standard-of-care antibiotics.[28]

Machine learning techniques have been explored to predict FMT success using stool taxonomic data. Kazemian et al[29] recently published a study using random forest classification to predict FMT success based on patient and donor metagenomic sequencing data on a cohort of 17

patients. The authors demonstrated an area under the curve of 98% but were unable to validate this method in an independent data set. Similarly, machine learning has been used to effectively predict which bacterial strains will engraft after FMT.[30] Our study is the first to our knowledge to use machine learning techniques to predict FMT success based on granular real-world clinical variables. The strengths of the random forest method include its high accuracy, resistance to overfitting, and ability to capture nonlinear interactions between large amounts of predictors. Based on the most potent variables in our random forest model, we propose that future prediction models include admit status, FMT donor type, sex, and stool type on antibiotics. The random forest model is predictive and does not adjust for confounders as necessary in an etiologic model, explaining the discrepancy in CDI severity variable importance between the logistic regression and random forest model. We hypothesize that merging discrete clinical information with metagenomic microbiome data will lead to highly accurate predictive models of FMT success in recurrent CDI. In addition, given the overall low failure rate of FMT for CDI, machine learning techniques will be valuable resources for identifying factors associated with such infrequent outcomes and speeding progress toward mitigating them even further.

This study is limited in its single-center retrospective design and small number of failures within the patient population. No stool samples were collected, and thus, no stool microbiota data could be investigated to further explore mechanisms of FMT failure. Recent guidelines recommend FMT for severe and fulminant disease not responding to antibiotics,[31] but the study results do not apply to fulminant CDI as the cohort did not have any patients with fulminant disease. In addition, although the effect appears clinically important with an OR over 4, our main finding that family stool donation is associated with FMT failure compared with stool banks is limited by a borderline *P*-value of .049. However, this arbitrary cutoff and categorization has been increasingly scrutinized in the field of biostatistics.[32]

In conclusion, the use of stool from a friend or family member may be less effective than stools banks in the treatment of CDI not responding to antibiotics. In addition, diarrhea on anti-CDI antibiotics is common among patients before FMT and does not predict FMT failure. As clinical indications for FMT expand, a deeper understanding of how to optimize treatment material will be important to optimizing FMT success.

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Authors' Contributions:
Jared A. Sninsky contributed to analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Ariel E. Watts contributed to study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Morgan M. Richey contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Kevin Donovan contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript content. Michael K. Dougherty contributed to critical revision of the manuscript for important intellectual content. Sarah K. McGill contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data, analytics, and study materials will be made available to other researchers through contact of the corresponding author.