

Fecal Microbiota Transplant is Highly Effective in Real-World Practice: Initial Results from the FMT National Registry

Short Title: Initial Results from FMT National Registry

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Abbreviations

AGA: American Gastroenterological Association

CDI: *C. difficile* infection

FDA: Food and Drug Administration

FMT: fecal microbiota transplantation

IBD: Inflammatory bowel disease

IBS: Irritable bowel syndrome

IDSA: Infectious Diseases Society of America

MRSA: methicillin-resistant *Staphylococcus aureus*

NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

NIAID: National Institute of Allergy and Infectious Disease

UC: ulcerative colitis

UTI: urinary tract infection

RCTs: randomized controlled trials

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ABSTRACT

Introduction: Fecal microbiota transplantation (FMT) is commonly used for treatment of *C. difficile* infections (CDI), although prospective safety data are limited and real-world FMT practice and outcomes are not well described. The FMT National Registry was designed to assess FMT methods and both safety and effectiveness outcomes from North American FMT providers.

Methods: Patients undergoing FMT in clinical practices across North America are eligible. Participating investigators enter de-identified data into an online platform including FMT protocol, baseline patient characteristics, CDI cure and recurrence, and short and long-term safety outcomes.

Results: Of the first 259 participants enrolled at 20 sites, 222 have completed short-term follow-up at 1 month, and 123 have follow-up to 6 months; 171 (66%) are female. All FMTs were done for CDI, and 249 (96%) used an unknown donor (e.g., stool bank). One-month cure occurred in 200 (90%); of these, 197 (98%) received only a single FMT. Among 112 with initial cure who were followed to 6 months, 4 (4%) had CDI recurrence. Severe symptoms reported within 1-month of FMT included diarrhea (5 (2%)) and abdominal pain (4 (2%)); 3 (1%) had hospitalizations possibly related to FMT. At 6 months, new diagnoses of irritable bowel syndrome were made in 2 (1%) and inflammatory bowel disease in 2 (1%).

Conclusions: This prospective real-world study demonstrated high effectiveness of FMT for CDI with a good safety profile. Assessment of new conditions at long-term follow-up is planned as this registry grows and will be important for determining the full safety profile of FMT.

Key Words: risk, microbiome, bacteriotherapy

INTRODUCTION

Recurrent *Clostridioides difficile* infection (CDI) is common and increasing within the United States¹. It is associated with significant morbidity and mortality² and frequent failure of standard medical treatments³. Fecal microbiota transplantation (FMT) has proven to be a highly efficacious therapeutic modality to prevent recurrent CDI⁴ and increasing data support its use in severe or refractory cases⁵. FMT is permissible for CDI not responsive to standard therapy under a policy of enforcement discretion of the United States Food and Drug Administration (FDA). This policy, the widespread availability of the therapeutic substrate, and the ease of administration have facilitated the use of FMT for treatment of CDI. However, early adoption and expansion of FMT in clinical practice has allowed FMT to bypass the standard investigatory pathway in which large randomized controlled trials (RCTs) contribute important short- and long-term safety data before a product comes to market.

While the value of FMT in treating recurrent CDI is clear, the potential long-term consequences are not known. The gut is estimated to contain 1000 bacterial species containing 100-fold more genes than the human genome. Viruses, bacteriophages, archaea and fungi contribute to this microbial community⁶ which functions as an 'organ' with an immense impact on human health and disease, including host metabolism, physiology, nutrition and immune function⁷. Recent evidence demonstrates long-term engraftment of donor microbes into the recipients of FMT⁸. *A priori* knowledge is not available regarding the impact of transferring these complex communities from one individual to another, although animal models and human studies indicate that manipulation of gut microbiota can affect host susceptibility to diseases such as obesity⁹ and inflammatory bowel disease (IBD)^{10-12 10-12 10-12 10-12 10-12 10-12 10-12 10-12 10-12}. As the practice of FMT and related therapeutic methods rapidly expand, it is crucial to determine the effectiveness and best practices of FMT techniques, and to assess the short-term and long-term safety. Furthermore, understanding FMT effectiveness and safety in "real-world" clinical settings is important

because many recurrent CDI patients are not eligible for clinical trials due to common comorbidities such as IBD and immunocompromised status¹³ and because interest in FMT for other indications is increasing.

To address these needs, the American Gastroenterological Association (AGA) Institute, in partnership with other professional organizations, has developed an FMT National Registry to collect clinical and patient-reported outcomes. This registry, funded by a grant from the National Institute of Allergy and Infectious Diseases (NIAID), primarily aims to assess the short-term and long-term safety of FMT and other gut-related microbiota products. Secondary objectives include characterizing the effectiveness of FMT and other gut-related microbiota products, gathering information on FMT practice in North America, and promoting scientific investigation in FMT and the gut microbiome. Here we report on the first 259 participants enrolled in the FMT National Registry.

METHODS

Study Design

The FMT National Registry is an ongoing, prospective, observational, multicenter registry of North American participants who receive FMT for any indication and began enrolling patients in December 2017. The registry is administered by the AGA with grant support by the NIAID (award number R24AI118629). Partner organizations include the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), the Infectious Diseases Society of America (IDSA), and the Crohn's & Colitis Foundation.

This observational registry has no study-mandated protocol for FMT or follow-up visits. Rather, participants are treated at the discretion of their providers. Diagnosis of CDI and need for FMT or

subsequent anti-CDI therapies was determined by individual registry sites. The registry was approved by Western Institutional Review Board, Inc. and all subjects provide written informed consent. De-identified data are entered by investigators at participating sites into electronic case report forms on a data capture system maintained by Viedoc™ (ACI Clinical, Bala Cynwyd, PA). Data collection is overseen remotely by AGA under the supervision of a steering committee comprising experts in FMT, gut microbiome, clinical research, epidemiology, and informatics. Participant safety is reviewed at least yearly by an Observational Study Monitoring Board.

Participating sites were primarily self-identified through an online survey created by AGA to gauge interest in the registry. Other sites were referred by members of the steering committee.

Subjects

Inclusion criteria are the ability to provide informed consent, receipt of FMT or another gut microbial therapeutic product within 90 days after providing consent, and access to internet and/or telephone. The only exclusion criterion is incarceration.

Data Collection

Data are collected regarding FMT methods (e.g., screening of donor and recipient, stool preparation, FMT delivery method), baseline characteristics of donors and recipients of FMT (e.g., demographic information, details on indication for FMT, body mass index, medical history, medications) (**Supplement 1**). Severity of CDI was classified per published guidelines¹⁴. Pre-defined safety (short-term symptoms, new medical conditions, other adverse events) and effectiveness (e.g., cure and recurrence for CDI, IBD status) outcomes are provided on the electronic case report form (**Supplement 2**), which also allows free-text entry of additional outcomes.

Data are collected by the participating sites at baseline and at the following timepoints after the participant's FMT procedure: 1 month, 6 months, 1 year, and 2 years. The registry protocol allows for these follow up data to be collected either at clinic visits or by telephone interview, as per local preferences at each site. This publication reports data at baseline, 1 month and 6 months. The data for this publication were extracted from the database on September 2, 2019.

Outcomes for Analysis

The primary outcome of effectiveness was cure of CDI assessed at 1 month (window 20-60 days) after FMT. Cure was defined as resolution of diarrhea without need for further anti-CDI therapy. We also assessed cure of CDI at 6-months (window 120-240 days) after FMT.

Safety outcomes included patient symptoms, infections, hospitalizations, deaths, and changes in current medical conditions or development of new medical conditions. One-month adverse events included those reported up to 60 days after FMT, whereas 6-month adverse events included those reported between 61 to 240 days after FMT.

Results are reported descriptively without hypothesis testing. For categorical variables, proportions are presented. For continuous variables, mean, median, standard deviation, and range are provided.

RESULTS

Demographics

Between December 5, 2017 and September 2, 2019, 259 participants with post-FMT follow-up were enrolled at 20 sites (**Figure 1**).

Table 1 lists baseline characteristics of the 259 participants. Treated participants ranged in age from 1-98 years with a median age of 63 years. Twenty (8%) of the participants were <18 year of age. Recipients were more commonly female than male (171 (66%) vs. 88 (34%)) and 238 (92%) were white. Of note, baseline comorbidities included irritable bowel syndrome (IBS) in 30 (12%), ulcerative colitis (UC) in 24 (9%), and Crohn's disease in 19 (7%). Regional distribution in the U.S. was primarily in the Northeast (45%) and Midwest (43%).

Indications

All participants were treated with FMT for a diagnosis of CDI. The majority were diagnosed with CDI based on symptoms and stool testing, including polymerase chain reaction (163 (63%)), enzyme immunoassay (54 (21%)), or both (20 (8%)) (**Table 2**).

Of the 259 participants with reported baseline CDI severity, most were moderate (115 (44%)) or mild (92 (36%)) (**Table 2**). Duration of CDI diagnosis pre-FMT varied from less than one week to 9 years with a median duration of 20 weeks. The mean number of CDI episodes reported prior to FMT was 3.5 (range 1 to 15). Among the 15 cases with 1 prior CDI episode, 4 were severe, 7 moderate and 4 were mild, all were presumed to have failed standard anti-CDI therapy. Almost all participants (236 (91%)) had a prior course of vancomycin and 141 (55%) had also received a vancomycin taper or pulse regimen. The median duration of vancomycin treatment was 14 days (range 1-203 days) and 146 of these participants (62%) had 2 or more courses of treatment. Among other prior CDI treatments, 103 (40%) had received metronidazole and 73 (28%) had been treated with fidaxomicin.

FMT Methodology

Almost all participants (249 (96%)) received FMT using an unknown donor, primarily from stool banks (OpenBiome (167 (67%)), other stool banks (73 (24%)) (**Table 3**). Sites using an alternate source of stool described site specific donor identification and screening techniques. The median volume administered

was 250 ml (range 21-400 ml). The primary method of FMT delivery was colonoscopy (221 (85%)) followed by upper endoscopy (15 (6%)) (**Table 3**). In all cases the site investigators planned a single dose protocol of FMT for CDI therapy.

Outcomes

Effectiveness

Of the 259 participants, 222 returned within the 1-month follow-up window. Of these, 200 participants (90%, 95% CI 85-93%) had CDI cure, with 197 (98%) requiring only a single FMT to achieve cure (**Figure 2**). Participants not included in this effectiveness outcome calculation included those whose first visit occurred before day 20 (n=9), after day 60 (n=28), or who were missing first visit data (n=6). Of the participants whose first visit occurred before 20 days, all were reported as cure and 6 participants remained cured at subsequent follow-up points; 3 participants did not have further follow up beyond this first visit. Post-hoc analysis of the 256 participants who had a follow-up visit recorded at least 20 days after FMT (first day of the 1-month visit window) was performed, and 224 (88%, 95% CI 83-91%) were reported as cure. Analysis of an intent-to-treat population of all participants entered, including those lost to follow-up, still reveals a cure rate of 224/259 (86%, 95% CI 82-90%).

Of the 259 participants, 123 had both 1-month and 6-month follow-up within the pre-specified windows. Of the 112 participants cured at 1-month and with follow up at the 6-month time point, 4 (4%) had developed recurrent CDI at a median of 8 weeks (range 8-14 weeks) post-FMT (**Figure 2**). Of the 11 participants failing initial FMT who were followed to 6 months, 7 (64%) were reported as cured at this later timepoint. Treatments administered to these 7 participants included metronidazole and/or vancomycin (6 (86%)) or repeat FMT (1 (14%)). Participants not included in the 6-month effectiveness outcome calculation included those who reported cure at the first visit but withdrew (n=4) or whose

visit occurred after the data pull cutoff (n=80). Post-hoc analysis of 145 participants with data reported within the 6-month visit window, regardless of whether they had 1-month follow-up visit, was performed and 128 (88%, 95% CI 82-93%) were reported as cure.

Short-term (one-month) adverse events

Three procedure-related complications occurred: 1 colonoscopic perforation and 2 episodes of gastrointestinal bleeding. The perforation occurred at a biopsy site in an 82-year-old woman with a history of microscopic colitis; the participant underwent a colectomy with full recovery. One episode of mild and self-limited rectal bleeding was reported at telephone follow-up after colonoscopic FMT. One participant experienced post-polypectomy bleeding which required hospitalization.

Post-FMT symptoms were common with 106 (45%) participants reporting at least one symptom. The most common symptoms were non-CDI diarrhea (n=69), abdominal pain (n=39), bloating (n=34) and constipation (n=24). A total of 212 symptoms was reported, of which 13 (6%) were severe (**Table 4**).

Infections were reported in 11 participants (5%), including 2 (1%) which were felt by the site investigator to be possibly related to the procedure: *Bacteroides fragilis* bacteremia in one participant with severe diarrhea pre- and post-FMT, and enteropathogenic *E. coli* on a multiplex polymerase chain reaction stool panel in a participant who reported soft-stools following FMT. Other infections in 9 participants were felt to be unrelated and included urinary tract infection (UTI) (n=4), pneumonia (n=3), *E. coli* bacteremia (n=1) and tooth infection (n=1) (**Table 4**).

Hospitalizations were reported in 27 (12%) participants within 1 month after FMT. The most common reason for hospitalization was CDI recurrence (n=6). Three hospitalizations were reported as possibly related to the FMT procedure: continued diarrhea, abdominal pain, dehydration, and fever (n=1), UC flare (n=1), and perforation (n=1). No participant deaths were reported at 1-month follow-up.

Participants who missed the visit (n=6) or whose visit fell after 61-days post FMT (n=22) were not included in the short-term safety analysis.

Six-month adverse events

Among the 156 participants with data collected at 6-month follow-up, 6 participants (4%) had one or more new infections diagnosed between 1 and 6 months including pneumonia; *Campylobacter infection*; cellulitis and infected arteriovenous fistula with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia; pneumonia with streptococcus pharyngitis; UTI; and pneumonia, UTI and acute kidney injury +/- aspiration pneumonia. (**Table 5**) All infections resolved.

Hospitalizations were reported in 30 participants (19%) between 1 and 6 months after FMT (**Table 5**). The most common reason was an infection other than CDI: UTI (n=2); pneumonia (n=1); MRSA (n=1); septicemia (n=1); and 1 participant with cellulitis, infected arteriovenous fistula and MRSA bacteremia. Three participants were hospitalized for CDI recurrence.

Two (1%) participants had a new diagnosis of IBS and 2 (1%) had a new diagnosis of IBD (both UC) within 6 months after FMT (**Table 5**).

Four participants died, but no deaths were attributed to FMT; the causes reported by the site investigators were chronic obstructive pulmonary disease, ovarian cancer, septicemia, and worsening dementia.

Discussion

This is the largest prospective study to date of effectiveness and safety outcomes after FMT. CDI cure rates were excellent at approximately 90% and in line with those reported in RCTs of FMT¹⁵⁻¹⁸ and in a National Pediatric FMT Registry¹⁹. Thus, patients can expect to achieve high rates of success with FMT for refractory CDI in standard clinical practice. In addition, CDI cure could be achieved with only 1 FMT

in virtually all cases. Finally, we found FMT response to be durable, with recurrence in the 6 months after successful FMT seen in only 4% of participants, occurring most often within 2 months. For those with unsuccessful FMT at one month, most could still achieve cure by 6 months using either standard antibiotic therapy or following repeated FMT.

Risk of infection transmission from FMT has been of great concern, highlighted by a recent FDA report of 2 cases of extended spectrum beta-lactamase producing *E. coli* infections (one fatal) believed to have been transmitted by donor stool²⁰. Most donors in our cohort were from a stool bank that screens extensively for transmissible pathogens, including multi-drug resistant organisms. Short-term infections reported in registry participants, so far, have been few in number, occurring in 5% of those treated, with only 1% felt possibly related to the FMT. Indeed, infectious complications after FMT appear remarkably rare, as was reported in a recent systematic review which showed infections occurred in only 2.5% of over 1,000 patients treated²¹. Even high-risk immunocompromised patients appear to have a low risk of contracting an infection related to FMT^{22, 23}. However, infections after FMT may not be recognized or recorded in retrospective studies not designed specifically to assess safety outcomes, highlighting the importance of continued collection of data such as these in prospective studies with pre-defined safety and effectiveness outcomes.

Other short-term adverse events after FMT can be the result of the procedure used to administer the treatment. Fatal aspiration pneumonia was previously reported as a complication of FMT administered by nasoduodenal tube²⁴. Most sites in this registry administer FMT colonoscopically, and 3 colonoscopy-related complications were reported. They were considered related to the procedure itself rather than the FMT. There may be advantages to administering FMT via lower endoscopy, including possibly increased efficacy^{25, 26} and the ability to examine the colon for other underlying pathology, such as IBD. However, it is important to weigh the risk of procedural complications and associated sedation, as well as medical costs, against the benefits, especially in patients who are

financially vulnerable, frail, or have significant cardiopulmonary comorbidities. Indeed, the preferred method of administration may vary depending on the clinical situation and local expertise. The majority of FMTs in this country are being done by gastroenterologists using material from donor stool banks with the preferred method of administration being colonoscopic. As the registry expands, we plan to target additional sites that use other methods of delivery, as we hope to be able to compare the effectiveness and safety of FMT administered by different routes, such as capsule, enema, or naso-intestinal tubes.

The risk of further CDI recurrences is known to increase with each subsequent CDI episode, with rates as high as 65% after a second recurrence^{3,27}. Though uncontrolled, our data are compelling in that the cycle of recurrent CDI was broken in a large number of participants who had failed 2 or more previous courses of conventional antibiotic therapy. RCTs have restrictive inclusion and exclusion criteria and thus are not fully representative of an unselected real-world population of patients with CDI. In fact, the majority of patients with recurrent CDI do not qualify for RCTs of microbiota-based therapeutics¹³ because of co-comorbidities such as IBD or immunocompromised status, highlighting the value of registry studies such as this, which allow the collection of important effectiveness and safety data that are more reflective of the real-world population.

Weaknesses of this study are inherent to the design and included missing or incomplete data, multiple follow-up visits falling outside of pre-specified windows, patients lost to follow-up, and potential for recall bias when patients were queried at follow-up. Donor screening protocols also varied across the participating sites, leading to possible differences in the potential for transmission of infectious agents such as enteropathogenic *E. coli*. Additionally, because this was an observational study rather than a clinical trial, FMT and post-FMT practice was not mandated but rather at the discretion of FMT providers at each site. Indications for FMT, diagnoses of CDI, and determinations of cure were made based on clinical grounds by site investigators. Transient episodes of diarrhea which resolved

without further anti-CDI therapy were not considered failures of FMT and differing CDI testing methods (e.g., PCR, toxin enzyme immunoassay) were used by investigators. In real-world settings, the diagnosis of recurrent CDI is commonly made based on compatible symptoms and anti-CDI therapy started without confirmatory testing. Registry staff queried site investigators to obtain missing or incomplete data or for clarification or additional information around serious adverse events. Although this report includes results from 20 different geographically diverse centers around the U.S., we cannot conclude that they are wholly representative of FMT practice and results nationally. The Registry sites tend to be larger volume centers with an interest in FMT

We developed the FMT National Registry in order to provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness²⁸. Our registry is designed to provide long-term assessment for up to 10 years to answer the most pressing safety question regarding FMT: whether FMT increases the risk of developing other medical conditions in the years after it is performed. Indeed, this was a lesson the medical community learned from the inadvertent transmission of human immunodeficiency virus and hepatitis C virus by blood transfusion. A variety of conditions postulated to potentially be influenced by the gut microbiota (e.g., diabetes, cancer, cardiovascular events, autoimmune disease) are pre-specified to be collected from physicians for up to 2 years and patients for up to 10 years in the Registry. To assess whether such conditions are increased in patients receiving FMT, we plan to use a retrospective control group from an insurance claims database of patients with recurrent CDI treated with at least 3 courses of antibiotics rather than FMT.

We anticipate adding registry sites within the next 6 months, which will increase the number, as well as geographic and demographic diversity, of participants recruited. Obtaining information on current FMT methods in North America is an important first step in characterizing FMT practice with the future goal of standardizing and optimizing FMT. In addition, several gut microbiota-derived products

are in late phases of clinical development and likely will be approved for use in the near future. These products are hoped to reduce concerns regarding donor screening and infection transmission, but their real-world safety and effectiveness will be important to determine. We also anticipate the Registry will evaluate patients treated with these new products once released.²⁹⁻³¹

Real-world evidence is becoming increasingly important in health care and is a recent interest of the FDA in monitoring for adverse events and regulatory decision making³². FMT practitioners together with the research community have the responsibility to protect the safety of patients receiving FMT and the opportunity to gain tremendous new insights into the biology of the human gut microbiome.

REFERENCES

1. Ma GK, Brensinger CM, Wu Q, et al. Increasing Incidence of Multiply Recurrent *Clostridium difficile* Infection in the United States: A Cohort Study. *Ann Intern Med* 2017;167:152-158.
2. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015;372:825-34.
3. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol* 2002;97:1769-75.
4. Moayyedi P, Yuan Y, Baharith H, et al. Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: a systematic review of randomised controlled trials. *Med J Aust* 2017;207:166-172.
5. Fischer M, Sipe B, Cheng YW, et al. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: A promising treatment approach. *Gut Microbes* 2017;8:289-302.
6. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. *Genome medicine* 2016;8:51-51.
7. Guinane CM, Cotter PD. Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. *Therapeutic advances in gastroenterology* 2013;6:295-308.
8. Smillie CS, Sauk J, Gevers D, et al. Strain Tracking Reveals the Determinants of Bacterial Engraftment in the Human Gut Following Fecal Microbiota Transplantation. *Cell Host Microbe* 2018;23:229-240.e5.
9. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 2006;444:1027-31.
10. Borody TJ, Warren EF, Leis S, et al. Treatment of ulcerative colitis using fecal bacteriotherapy. *J Clin Gastroenterol* 2003;37:42-7.
11. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015;149:102-109.e6.

12. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;389:1218-1228.
13. Kelly CR, Fischer M, Grinspan A, et al. Patients Eligible for Trials of Microbe-Based Therapeutics Do Not Represent the Population With Recurrent *Clostridioides difficile* Infection. *Clin Gastroenterol Hepatol* 2019.
14. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013;108:478-98; quiz 499.
15. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013;368:407-15.
16. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection: A Randomized Trial. *Ann Intern Med* 2016;165:609-616.
17. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *Jama* 2017;318:1985-1993.
18. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015;41:835-43.
19. Nicholson MR, Mitchell PD, Alexander E, et al. Efficacy of Fecal Microbiota Transplantation for *Clostridium difficile* Infection in Children. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2019:S1542-3565(19)30427-6.
20. Administration USFaD. Food and Drug Administration. Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation – Screening and Testing of Stool Donors for Multi-drug Resistant Organisms. . Rockville, MD, 2019.
21. Wang S, Xu M, Wang W, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. *PLoS One* 2016;11:e0161174.
22. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014;109:1065-71.
23. Shogbesan O, Poudel DR, Victor S, et al. A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplant for *Clostridium difficile* Infection in Immunocompromised Patients. *Can J Gastroenterol Hepatol* 2018;2018:1394379.
24. Baxter M, Ahmad T, Colville A, et al. Fatal Aspiration Pneumonia as a Complication of Fecal Microbiota Transplant. *Clin Infect Dis* 2015;61:136-7.
25. Quraishi MN, Widlak M, Bhalal N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2017;46:479-493.
26. Cohen NA, Livovsky DM, Yaakovovitch S, et al. A Retrospective Comparison of Fecal Microbial Transplantation Methods for Recurrent *Clostridium Difficile* Infection. *Isr Med Assoc J* 2016;18:594-599.
27. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. *Infect Control Hosp Epidemiol* 1999;20:43-50.
28. Gliklich RE DN, Leavy MB, editors. *Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd Edition.* 2014.
29. Therapeutics F. Finch Therapeutics Announces Positive Topline Results from Randomized Controlled Trial of CP101, an Oral Microbiome Drug, for the Prevention of Recurrent *C. difficile* Infection, 2020.

30. Wire B. Rebiotix and Ferring Announce World's First With Positive Preliminary Pivotal Phase 3 Data for Investigational Microbiome-based Therapy RBX2660, 2020.
31. Therapeutics S. Seres Therapeutics to Host Virtual SER-109 Focused Symposium on May 27, 2020, Ahead of Phase 3 ECOSPOR III Study Read-Out, 2020.
32. Franklin JM, Glynn RJ, Martin D, et al. Evaluating the Use of Nonrandomized Real-World Data Analyses for Regulatory Decision Making. *Clin Pharmacol Ther* 2019;105:867-877.

Figure 1. Distribution of registry sites by total number of subjects enrolled.

Table 1. Subject demographics.

Characteristic	N (%)
<i>Age</i>	
< 18 years	20 (8)
18 – 55 years	77 (29)
> 55 years	162 (63)
<i>Sex</i>	
Female	171 (66)
Male	88 (34)
<i>Race</i>	
White	238 (92)
Black/African American	5 (2)
Asian	3 (1)
Other	4 (2)
Unknown	9 (3)
<i>Ethnicity</i>	
Not Hispanic/Latino	246 (95)
Hispanic/Latino	11 (4)
Not reported	2 (1)
<i>Region</i>	
U.S. Northeast	117 (45)
U.S. Midwest	111 (43)
U.S. South	18 (7)
U.S. West	13 (5)
<i>Comorbidities at baseline (\geq 5% prevalence)^a</i>	
Hypertension	82 (32)
Hyperlipidemia	70 (27)
Anxiety	48 (19)
IBD	45 (17)
Ulcerative colitis	24 (9)
Crohn's disease	19 (7)
Indeterminate colitis	2 (1)
Depression	40 (15)
Cancer	35 (14)
Hypothyroidism	32 (12)
Cardiovascular disease	31 (12)
Irritable bowel syndrome	30 (12)
Type 2 diabetes	28 (11)
Asthma or allergic/atopic conditions	15 (6)

^a Note some participants had more than one comorbidity.

Table 2. FMT indication and related characteristics.

Characteristics	N (%)
<i>FMT indication</i>	
CDI	259 (100)
<i>Method of CDI diagnosis</i>	
Symptoms and PCR ¹	163 (63)
Symptoms and EIA ¹	54 (21)
Symptoms, EIA and PCR ¹	20 (8)
Symptoms only	12 (5)
PCR only ¹	8 (3)
EIA only ¹	1 (<1)
Not reported	1 (<1)
<i>CDI severity</i>	
Mild	92 (36)
Moderate	115 (44)
Severe	48 (19)
Severe-complicated	2 (1)
Not reported	2 (1)
<i>CDI duration</i>	
< 1 month	14 (5)
1-6 months	149 (58)
7-12 months	61 (24)
13-24 months	17 (7)
> 24 months	16 (6)
Not reported	2 (1)
<i>Number of prior CDI episodes</i>	
1	15 (6)
2	34 (13)
3	110 (42)
4	56 (22)
5 or more	42 (16)
Not reported	2 (1)
<i>Prior treatments for CDI</i>	
Vancomycin	236 (91)
Vancomycin taper/pulse	141 (54)
Metronidazole	104 (40)
Fidaxomicin	73 (28)
Probiotics	44 (17)
Other treatments	14 (5)
No prior treatments	5 (2)

¹ EIA = enzyme immunoassay; PCR = polymerase chain reaction

Table 3. Summary of FMT methodology.

	N (%)
<i>Stool donor type</i>	
Unknown donor	249 (96)
OpenBiome	167 (67)
Other stool bank	73 (29)
Source not reported	9 (4)
Known donor	8 (3)
Not reported	2 (1)
<i>Primary method of FMT delivery</i>	
Colonoscopy	221 (85)
Upper endoscopy	15 (6)
Oral capsule	8 (3)
Sigmoidoscopy	2 (1)
Naso-intestinal tube	2 (1)
Colonoscopy and upper endoscopy (same procedure date)	2 (1)
Other	3 (1)
Not reported	6 (2)

Figure 2. FMT effectiveness.

Table 4. Adverse events reported up to 1 month after FMT.

	N (%)
<i>Common symptoms of any severity with more than 2% prevalence</i>	
Diarrhea	69 (30)
Abdominal pain	39 (17)
Bloating	34 (15)
Constipation	24 (10)
Nausea and/or vomiting	15 (6)
<i>Severe symptoms</i>	
Diarrhea	5 (2)
Abdominal pain	4 (2)
Bloating	1 (<1)
Constipation	1 (<1)
Other	2 (1)
<i>New infections</i>	
None	219 (95)
Unrelated to FMT	9 (4)
Possibly related to FMT	2 (1)
<i>Bacteroides fragilis</i>	1 (<1)
Enteropathogenic <i>E. coli</i>	1 (<1)
Not reported	1 (<1)
<i>Hospitalizations</i>	
None	204 (88)
Unrelated to FMT	24 (10)
Possibly related to FMT	3 (1)
Perforation	1 (<1)
Ulcerative colitis flare	1 (<1)
Diarrhea, abdominal pain, fever	1 (<1)

Table 5. Adverse events reported between 1-6 months after FMT.

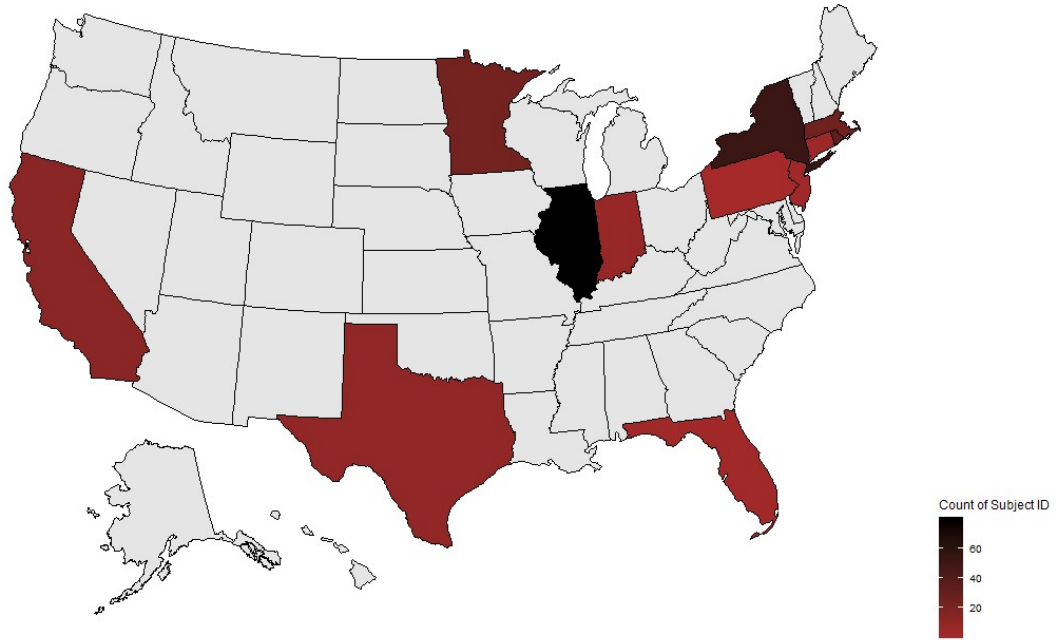
	N (%)
<i>New diagnoses</i>	
No	125 (80)
Yes ^a	21 (13)
Irritable bowel syndrome - diarrhea	2 (1)
Ulcerative colitis	2 (1)
Other ^b	22 (14)
Not reported	10 (6)
<i>Serious infections</i>	
No	140 (90)
Yes ^a	6 (4)
Pneumonia	1 (<1)
Urinary tract infection	1 (<1)
<i>Campylobacter</i> infection	1 (<1)
Cellulitis	1 (<1)
Infected AV fistula/MRSA bacteremia	1 (<1)
<i>Streptococcus pharyngitis</i>	1 (<1)
Pneumonia/Acute kidney injury +/- aspiration pneumonia/Urinary tract infection	1 (<1)
Not reported	10 (6)
<i>Hospitalizations</i>	
No	126 (81)
Yes ^a	30 (19)
Infection other than CDI	8 (6)
CDI recurrence	3 (2)
Other ^c	30 (20)
<i>Deaths</i>	
Unrelated to FMT	4 (3)
Related to FMT	0 (0)

^a Note some participants had more than one diagnosis or reason for hospitalization.

^b All other conditions were N = 1: Abdominal aortic aneurysm, Barrett's esophagus, belching, cardiovascular disease, COPD, colon cancer, dermatitis, fistula between Indiana pouch and bowel, GERD, hair loss, jaw cancer, left heart failure, left inguinal hernia, neurologic disorder, osteopenia, osteoporosis, overflow diarrhea, pelvis floor dysfunction, pregnancy, prostate cancer, snoring, urinary tract infection.

^c Other reasons for hospitalization included acute episode of croup, acute right anterior cerebral artery stroke, breast implant removal, breathing, cirrhosis, colitis, constipation, Crohn's disease flare, dehydration (2 cases), diverticulitis, abnormal liver function tests, fainting, hysterectomy, intestinal obstruction, lung transplant symptoms, overflow diarrhea, peritoneal dialysis catheter placement, potential ulcerative colitis flare, primary sclerosing cholangitis flare (worsening of left hepatic biliary duct inflammation), robotic prostatectomy, seizure, severe sepsis/septic shock, surgery for recurrent colon cancer, ulcerative colitis flare, ulcerative colitis laparoscopic ileal pouch anal anastomosis with ileostomy, urinary retention, urinary tract infection, vomiting, and weakness.

State Distribution of Subject ID



Cure
= 200 (90)

Failure
= 22 (10)

Initial cure
= 112 (91)

Initial failure
= 11 (9)

Remained cured
= 108 (96)

Remained failure
= 4 (36)

Recurrent CDI
= 4 (4)

Subsequent cure
= 7 (64)

What You Need to Know

Background and context: Fecal microbiota transplantation (FMT) is widely used for treatment of *C. difficile* infection unresponsive to standard therapy, although a paucity of prospective and real-world data exists.

New Findings: FMT led to a cure of *C. difficile* infection in 90% of patients in a registry including 20 North American FMT practice sites.

Limitations: Follow-up beyond 6 months is not yet available.

Impact: The effectiveness and safety of FMT is similar in a real-world experience to that reported in research studies.

Short summary: Approximately 90% of patients who undergo FMT for *C. difficile* infection can expect to be cured of the infection with few serious side effects due to FMT.