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Outcomes of Fecal Microbiota Transplantation for *Clostridioides difficile* Infection in South Australia

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Background. Fecal microbiota transplantation (FMT) sourced from a bank of prescreened anaerobically processed frozen donor stool has been available in South Australia since 2013. This study aimed to evaluate the real-world clinical and safety outcomes of FMT for recurrent, refractory, and/or severe or fulminant *Clostridioides difficile* infection (CDI) facilitated via this centralized facility.

Methods. Donor screening test data were prospectively collected on all donors who passed prescreening evaluations between April 2013 and August 2023. The South Australian FMT for CDI database prospectively recorded outcomes for consecutive patients who underwent FMT for CDI from August 2013 to May 2023 in South Australia.

Results. An overall 98 potential donors passed prescreening assessments and underwent laboratory screening tests: 32 (33%) had tests that failed, 5 (5%) had incomplete screening, and 61 (62%) passed. Detection of an extended-spectrum β-lactamase–producing organism (9/65, 14%) was the common reason for ineligibility following completion of screening tests. In total 220 cases of CDI were recorded, and follow-up data were available in 216. Primary cure occurred in 84% of cases (182/216): 88% (132/150) for recurrent CDI, 76% (50/66) for refractory CDI, 85% (51/60) for severe disease, and 65% (17/26) for fulminant disease. Repeat FMT was delivered in 23 of 34 cases (68%), with secondary cure in 74% (17/23 cases). Serious adverse events were observed in 6 patients overall (3%). No deaths were directly attributable to FMT.

Conclusions. FMT was safe and efficacious for management of recurrent and refractory CDI over a 10-year period in a real-world prospective Australian cohort. Further studies to optimize the use of FMT for severe and fulminant CDI are warranted.

Keywords. *Clostridioides difficile*; donor; FMT; screening.

Clostridioides difficile infection (CDI) is a leading cause of health care–related infection worldwide and is associated with significant mortality, morbidity, and health care cost [1, 2]. Infection ranges from mildly symptomatic to fulminant colitis [3, 4]. Recurrent CDI is an increasingly challenging problem, with a rate of recurrence of approximately 20% after successful initial therapy, 40% after a first recurrence, and >60% after ≥2 recurrences [5–7]. Severe and fulminant CDI has limited therapeutic options and carries a high mortality rate of 36% to 58%, which remains high in patients following colectomy [8–11].

Fecal microbiota transplantation (FMT) has proved to be an effective treatment for recurrent CDI in multiple randomized controlled trials, with a pooled efficacy of 91% following repeat FMT and 84% following a single FMT [12]. FMT is recommended in treatment guidelines worldwide for use in this setting [13–16]. In addition, FMT is recommended as a treatment option for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly for poor surgical candidates [13–16].

To ensure safety, regulatory authorities internationally have begun to formally regulate FMT manufacture, storage, release, and supply. However, as a complex microbial product that cannot be completely standardized, many regulatory challenges remain. In Australia, formal regulation of FMT product commenced with the implementation of the Therapeutic Goods (Standards for Faecal Microbiota Transplant Products) (TGO 105) Order 2020 by the Therapeutic Goods Administration. FMT product manufactured in a central facility, stored, and then distributed is regulated as a class 2 biological and must meet the standard of good manufacturing practice.

In South Australia, FMT manufactured from prescreened donors has been undertaken via centralized facilities and distributed to hospitals since 2013 [17, 18]. From inception, data

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have been prospectively collected on FMT stool donor screening and the outcome of recurrent, refractory, and/or severe or fulminant CDI managed with FMT. The aim of this study was to evaluate the clinical and safety outcomes of FMT manufactured from screened donors for recurrent, refractory, and/or severe or fulminant CDI in South Australia.

METHODS

Stool Donor Screening

Data were analyzed from all potential donors who completed screening laboratory testing from the establishment of the donor screening program in April 2013 until August 2023. Donor demographic data and the methodology and results of blood, stool, and swab tests were collected prospectively. The criteria for eligibility, the laboratory tests used, and the frequency of testing evolved over the study period and have been published (for donor screening protocols, see Supplementary eAppendix 1) [19–22].

All donors were prescreened with a medical history that included risk assessment for microbiome-mediated and infectious diseases prior to testing. Donors whose screening failed prior to laboratory testing were excluded. Testing episodes were classified as "passed" if the donor fulfilled all the eligibility criteria required at the time of testing, "failed" if any part of the testing episode failed, and "incomplete" if not all required testing was undertaken. All screening tests were completed at SA Pathology, Adelaide, Australia. Potential donors were excluded if their screening failed prior to laboratory testing or they did not undertake laboratory testing, as the data set for this cohort was incomplete.

FMT Manufacture

Stool was processed into liquid FMT product according to methods that have been previously described [19]. From 2013 to 2018, the FMT product was manufactured in a centralized facility associated within an academic institution. From 2019 onward, FMT was manufactured at BiomeBank, Thebarton, South Australia. From July 2021, the product was manufactured in a good manufacturing practice–licensed facility. Only 1 major change was implemented in product manufacturing among the facilities. At the initial facility, stool was homongenized with an autoclavable blender, and at BiomeBank a homogenizing stomacher was used. Treatment batches consisted of pooled stool (25%) blended with normal saline (65%) and glycerol (10%) under anaerobic conditions and frozen immediately at −80 °C.

FMT Delivery

In this real-world study, FMT delivery mode and volume were not controlled and were at the discretion of the treating clinician. When delivered colonoscopically, 200 mL of thawed liquid FMT product (50 g of stool) was the standard delivery volume for all patients. For enema delivery, 50 mL was the standard volume for all patients, and most patients received 4 doses over 4 days (total stool, 50 g). Upper gastrointestinal delivery methodology varied (between 100 and 200 mL) and was dependent on patient circumstances, as this route was predominantly reserved for patients for whom lower gastrointestinal delivery was considered unsafe. From 2018, the local protocol for treating patients with severe CDI changed from a single-dose FMT to sequential treatment modeled on data produced by Fischer et al [23]. The revised protocol involved patients receiving FMT by colonoscopy, followed by sequential daily FMT enemas until clinical improvement in symptoms.

FMT for CDI

The South Australian FMT for CDI database prospectively recorded outcomes from consecutive South Australian patients with CDI who underwent treatment with FMT manufactured by the centralized facilities. Data were collected as follows for all adult patients who received FMT for CDI from August 2013 to May 2023: baseline demographics, medical comorbidities, number of episodes of CDI, indication for FMT, severity indicators, adverse events, primary and secondary cure at 90 days, and 12-month and 5-year all-cause mortality.

CDI cases were defined in accordance with Australian consensus guidelines [14, 24]. CDI was defined as clinical features suggestive of CDI (diarrhea, ileus, toxic megacolon) with either microbiological evidence of toxin-producing *C difficile* or pseudomembraneous colitis demonstrated on colonoscopy. The presence of *C difficile* was confirmed via detection of *C difficile* DNA by polymerase chain reaction testing for the toxin B gene. Testing methodologies did not change over the study period, though the testing occurred at more than 1 microbiology laboratory across South Australia. Cytotoxin testing was not performed at any site. Recurrent CDI was defined as CDI that recurred within 8 weeks of onset of a previous episode, after resolution of symptoms. Refractory CDI was defined as CDI that failed to demonstrate clinical improvement following 3 to 4 days of recommended therapy. The time frames of 8 weeks for recurrent CDI and 3 to 4 days for refractory CDI were not specified in the 2011 Australian guidelines. Cases prior to publication of the 2016 guideline were retrospectively reviewed to ensure that all met the revised criteria. Severe CDI was defined as an episode of CDI with 1 or more of the following features in the absence of other clinical explanation: fever (>38.5 °C), rigors, hemodynamic instability, peritonitis or evidence of bowel perforation, ileus or toxic megacolon, white blood cell count $>15 \times 10^9$/L and <20% neutrophils, elevated lactate level, rise in creatinine level (>50% above baseline), albumin <25 mg/L, imaging finding (large intestine distension, colonic wall thickening, fat stranding, or unexplained ascites), or endoscopic finding of pseudomembranous colitis [14, 24, 25]. Fulminant

infection was retrospectively evaluated and defined according to the American College of Gastroenterology criteria as patients meeting criteria for severe CDI plus the presence of hypotension, shock, ileus, or toxic megacolon [3]. If patients met the criteria for fulminant infection, they were not additionally classified as severe. A patient with recurrent or refractory CDI may have also had severe or fulminant disease.

Primary cure was defined as no relapse of CDI within 90 days of initial FMT treatment. Secondary cure was considered no relapse of CDI within 90 days of a second FMT treatment, following relapse after initial treatment. Safety evaluations were at 90 days after initial FMT and 90 days after subsequent FMT if follow-up FMT was required for relapse after initial improvement. Criteria for immune suppression can be found in Supplementary eAppendix 2.

Patient Consent Statement

The donor screening component of the study was approved by Bellberry Limited (HREC2020-03-288) and the Royal Adelaide Hospital Research Ethics Committee (HREC/12/RAH/186). All participants gave full written informed consent. The FMT for CDI database was approved as a quality improvement project, and ethical approval was waived by the Central Adelaide Local Health Network Research Services.

RESULTS

Stool Donor Screening

Ninety-eight potential stool donors underwent clinical assessment, followed by blood, stool, and/or swab testing from 17 April 2013 to 7 August 2023: 43 donors were female and 51 were male; the mean age was 32.2 years (SD, 8.6). Four donors had incomplete data regarding age and gender.

In total, 97 donors completed at least 1 blood testing episode, and 95 donors completed at least 1 stool testing episode. The number of times that a donor required testing changed across the study period, as the testing approach moved from a test prior to donation to a test at the beginning and end of a donation period. There were 250 donor screening testing episodes. The mean number of testing episodes per donor was 2.45 (SD, 3.0).

Out of 98 donors, 32 (33%) were not enrolled because their initial screening test episode failed. Five donors (5%) had incomplete initial screening test episodes. Sixty-one (62%) passed their initial screening test episode and were enrolled into the donor program. Of the 61 enrolled donors, 14 (23%) had a subsequent screening test episode that failed. Three of these donors were permanently ineligible per the result, and 11 were eligible after a period of ineligibility and rescreening.

The blood testing results for donor serologic tests are available in Supplementary eTable 1. All donors with a detected result (apart from hepatitis A total antibody, unless it was an episode of seroconversion) were declared ineligible to donate and not tested again. Of 95 potential donors, 5 (5.3%) returned a detected result for *Strongyloides* antibody. Of 79 donors, 2 (2.5%) returned a detected result for hepatitis B core antibody.

In 2019, bacterial culture was replaced by nucleic acid amplification test (NAAT) for specific bacterial pathogens. There were no detected pathogens by bacterial culture on 29 tests in 24 donors. The results of enteric pathogen NAAT and antigen testing are available in Supplementary eTable 2. One donor who had a detected result for Shiga toxin–producing *Escherichia coli* was declared ineligible and not tested again. Two donors had adenovirus group F (40/41) detected on NAAT: one was declared ineligible and not rescreened, and the other, who had a respiratory illness at the time of testing, was rescreened after a period of ineligibility and enrolled into the donor program. One potential donor had *Helicobacter pylori* antigen detected in stool. This donor also had a positive multidrug-resistant organism (MDRO) screen result and hepatitis B core antibody and was declared permanently ineligible.

MDRO Screening

All MDRO screening was performed via culture-based methods. Vancomycin-resistant enterococci screening was introduced in 2016 and continued through the rest of the study period. There were 187 vancomycin-resistant enterococci screens on 70 donors; none returned a positive result. Extended-spectrum β-lactamase (ESBL) and carbapenem-resistant Enterobacterales screening began in 2019 and continued through the rest of the study period. There were 182 ESBL screens completed on stool samples from 65 potential donors. Of 65 donors, 9 (14%) returned growth of an ESBL-producing organism. In 1 case, a previously enrolled donor returned a positive result after prior negative screens, with >12 months between the negative and positive testing episodes and no high-risk exposure events. All other potential donors had a positive result on initial screening; they were not enrolled and were deemed permanently ineligible. There were 183 carbapenem-resistant Enterobacterales screens on 64 donors, with 1 positive result. A meropenem intermediate *Enterobacter* species was identified in 1 donor: there was no transmissible resistance mechanism detected, and the donor was deemed permanently ineligible. Methicillin-resistant *Staphylococcus aureus* screening began in 2020 and continued for the duration of the study period. There were 140 methicillin-resistant *S aureus* nasal swabs completed on 39 potential donors with no positive results.

SARS-CoV-2 Testing

Asymptomatic SARS-CoV-2 screening by nasopharyngeal NAAT commenced for enrolled donors in December 2021 after local community transmission of COVID-19 was established in South Australia. Nineteen donors had asymptomatic surveillance SARS-CoV-2 testing performed, and 273 SARS-CoV-2 tests were completed. Three tests (1.1%) conducted on 3 donors

Table 1. Baseline Patient Characteristics for FMT Recipients (N = 220)

Patient Characteristic	No. (%)
Age, y, median (IQR)	67 (49–80)
Gender	
Female	131 (60)
Male	89 (40)
Comorbidity	
Inflammatory bowel disease	34 (15)
Crohn disease	16 (7)
Ulcerative colitis	16 (7)
Indeterminate	2 (1)
Immunosuppressed	60 (27)
Diabetes	35 (16)
Indication for FMT	
Recurrent CDI	152 (69)
Prior recurrence	
1	21 (14)
2	39 (26)
3	51 (34)
>3	39 (26)
Unknown	2 (1)
Refractory CDI	66 (30)
Severe CDI	60 (27)
Fulminant CDI	26 (12)
CDI indication unclear	2 (1)
Initial method of FMT delivery	
Colonoscopy	199 (91)
Flexible sigmoidoscopy	3 (1)
Upper gastrointestinal	7 (3)
Enema only	11 (5)

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.

returned a detected result: 2 were symptomatic of COVID-19 within 48 hours of the test and 1 remained asymptomatic. Donors with a positive SARS-CoV-2 result were excluded from donation for 6 weeks regardless of symptoms.

FMT Safety and Efficacy for CDI

A total of 220 cases of CDI managed with FMT in 209 patients manufactured from the screened donors were recorded in the study period. Patient demographics and disease and treatment characteristics are displayed in Table 1.

Ninety-day follow-up data were available in 216 of 220 cases (98%). Twelve-month and 5-year all-cause mortality was available for 99% (187/189) and 95% (52/55) of cases, respectively. By year, there were 3 cases of CDI managed with FMT in 2013, 13 in 2014, 14 in 2015, 13 in 2016, 20 in 2017, 30 in 2018, 26 in 2019, 29 in 2020, 30 in 2021, 32 in 2022, and 10 in 2023 (recruitment completed in May 2023). The mean number of CDI relapses prior to FMT was 2.3 episodes (SD, 1.6).

In the recurrent group, 116 of 152 (76%) received prior vancomycin without a taper, with or without metronidazole; 27 (18%) received vancomycin with or without metronidazole, with a vancomycin taper; and 9 (6%) received prior metronidazole only. In the refractory CDI group, 95% (63/66) of patients received vancomycin with or without concurrent metronidazole therapy, while 3 patients (5%) received vancomycin and metronidazole followed by fidaxomicin.

The rates of primary cure following initial administration of FMT was 84% (182/216). Primary cure by indication is demonstrated in Figure 1. In those who did not achieve primary cure, repeat FMT was delivered in 23 of 34 (68%) cases for relapsed or refractory CDI, with secondary cure achieved in 17 (74%) of those cases (Table 2). In total, 199 of 216 (92%) cases were cured at 90-day follow-up. FMT overall outcome (primary and secondary cure at day 90) was 141 of 150 (94%) for recurrent CDI, 58 of 66 (88%) for refractory CDI, 55 of 60 (92%) for severe CDI, and 20 of 26 (77%) for fulminant CDI.

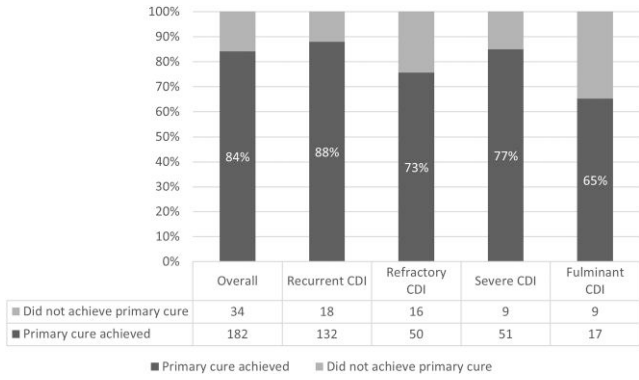

Figure 1. Overall cure rates following primary treatment with fecal microbiota transplantation. CDI, *Clostridioides difficile* infection.

Table 2. Characteristics and Outcomes of Patients Whose Initial FMT Treatment Failed (n = 34)

Patient Characteristic	No. (%)
Initial indication for FMT	
Recurrent CDI	18 (53)
Refractory CDI	16 (47)
Severe CDI [a]	9 (26)
Fulminant CDI [a]	9 (26)
Follow-up FMT	23 (70)
Method of FMT delivery	
Colonoscopy	18 (80)
Enema only	4 (15)
Missing data	1 (4)
Secondary cure following repeat FMT (n = 23)	
Recurrent CDI (n = 12)	9 (75)
Refractory CDI (n = 11)	8 (73)
Severe CDI (n = 7)	4 (57)
Fulminant CDI (n = 6)	3 (50)

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.
[a]Severe and fulminant CDI may have been classed as refractory to antibiotic therapy or recurrent.

Serious adverse events were observed in 6 patients overall (3%), 4 of whom had severe CDI. Two developed pneumonia, 1 myocardial infarction, 1 hemicolectomy postcolonoscopy for presumed barotrauma (which was not found on histopathologic samples postoperatively), 1 episode of per rectal bleeding, and 1 bowel perforation in the context of colorectal malignancy followed by death. Five patients underwent colectomy: 4 for fulminant CDI despite FMT and 1 for acute severe ulcerative colitis failing rescue medical therapy. The 12-month all-cause mortality was 12% (22/189), and the 5-year mortality was 25% (13/52). No patient deaths were directly attributable to FMT.

DISCUSSION

In this real-world cohort of patients with multiply recurrent and refractory CDI, FMT manufactured from the stool of screened donors was found to be safe and effective. Consistent with the literature, our data showed a primary cure rate of 84% [12]. For those who required further FMT, 74% of patients achieved secondary cure, leading to an overall cure rate of 92%.

The cohort had a particularly high proportion (40%) of patients receiving FMT for severe or fulminant CDI. There is a paucity of data on administration of FMT in severe or fulminant CDI. Tixier et al demonstrated an absolute risk reduction of 31.2% in mortality in highly comorbid cases with severe CDI that received FMT as compared with standard of care, with a number needed to treat of only 3.2 to prevent 1 death [26]. Similarly, Hocquart et al found a mortality odds ratio of 0.08 in patients with severe CDI who received FMT as compared with medical treatment alone, with a number needed to treat of 2 to prevent 1 death [27]. In our cohort, overall cure in patients with fulminant CDI following FMT was 77%. It has been reported that patients with severe or fulminant CDI and extensive pseudomembranes may require repeated FMT to achieve cure [23]. In our cohort, 6 of 9 patients with fulminant CDI had follow-up FMT after initial failure, with a cure rate of 50%. Optimizing FMT dosing in this patient population is an area that requires further evidence to guide practice.

Serious adverse events were uncommon, and most affected patients had severe CDI. No deaths were directly attributed to FMT. These data reflect the findings of a recent systematic review, which reported a low death rate directly attributable to FMT of 0.13% and found that most FMT-related adverse events were mild and self-limited [28]. All-cause mortality in our cohort was 12% at 12 months. This is relatively low when compared with previous reports, particularly as patients had recurrent, refractory, or severe disease, though it may relate to the younger overall age of the group (median, 67 years). In cohort studies and case series, 30-day mortality following CDI ranged between 8% and 19% and 1-year mortality between 11% and 37% [29]. Recurrent CDI has been associated with a 10-times higher rate of CDI-associated deaths than primary CDI [30].

Despite increasing evidence to support the safety and efficacy of FMT for CDI, there remains concern regarding the risk of disease transmission and clinician reluctance to accept the risk/benefit profile of FMT [31]. Over a 10-year period, the detection of pathogens in donors prescreened for risk was rare. The most common reason for donor ineligibility based on testing was gut ESBL carriage. While very few instances of disease transmission have been reported in association with FMT, pathogenic *E coli* appears to be the most important to date. In 2019, 2 patients developed an ESBL-producing *E coli* bloodstream infection transmitted via FMT manufactured from the same donor, with 1 death [32]. Screening for ESBL-producing organisms was mandated by the Food and Drug Administration in 2019 [33]. It has subsequently been reported that asymptomatic carriage of ESBL-producing organisms is high among stool donors in many countries. One group in Taiwan cited a carriage rate of 35.2% in potential donors prescreened for risk by questionnaire, and another in Hong Kong reported 86% ESBL carriage [34, 35]. Lower rates have been identified in donor cohorts from the United States (0.5%) and Netherlands (8.8%) [36]. The rate in our cohort (14%) falls in between these groups and likely reflect Australia's geographic location close to high-prevalence countries in South Asia and Southeast Asia.

In 2020, 4 cases of transmission of Shiga toxin–producing *E coli* via FMT were reported in the United States [37]. The failure to detect asymptomatic Shiga toxin–producing *E coli* colonization in the stool donor was related to insufficiently sensitive testing methodology. The optimal test methodologies for selection and detection of potential pathogens in healthy donors continue to evolve with advancements in available technologies and increasing understanding regarding the risks associated with FMT. Such technological advancements do come with increasing costs, which contribute to the rising cost of FMT products. Judicious selection of testing to maximize safety with a focus on high-risk pathogens, while ensuring that the product remains accessible to clinicians and patients, is an ongoing challenge in FMT manufacture.

This real-world study had several limitations inherent to the study design. Over the 10-year study duration, there were methodologic changes to the screening of donors and administration of FMT. The number of FMT treatments delivered, particularly in patients with severe CDI, changed across the study period and was not consistently captured. Data emerged during this 10-year period that changed management and local protocols. An example of this was the protocol from Fischer et al that showed benefit of sequential FMT dosing of patients with severe CDI [23]. The protocol for sequential FMT began in 2018, and the precise number of FMT enemas following

colonoscopy was not quantified in all cases. Follow-up of adverse events relied on clinician report, and it is possible not all were reported, particularly less severe events. FMT recipients were not actively screened for infectious disease transmission events. Extensive MDRO screening commenced halfway through the study period, and while no clinical MDRO infections were reported, it is not known if any MDRO transmission events may have occurred. Patients who received FMT for CDI are at significant baseline risk of MDRO colonization due to health care and antibiotic exposure, thereby limiting the ability to retrospectively evaluate for this.

CONCLUSION

Our study demonstrates the efficacy and safety of FMT manufactured from the stool of screened donors for the treatment of recurrent, refractory, and severe or fulminant CDI over a 10-year period. Despite extensive screening, pathogens were rarely detected in healthy donors apart from ESBL colonization. FMT appeared to be efficacious for severe CDI; however, this finding requires further evaluation with a focus on optimizing the timing and frequency of FMT delivery.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. C. T. was the primary author of the manuscript. B. A. assisted with data collection, analysis, and writing of the manuscript. R. M. M. assisted with data collection and edited the manuscript. L. E. assisted data collection. R. V. B. assisted with design of the study and edited the manuscript. S. P. C. assisted with the design of the study and data collection and was the primary editor of the manuscript.

Potential conflict of interest. R. V. B., S. P. C., and E. C. T. are shareholders in and employees of BiomeBank. All other authors report no potential conflicts.

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