



# Reducing Cost and Complexity of Fecal Microbiota Transplantation Using Universal Donors for Recurrent *Clostridium difficile* Infection

Kyeong Ok Kim · Margot A. Schwartz · Otto S. T. Lin ·  
Michael V. Chiorean · Michael Gluck

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## ABSTRACT

**Introduction:** Fecal microbiota transplantation resolves recurrent *Clostridium difficile* infections in greater than 82% of patients. Highly screened, processed universal donor fecal material is available. We compared cost and scheduling efficiency of fecal microbiota transplantation by universal donors to patient-directed donors.

**Methods:** Medical records from a prospectively maintained database of recurrent *C. difficile* patients who underwent fecal microbiota transplantation between 2012 and 2017 were reviewed retrospectively. Patient-directed donor stool was prepared in our microbiology laboratory using protocol-based screening. We transitioned to purchasing and using universal donor

fecal material in 2015. Clinical outcomes, adverse events, time between consult to infusion, consultation fees, and material costs were compared. This was a retrospective comparison of two historical cohorts.

**Results:** A total of 111 fecal microbiota transplantations were performed on 105 patients (56 from patient-directed donors and 55 from universal donors). Median recipient age was 66 years (18–96) with male to female ratio of 1:2.7, equivalent in both cohorts. Total consultation fees were significantly lower in the universal donor group owing to fewer infectious disease consultations. Costs for donor screening and stool preparation were lower in the universal donor cohort (\$485.0 vs. \$1189.90 ± 541.4,  $p < 0.001$ , 95% CI 559.9–849.9). Time from consultations to infusion was shorter in the universal donor cohort (18.9 ± 19.1 vs. 36.4 ± 23.3 days,  $p < 0.001$ , 95% CI 9.521–25.591). Recurrences within 8 weeks after fecal microbiota transplantation were equivalent ( $p = 0.354$ ). Adverse events were equivalent.

**Conclusions:** Fecal microbiota transplantation using universal donors versus patient-directed donors for recurrent *C. difficile* showed comparable efficacy and short-term complications. The use of universal donors resulted in significant cost savings and scheduling efficiency.

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K. O. Kim  
Gastroenterology and Hepatology, Yeungnam  
University College of Medicine, Daegu, Korea

K. O. Kim · O. S. T. Lin · M. V. Chiorean ·  
M. Gluck (✉)  
Digestive Disease Institute, Virginia Mason Medical  
Center, Seattle, USA  
e-mail: Michael.Gluck@viriniamason.org

M. A. Schwartz  
Section of Infectious Disease, Virginia Mason  
Medical Center, Seattle, USA

**Keywords:** Fecal microbiota transplantation; Patient-directed donor fecal material; Recurrent *Clostridium difficile* infection; Reduction in costs; Universal donor fecal material

## INTRODUCTION

Recurrent *Clostridium difficile* infection (rCDI) complicates 20–30% of patients who are initially infected with *Clostridium difficile* [1, 2] and can result in long durations of severe diarrhea, debilitating illness, inability to work, and treatment with expensive antibiotics that have variable efficacy. Fecal microbiota transplantation (FMT), introduced in 1958 [3], has been shown to be safe and effective in the treatment of rCDI with cure rates between 82% and 94% [4–6]. FMT restores the gut microbiota diversity that was reduced by exposure to antibiotics. The transplanted microbes return functional gut ecology in variable but not fully elucidated ways. One hypothesis suggests inhibition of *C. difficile* by producing bacteriocins or by competing with *C. difficile* for nutritional resources due to the degradation of secondary bile acids [7]. Current guidelines suggest FMT as a second-line treatment for rCDI [8–10].

Although both efficacy and safety of FMT in the short term have been proven, the safety will be assessed through an American Gastroenterological Association (AGA)-sponsored registry attempting to characterize long-term risks and adverse events. Historically, stool for FMT was provided by healthy, non-infected family members or acquaintances chosen by the patient as patient-directed donors (PD). The potential donor was then screened by an in-person or telephone interview and questionnaire and by examination of stool and serum for transmissible pathogens. Recommended screening protocols vary between practices but largely identify known infectious agents, previous exposure to them, and risky lifestyle behaviors [11]. To date, infectious complications have been reported in two patients who received FMT [11]. In a large series of immunocompromised patients who received FMT, no serious infectious complication occurred [12]. At most centers, if the potential donor

was found to have risk factors, another one was sought who met the screening criteria. Occasionally no PD candidate could be found for a recipient, thereby resulting in delays as well as expense for screening done on the previous donor. Additionally, during the donor screening process, the potential FMT recipient may have suffered relapses and remained on antibiotics longer with resultant diminished quality of life and additional expense for antibiotics.

Currently, frozen fecal material obtained from highly screened universal donors (UD) is available, catalogued, and rigorously produced by non-profit organizations. Lee et al. in a non-inferiority study demonstrated that frozen fecal material has equivalent efficacy to fresh in resolving rCDI [13]. Currently, patients with rCDI have access to uniformly processed frozen donor stool that is rapidly available [14]. The standardized protocol used for screening UD is rigorous in eliminating pathogen transmission [15] and may be more stringent than at individual hospital laboratories [16]. A recent report showed that FMT using UD cured 86% of patients with rCDI and with few adverse events [13, 17]. FMT from an established stool bank theoretically could improve scheduling, reduce cost using economies of scale, and maintain or improve safety [17, 18]. Although one review article noted that FMT was more cost-effective than antibiotics for rCDI [19], no study has evaluated the cost-effectiveness of FMT provided by UD versus PD. The current manuscript compares the clinical outcomes, cost-effectiveness, and scheduling efficiency of FMT done by UD and PD.

## METHODS

### Subjects

The medical records of 105 consecutive patients in a prospectively maintained database who underwent FMT between January 2012 and October 2017 were reviewed retrospectively. Patients 18 years and older who underwent FMT due to rCDI were included in the analysis. There were no other exclusion criteria. FMT was performed after two or more recurrences of

*C. difficile* or after the first recurrence if associated with significant morbidity or hospitalization. The patients were classified on the basis of the source of donor into PD and UD groups. Our institution performed FMT using PD from 2011 through early 2015. After that, once we had the availability of UD stool from a non-profit, commercial stool bank, and a system for ordering, storage, and processing, we transitioned exclusively to using UD for FMT.

CDI was defined as three or more stools conforming to the container for two consecutive days and a positive stool test for *C. difficile* toxin by either polymerase chain reaction (PCR) or combined toxin and glutamate dehydrogenase antigen by enzyme immunoassay. Recurrent CDI was defined as another episode of CDI after initial successful treatment. On the basis of the American College of Gastroenterology guideline, mild-to-moderate disease was defined as diarrhea without additional signs or symptoms meeting severe disease criteria. Severe disease was defined by serum albumin lower than 3 g/dl and/or leukocytosis in excess of 15,000 cells/mm<sup>3</sup> with abdominal tenderness [8]. Clinical cure was defined when the diarrhea disappeared, without recurrence, and clinical resolution was achieved within 8 weeks after FMT.

Data regarding patient demographics, clinical symptoms, previous treatment history, and type of donor material were collected from the institution-based electronic medical record (EMR) as were data reflecting subsequent clinic visits and follow-up telephone conversations. Adverse events associated with the procedure and for a minimum of 30 days afterwards were also assessed as were the costs for the donor screening, stool processing, and UD purchased fecal material. The fee for consultation was determined by standard clinic charges. Costs for FMT included blood and stool screening tests as well as laboratory personnel's time and equipment for stool preparation (Table 1).

### Processing the Transplanted Fecal Material

When patients were referred for FMT, consultations with the gastroenterologist (GI) and/or

**Table 1** Costs for fecal microbiota transplantation (FMT) screening stool tests

Microbe	Screening test	Billable expense (\$) (2013)
<i>Clostridium difficile</i> toxin by PCR	Verigene PCR	102.00
Bacterial enteric pathogens ( <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i> , <i>Vibrio</i> , <i>Aeromonas</i> , <i>Plesiomonas</i> )	Stool culture with selective media	122.00
<i>Giardia</i> antigen	Sendout test—Quest Labs: Giardia Antigen, EIA	74.00
Acid-fast stain for <i>Cyclospora</i> , <i>Isospora</i> , <i>Cryptosporidium</i>	Modified acid-fast smear of concentrated specimen	68.00
Ova + parasite exam	Microscopic exam of ethyl acetate concentration & trichrome permanent smear	112.00
<i>Rotavirus</i> antigen	Sendout test—Quest Labs: EIA assay	46.00
HIV 1 and HIV 2	4th generation CMIA (chemiluminescence immunoassay) Abbott i2000	56.00
Hepatitis A IgM	Abbott i2000 CMIA	68.00
Hepatitis B	Abbott i2000 CMIA	68.00
Anti HBc (IgM + IgG)	Abbott i2000 CMIA	135.00
Anti HBs antigen	Abbott i2000 CMIA	68.00
Hepatitis C antibody	Abbott i2000 CMIA	68.00

**Table 1** continued

Microbe	Screening test	Billable expense (\$) (2013)
Syphilis serology (IgG)	BioRad IgG	82.00
Sample		
Donor fecal sample prep	NA	48.00
Total cost/expense		\$1117.00

infectious disease specialist (ID) were performed to determine the appropriateness of FMT, guide donor identification, and protocol-based screening as well as providing pre-colonoscopy discussions with the gastroenterologist. Prior to FMT, patients were instructed to continue vancomycin orally until 2–3 days before transplant. Fecal material was provided by either a PD or UD. In the PD cohort, donor stool was usually obtained from a healthy household member, relative, or friend. Potential donors were evaluated for exposure to antibiotics, recent diarrhea, travel history, immune disorder, immunosuppressive medications, and infections. Blood tests were sent for viral hepatitis (A, B, C), human immunodeficiency virus, and syphilis within 4 weeks of FMT. Additionally, the donor feces were tested for *C. difficile* antigen and toxin, parasites, enteric pathogens, cryptosporidium, giardia, cyclospora, and rotavirus.

After completion of donor selection and screening, fresh, formed donor stool was delivered to the microbiology laboratory on the day of FMT. The stool was diluted in normal saline, mixed in a sterile bag at room temperature, filtered through moistened five-layer sterile gauze in a funnel then stored in a restricted safety cabinet to be delivered as a 300-cc aliquot within 4 h of presentation to the endoscopy suite.

Fecal material from UD (FMP 250) was purchased in 250-cc containers from OpenBiome (Microbiome Health Research Institute,

Somerville MA), a nonprofit stool bank. The fecal material was prepared in standardized fashion and provided by healthy donors. Specifics about the screening process are available on the OpenBiome website [20]. The UD fecal material was processed and stored at  $-80^{\circ}\text{C}$  until being delivered to our hospital on dry ice, then stored in our freezers at  $-20^{\circ}\text{C}$  until use [18].

In the endoscopy suite, the fecal material was brought to room temperature over 1 h in a water bath and administered via colonoscopy following a polyethylene glycol bowel preparation. No FMT was performed by enema. Colonoscopy-delivered FMT was performed by one of three endoscopists following a protocol of infusing the vast majority of fecal material in the terminal ileum and cecum. Patients were asked to remain supine for at least 1 h, and loperamide 2 mg was given both before and after the procedure. Adverse events were monitored by clinic visits and by chart review. Outcomes and adverse events were determined by follow-up phone calls, visits, or chart review approximately 4–8 weeks after the FMT.

### Statistical Analysis

Costs for consultative fees and FMT processing (including donor screening and stool preparation) were compared. Lead time, a surrogate for scheduling simplicity, was determined by measuring the number of days from the decision to perform FMT to the infusion of fecal material and was compared between groups. Secondly, clinical outcomes including acute adverse event, clinical cure, and recurrence rate within 8 weeks were compared.

Continuous variables were expressed as mean  $\pm$  SD or median with ranges. The categorical variables were compared using Pearson's chi-square analysis or Fisher's exact test, and continuous variables were compared by Student's *t* test. Statistical significance was determined when the *p* value was less than 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences, IBM SPSS version 23.0 (IBM Corp., Armonk, NY). This study was approved by our institutional review

board, and written informed consent by the patients was waived because of the retrospective nature of our study (IRB17-122). The authors complied with IRB-designated training and ethical standards.

## RESULTS

### Baseline Characteristics

The median age of the 105 patients was 66 years (18–96), with a male to female ratio of 1:2.7. Seventy percent of the patients had at least one serious comorbid condition (Table 2). Median duration of CDI prior to FMT was 7.5 months (2–130) and a mean number of recurrences of  $3.3 \pm 1.6$  episodes. Fifty-five FMTs were performed by UD in 54 patients. In the PD cohort, 51 patients underwent 56 FMTs. Disease duration was longer in UD ( $17.9 \pm 3.2$  months versus  $9.4 \pm 7.1$  months,  $p = 0.013$ , 95% CI 9.521–25.99). All patients presented with diarrhea and a positive test for *C. difficile* toxin. Forty percent of UD recipients and 53.6% of PD recipients had more than six diarrheal stools/day ( $p = 0.350$ ). There was no difference between PD and UD recipients regarding fever, weight loss, and abdominal pain. Disease severity and previous use of fidaxomicin for treatment of rCDI were equivalent in both cohorts (Table 2).

### Comparison of Procedure, Outcome, and Total Cost

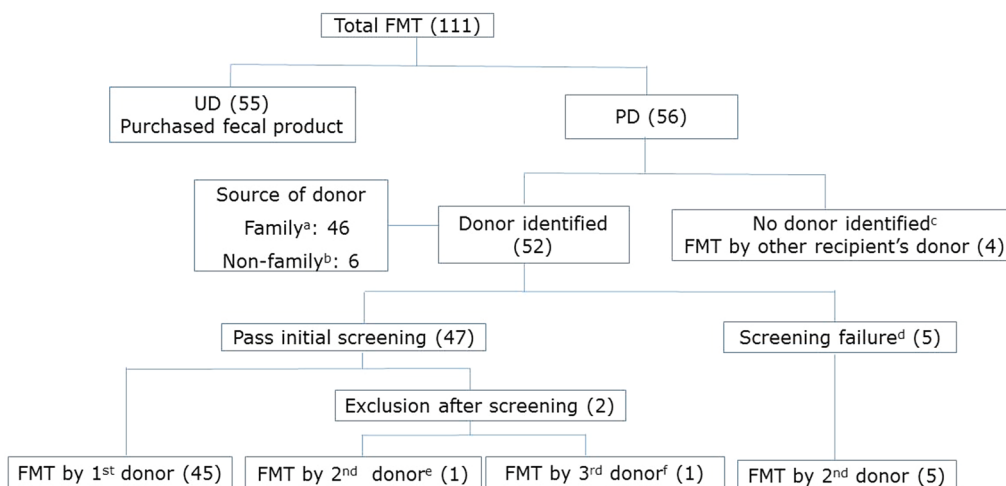
Fifty-six FMTs were performed on 51 patients in the PD cohort. The majority of the donors for PD include 25 first- or second-degree relatives, 18 spouses, 9 unrelated donors, and 4 shared donors. Forty-five FMTs were performed with the first screened donor. Six recipients required a second screened donor, and one recipient required a third screened donor. Thus, seven initially asymptomatic screened donor candidates were excluded. Reasons for excluding these potential donors included finding organisms on stool tests such as *Blastocystis hominis*, *Endolimax nana*, *Entamoeba coli*, and rotavirus.

**Table 2** Baseline characteristics of the patients according to donor type

	Universal donor <i>n</i> = 55	Patient-directed donor <i>n</i> = 56	<i>p</i> value
Mean age, (mean $\pm$ SD, years)	60.6 $\pm$ 20.3	64.6 $\pm$ 15.5	0.247
Gender (M/F)	1:1.9	1:4.0	0.090
Comorbidity, <i>n</i> (%)	46 (83.6)	33 (58.9)	0.338
Diabetes	7 (12.7)	12 (21.4)	
Heart disease	12 (21.8)	14 (25)	
Chronic obstructive pulmonary disease	5 (9.0)	10 (17.9)	
Inflammatory bowel disease	9 (16.4)	6 (10.7)	
Chronic kidney disease	5 (9.0)	7 (12.5)	
Duration of infection, (mean $\pm$ SD, months)	17.9 $\pm$ 3.2	9.4 $\pm$ 7.1	0.013
No. of recurrences	3.1 $\pm$ 1.8	3.0 $\pm$ 1.9	0.761
Severe rCDI, <i>n</i> (%)	2 (3.6)	1 (1.8)	0.559
Associated symptoms			
Diarrhea $\geq$ 6 times a day	22 (40)	30 (53.6)	0.350
Abdominal pain	22 (40)	24 (42.9)	1.000
Fever	6 (10.9)	9 (16.1)	0.507
Weight loss	11 (20)	9 (16.1)	0.464
Fidaxomicin use prior to FMT	8 (14.5)	12 (21.4)	0.423

One donor was excluded because antibiotics were needed after screening but before the scheduled stool donation. Another potential





**Fig. 1** Source of donors and the donor selection process. <sup>a</sup>Family donor includes son (4), daughter (13), spouse (18), parents (1), siblings (5), grandchildren (2), and son- or daughter-in-law (3). <sup>b</sup>Non-family donor includes friends (4) and domestic partner (2). <sup>c</sup>No donor identified means the recipients who could not find a potential donor, and they shared another recipient's donor after obtaining consent. <sup>d</sup>Screening failure was due to 2 potential donors

with positive *Blastocystis hominis*, 2 with *Endolimax nana*, and 1 with *Entamoeba coli*. <sup>e</sup>In this FMT, the first donor was excluded because of newly developed diarrhea between screening and the procedure. <sup>f</sup>In the FMT by a third donor, a first candidate was excluded secondary to need for use of antibiotics due to newly developed dental abscess during waiting time and a second candidate due to a positive test for rotavirus

donor developed diarrhea after successful screening but within a few days of the scheduled stool donation for FMT. Four patients in the PD cohort were unable to find donors but consented to receive fecal material from a screened but unrelated donor (the shared donors). The PD recipient was then scheduled on the same day as another patient who had an identified donor. The unrelated donor was asked and consented to provide fecal material for his/her intended recipient plus another recipient without a potential donor. Two FMTs were then performed from the shared/mutual donor (Fig. 1).

The mean consultation fee was lower in the UD group ( $\$626.6 \pm 216.5$  vs.  $\$903.1 \pm 26.2$ , 95% CI 217.6–335.4,  $p < 0.001$ ), since all PD recipients had both ID and GI consults, while only 45.5% of UD recipients had both consultations. Between 2011 and 2015, all patients were referred to ID to coordinate patient-directed FMT. Once UD was available, ID consultation was at the discretion of the referring provider or by the gastroenterology service. Thus, ID consultation was made on a more

selective rather than a routine basis for clinical management of the patient prior to FMT. The total cost of each donor's laboratory screening ( $\$1069$ ) and stool preparation ( $\$48$ ) in the PD group was  $\$1117$  per recipient as shown in Table 1. However, the adjusted costs resulting from those who needed repeat donor laboratory screening ( $\$2186$  in 2nd screening and  $\$3255$  in 3rd screening) or who had no donor identified ( $\$0$ ) resulted in a mean cost for FMT in the PD cohort of  $\$1189.9 \pm 541.4$ . Meanwhile, the cost for screened universal donors, including preparation and delivery, was  $\$485$ /unit for FMT by UD. The UD stool price was set by OpenBiome. The total cost for FMT was significantly different between groups ( $p < 0.001$ , 95% CI 559.9–849.9) (Table 3).

FMT was performed at mean of  $18.9 \pm 19.1$  days in the UD cohort and  $36.4 \pm 23.3$  days after the decision in the PD cohort, a statistically significant difference ( $p < 0.001$ , 95% CI 9.5–25.6). Initial resolution of diarrhea and improvement in clinical status was achieved in 50 cases (90.9%) in the UD cohort and 53 (94.6%) in the PD cohort.

**Table 3** Lead time and costs for fecal microbiota transplantation (FMT)

	Universal donor <i>n</i> = 55	Patient-directed donor <i>n</i> = 56	<i>p</i> value
Mean lead time from decision to perform FMT to infusion (days)	18.9 ± 19.1	36.4 ± 23.3	< 0.001
Mean consult fee, dollars (\$)	626.6 ± 216.5	903.1 ± 26.2	< 0.001
Mean cost for FMT <sup>a</sup> , dollars (\$)	485.0	1189.9 ± 541.4	< 0.001
(sum of A + B)			
(A) Donor screening <sup>b</sup>	–	1145.4 ± 533.8	NA
(B) Stool preparation <sup>c</sup>	–	44.6 ± 12.5	NA

Values are expressed as mean ± SD

<sup>a</sup> Total cost per 1 FMT was calculated by the sum of cost for donor screening per procedure (\$1069) and 1 stool preparation (\$48)

<sup>b</sup> 45 FMT could be done at first screening, 6 cases at second screening (\$2138/case), and 1 case after third screening (\$3207/case)

<sup>c</sup> Cost of 52 donor identified cases was \$48/case and 4 shared donor cases \$0

Recurrence of diarrhea with a positive stool test for *C. difficile* within 8 weeks after FMT was comparable (6.0% in UD versus 7.5% in PD,  $p = 0.354$ ). Finally, clinical cure was achieved in 85.5% of the UD cohort and 87.5% in the PD group ( $p = 0.832$ ).

The most common complaint after FMT was non-*C. difficile*-associated diarrhea and was similar in both groups: 14.5% in the UD cohort and 17.9% in the PD cohort ( $p = 0.806$ ). Acute bloating after FMT was also common in both groups either due to the FMT or colonoscopy in spite of all procedures done with carbon dioxide as the insufflation gas: 7.1% in the PD cohort versus 10.9% in the UD cohort ( $p = 0.984$ ).

One serious complication in a PD recipient was a perforated sigmoid colon requiring surgery. Another PD recipient was admitted overnight with abdominal pain and leukocytosis that resolved with conservative treatment and no antibiotics. No serious complications to date have occurred in the UD recipient cohort.

## DISCUSSION

FMT has become the standard of care for patients with rCDI as a result of large case series and randomized clinical trials demonstrating its superiority to traditional antibiotics including

tapering regimens [6, 7, 10]. Newer therapies including fidaxomicin and bezlotoxumab have not been widely accepted among providers, often because of the cost [21–23]. Probiotics appear to have some benefit in decreasing rCDI incidence, but they are not advocated for treatment of rCDI as much as prevention [10, 24].

While many facilities use fresh fecal material from donors known to the recipients, ethical concerns emerge, including issues of coercion, confidentiality, and the unfortunate situation that a donor's stool may be rejected as a result of testing positive for a stool or blood pathogen. This situation can cause emotional or psychological harm to both donor and recipient. Coordinating donors and recipients poses further challenges for patients receiving FMT and their medical teams. A screened donor may not be available until days to weeks after initial consultation of the recipient, thereby extending antibiotic exposure and costs for the recipient. Some patients who cannot identify any donors then must “piggyback” to another donor who has consented to provide fecal material [16]. Finally, donor screening, preparation of fecal material, and laboratory testing are generally not paid for by insurance companies, requiring the recipient to cover the costs or, more likely, the institution writing off those

nonreimbursable charges. Our most conservative charge for the donor laboratory tests and preparation of fecal material was in excess of \$1000, matching other published reports [25].

Several studies have reported that frozen stool showed comparable efficacy to fresh stool for FMT in rCDI [13, 26]. The ability to store frozen stool for prolonged periods of time from healthy volunteers has allowed stool banks to use economies of scale by having highly screened donors who then continue periodic screening and provide samples that can be diluted to volumes of 250 cc that are then distributed. Up to eight aliquots can be produced from each donated fecal sample, hence avoiding wasted specimens and allowing more doses to be used in varied geographic regions [17].

Stool banks maintain careful quality controls and registries of healthy donors. Some researchers have expressed concern that universal donors may transmit a yet undetected disease to many recipients, analogous to hepatitis C transmission by blood products prior to availability of serum tests—a justified safety concern. This concern further emphasizes the need to screen all potential donors with a thorough history in addition to screening blood and fecal material [16]. If a disease were to emerge much later in a recipient that had previously not been tested for or recognized, one could trace back to the donor to determine if other recipients were similarly affected. Other theoretical advantages of using UD stool include the lack of any personal connection or obligation between donor and recipient. Owing to these advantages, our hospital converted to UD for FMT in 2015. It became apparent that no study had yet assessed the cost-effectiveness and convenience of FMT using a stool bank. Our study specifically focused on the hypothesis that UD provided both cost savings and scheduling improvements.

The current study demonstrates, as do previous studies, cure rates approaching 90% with PD and UD [5, 27–29]. Additionally, adverse events were similar in both groups as found in a previously published randomized clinical trial by Lee et al. that provided the evidence of safety for stool banks [13].

The current study also demonstrates that the duration from planning FMT to performing it was significantly decreased from 36 days in the PD cohort to 19 days in the UD cohort. Scheduling a non-urgent colonoscopy at our institution for any cause is about 7 days and therefore would not be a factor in increasing lead time. Decreasing the time from the decision to do FMT would allow both recipient and, if used, the donor to have fewer disruptions of life including work, travel, and expenses. In the UD cohort, patients were not burdened by finding a donor. Currently, our center attempts to schedule both the initial consult and procedure in substantially fewer than 19 days by sending preparatory literature regarding FMT for the recipient to read. If the patient does not meet criteria for FMT, the colonoscopy with FMT is not scheduled. As a center located many hours from referral sources, patients can organize a single visit with preparation for the colonoscopy in nearby hotels, then receiving FMT the next day. A goal going forward is to reduce the mean time between consult and procedure to 1 or 2 days, disrupting lives less frequently.

In the vast majority of cases in PD, our institution was not able to recoup donor-related costs. In the UD cohort, there was a single cost for fecal material, shipping, and handling. Stool banks often double screen by performing repeat screening tests on donors 60 days after the stool donation as a layer of added safety [20]. If our institution were to follow double screening of donors, the cost for PD would approach or exceed \$2000/donor.

There were several limitations in our study. As a retrospective study, bias may have been introduced unwittingly. Patient's attitudes regarding receiving fecal material from anonymous donors versus patient directed were not quantitated but qualitatively appeared fully tolerant. Data on patients who were referred did not uniformly have complete historical or laboratory information. Disease duration was significantly greater in the UD cohort and that may have affected the efficacy of FMT, although in this study of 105 patients efficacy was equivalent. Some data were incomplete regarding the duration from FMT to symptom



resolution, since patients returned to their primary providers who may not have communicated complete follow-up information to our center. Fortunately, this was an infrequent occurrence. This study also did not attempt to compare costs of alternative modes of FMT administration such as by oral capsules, enemas, or infusion through naso-enteric tubes.

## CONCLUSIONS

This study demonstrated that FMT by UD in patients with rCDI was as effective and safe as by PD. FMT by UD had the added benefits of primarily reducing costs and secondarily scheduling complexity.

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**Disclosures.** Kyeong Ok Kim, Margot Schwartz, Otto S.T. Lin, Michael V. Chiorean, and Michael Gluck declare that they have no conflict of interest.

**Compliance with Guidelines.** This study was approved by our institutional review board,

and written informed consent by the patients was waived because of the retrospective nature of our study (IRB17-122). The authors complied with IRB-designated training and ethical standards.

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