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# Fecal Microbiota Transplantation for Recurrent *C difficile* Infection During the COVID-19 Pandemic: Experience and Recommendations

Sahil Khanna, MBBS, MS; Aaron Tande, MD; David T. Rubin, MD; Alexander Khoruts, MD; Stacy A. Kahn, MD; and Darrell S. Pardi, MD, MS

## Abstract

**Objective:** To report experience with fecal microbiota transplantation (FMT) for recurrent *Clostridioides difficile* infection (rCDI) and provide recommendations for management of rCDI and donor testing during the COVID-19 pandemic.

**Methods:** A retrospective study of patients with rCDI who underwent FMT from May 26, 2020, to September 30, 2020, with stool from well-screened donors with health and infectious screening and a newly implemented strategy for COVID-19 screening with every 2-week bookend testing with stool quarantine. Patients were followed up for development of rCDI and COVID-19.

**Results:** Of the 57 patients who underwent FMT for rCDI, 29 were tested for COVID-19 via nasopharyngeal polymerase chain reaction (PCR) and 22 via serology. All results were negative, except for 1 positive serology. Donor testing every 2 weeks for COVID-19 via serology and nasopharyngeal swab PCR was negative, except for 2 donors at 1 center who were excluded. Three patients had rCDI after FMT, and 1 underwent repeat FMT. One patient developed respiratory symptoms suggestive of COVID-19 and tested negative via nasopharyngeal PCR. Eleven patients who underwent COVID-19 testing for elective procedures or hospitalizations tested negative. No SARS-CoV-2 transmission was noted.

**Conclusions:** With appropriate donor screening, FMT can be performed safely for rCDI during the COVID-19 pandemic. Development of a validated stool assay for SARS-CoV-2 will simplify this process further.

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From the Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN (S.K., D.S.P.); Infectious Diseases, Mayo Clinic, Rochester, MN (A.T.); Section of Gastroenterology, Hepatology and Nutrition, University of Chicago Medicine, Chicago IL (D.T.R.); Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, MN (A.K.); and Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, MA (S.A.K.).

The cornerstone of management in pediatric and adult patients with multiply recurrent *Clostridioides difficile* infection (rCDI) is fecal microbiota transplantation (FMT).<sup>1</sup> Despite its investigational nature, FMT has widespread use under enforcement discretion from the United States Food and Drug Administration (FDA) owing to its remarkable success with recurrence rates dropping from an average of 60% to less than 15% seen in clinical practice and clinical trials.<sup>1,2</sup> It is well known that FMT is dependent on procurement of stool from well-screened, healthy donors. The donor screening protocols used in

FDA-directed clinical trials have more similarities to each other compared with the variability seen in clinical practice.<sup>3</sup> Guidance from the FDA is updated frequently, including in response to the infectious complications reported since June 2019 (extended spectrum beta-lactamase *Escherichia coli* systemic infections and diarrhea caused by Shiga toxin-producing *Escherichia coli* infections) and the COVID-19 pandemic.<sup>4-6</sup> Donor banks—such as OpenBiome (Cambridge, Massachusetts), a nonprofit stool bank—are the primary sources of stool for microbiota-restoration therapies for most providers in the United

States. With the COVID-19 pandemic, there has been a reduction in this supply, limiting availability of FMT. OpenBiome has ceased operations and is not providing stool at this time. OpenBiome has recently announced that it will begin testing stool for the presence of SARS-CoV-2, using a commercially available test, but details on positivity, sensitivity, and specificity are not available.<sup>7</sup>

COVID-19 is a multisystem infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.<sup>8,9</sup> Infection with this virus may cause diarrhea—thought to be caused by the presence of the angiotensin converting enzyme (ACE) II receptors in the intestine—and the viral ribonucleic acid (RNA) has been detected in stool, sometimes persisting in patients even after clearance from the respiratory tract.<sup>10</sup> Studies have shown that the frequency of SARS-CoV-2 RNA in the stool can range from 27% to 88% of patients with COVID-19, with the larger studies showing rates of about 53% to 55%.<sup>11-14</sup> The frequency of asymptomatic respiratory or gastrointestinal carriage is unknown, which is concerning with regard to potential stool donors acting as vectors of transmission of SARS-CoV-2 to a recipient via FMT. In addition, in several parts of the world, testing for SARS-CoV-2 is not widely available. The stockpile of donor stool collected before December 2019 has been rapidly declining or absent in many centers. Because of these challenges, availability of FMT has diminished for this vulnerable and often very sick patient population.

We recently published a pathway to evaluate and manage patients with rCDI during the pandemic and also included a guidance to test stool donors for SARS-CoV-2 (and embargo the stool before use).<sup>15</sup> Here, we present our experience with donor SARS-CoV-2 testing and the outcomes of patients who received FMT, using stool donated and collected after the pandemic started. In addition, we present suggested recommendations for safe FMT during the COVID-19 pandemic.

## METHODS

Mayo Clinic in Rochester, Minnesota, established an FMT program in August 2012, for the management of patients with recurrent and refractory *Clostridioides difficile* infection (CDI).<sup>16</sup> A standard donor program has been in effect since 2014, in which donors are screened at every donation with a history and exposure questions.<sup>16</sup> Donors undergo screening with blood and stool tests as previously published.<sup>16</sup> In the early stages of the COVID-19 pandemic, from March 2020 to April 2020, FMT procedures were on hold until the institution of this testing protocol. Subsequently, additional donor screening for COVID-19 exposure, symptoms, serology testing, and polymerase chain reaction (PCR) testing was instituted every 2 weeks (Table).<sup>15</sup> Stool donations are collected and kept quarantined until results of follow-up donor assessment were negative.

A similar donor program has been established at the University of Minnesota. Donors are required to maintain a daily temperature log, which starts at least 28 days before donation and continues through at least 14 days after donation. Donors complete a new questionnaire (COVID-19 Risk

TABLE. COVID-19 Screening for Donors

	Yes	No
Have you had a contact with a person known to have COVID-19 infection?		
Have you experienced any of the following symptoms in the past 48 hours?		
	Yes	No
Fever or chills		
Cough		
Shortness of breath or difficulty breathing		
Fatigue		
Muscle or body aches		
Headache		
New loss of taste or smell		
Sore throat		
Congestion or runny nose		
Nausea or vomiting		
Diarrhea		

Assessment Donor Questionnaire) every time they make a stool donation and at least twice weekly, as long as they remain active donors (starting 28 days before donation and at least 14 days after donation). Polymerase chain reaction-based tests are performed on respiratory secretions collected with nasopharyngeal swabs every 14 days, starting 14 days before donation and 14 days after donation, with a maximum interval of 14 days between tests.

At Mayo Clinic, PCR testing for SARS-CoV-2 was performed using a laboratory-developed real-time PCR, as described in detail by Rodino et al.<sup>17</sup> Serologic testing was performed using either the Roche Elecsys Anti-SARS-CoV-2 IgG assay (Roche Diagnostics, Inc., Rotkreuz, Switzerland) or the VITROS Anti-SARS-CoV-2 IgG (Ortho-Clinical Diagnostics, Inc., Raritan, New Jersey), both of which are US FDA Emergency-Use Authorized tests. At the University of Minnesota, PCR-based tests are performed using the Cepheid Xpert SARS-CoV-2 assay (Cepheid, Sunnyvale, California) and the DiaSorin Molecular Simplexa COVID-19 Direct assay system (DiaSorin, Saluggia, Italy). Donors are required to maintain a temperature log and complete a new questionnaire on COVID-19 risk assessment every time they make a stool donation and at every screening interval.

According to institutional protocols, vetted via infection prevention and control and with guidance from the national gastroenterology societies, all recipients undergoing procedures were screened for COVID-19 symptoms and exposure. A colonoscopy was not considered as a respiratory aerosol-generating procedure. Patients requiring moderate sedation with midazolam and fentanyl were not deemed to need COVID-19 swabs ahead of time. Patients who were undergoing upper endoscopy, along with a colonoscopy, for any reason, or who were undergoing the procedure under anesthesia-assisted sedation, were required to undergo COVID-19 screening before the procedure.

Patients with recurrent CDI diagnosed with PCR for CDI or enzyme immunoassay

for the toxin production were included. The majority of patients were diagnosed with a PCR assay. In patients with multiple causes of diarrhea, such as those with inflammatory bowel disease (IBD), response to antibiotic treatment was used as a marker of a diagnosis of CDI. Complete response to antibiotics was defined as return to baseline bowel pattern, and partial response was defined as an improvement in bowel pattern but not completely returning back to baseline. In patients with response to antibiotics, the decision was made to proceed with FMT after a detailed discussion of risks, benefits, and alternatives.

Patients who underwent FMT at Mayo Clinic from May 26, 2020, to September 30, 2020, were included in this retrospective analysis. After donor screening, donor stool is processed in an anaerobic chamber. Donor stool is diluted 1:5 (weight by volume) in a diluent (90% normal saline and 10% glycerol) and then filtered. Donor stool is kept frozen at  $-80^{\circ}\text{C}$  ( $-112^{\circ}\text{F}$ ). Symptomatic patients need to undergo a brief period of therapy with antibiotics to manage active and acute symptoms of CDI. Stool recipients then undergo a bowel preparation for colonoscopy, and discontinue antibiotics 24 hours before FMT. On the day of the procedure, the stool is thawed to room temperature. For FMT, 1 dose is used from 1 donor and is 50 grams of donor stool in 250 cc of diluent, which is implanted into the recipient colon in the cecum by means of a colonoscopy. No additional antibiotics are recommended after FMT.

After undergoing FMT, patients were actively followed at 1 week for improvement in symptoms and development of new symptoms and thereafter instructed to contact in case of symptoms. For development of COVID-19, patients were followed at 1 week actively and subsequently through a review of the electronic medical record. Patients were followed up for at least 4 weeks for this study.

The Mayo Clinic Institutional Review Board (IRB) approved the study to follow up outcomes after FMT. Data were collected by means of review of the electronic medical

record, donor screening logs, and patient follow-up. Data were entered into JMP version 14.0 (SAS Institute, Cary, North Carolina) for statistical analyses. Demographic and clinical variables were summarized using descriptive statistics. Continuous variables are reported as mean (standard deviation) or median (range), and categorical variables are reported as proportions.

## RESULTS

### Mayo Clinic Donor Experience

Two standard donors have been in the donor program during this pandemic. In addition to the usual donor screening, COVID-19 testing has been performed every 2 weeks for donors. Symptom assessment for COVID-19 is performed at every testing time point and at every stool donation. The first donor (long-term stool donor) has been in the COVID-19 assessment program since May 7, 2020, and continues to date. The second donor was added to the program on August 4, 2020. Donor assessment results for COVID-19 have been negative by nasopharyngeal PCR and serology through 14 rounds of testing for the first donor and 8 rounds of testing for the second donor. No donors have been excluded because of COVID-19 infection to date. The donated stool samples are not tested for presence of SARS-CoV-2, as there is no validated stool test available for the presence of SARS-CoV-2.

### University of Minnesota Donor Experience

Three active donors continued to participate in the program through this period, and 3 people were recruited as potential candidates after negative screening on comprehensive questionnaires and physical examinations. Two of these 6 people tested positive for SARS-CoV-2. One active donor tested positive for SARS-CoV-2 14 days after production was completed. The donor was asymptomatic. The material was not released out of quarantine for clinical use. One newly recruited person reported exposure to COVID-19 and was immediately suspended from the program. The donor stool was not

used for FMT. Later, this person tested positive for SARS-CoV-2 outside of the donor program. This person never donated stool for production. The donor material generated from this screening at the University of Minnesota has not been used so far because of the existing stockpile manufactured before December 1, 2019. The donated stool samples have not been tested so far for presence of SARS-CoV-2 because of lack of access to a validated stool test for the presence of SARS-CoV-2.

### FMT Recipients

From May 26, 2020, to September 30, 2020, 57 patients have undergone FMT for rCDI at Mayo Clinic. The median age was 63.9 years (range: 19.9 to 93.2), and 35 (61.4%) were women. The median number of CDI episodes before FMT was 3 (range: 2 to 7). All patients received antibiotics for CDI (48 on vancomycin and 9 on fidaxomicin) until 24 hours before FMT. Of these patients, 10 had underlying IBD. Of these patients, 52 (91.2%) had risk factors for CDI (most commonly, antibiotic exposure in 48 patients); all had symptoms of CDI with recurrent episodes. Overall, 55 (96.5%) patients had a complete (n=33) or partial (n=22) response to antibiotics for CDI, and 2 patients (1 had underlying IBD) underwent FMT for CDI with no response to antibiotics.

Overall, 53 (93%) underwent FMT via colonoscopy and 4 (7%) via combined upper endoscopy and lower endoscopic procedure (1 pouchoscopy, 1 flexible sigmoidoscopy in a patient with partial colectomy, 2 with a colonoscopy). Before FMT, 22 (38.5%) patients underwent testing for COVID-19 via serology, and 29 (50.8%) patients underwent testing for COVID-19 via nasopharyngeal swab PCR. These tests were done in accordance with institutional guidance, in which patients undergoing upper endoscopic procedures or procedures under anesthesia-assisted sedation underwent preprocedural testing. None of the patients tested positive for COVID-19 via PCR, and 1 patient tested positive for serology (did not have known symptomatic COVID-19) before FMT.

### Outcomes

During follow up, 19 patients developed recurrent symptoms suggestive of CDI and were tested for CDI; 3 tested positive. One patient had primary FMT failure (recurrent symptoms with no additional risk-factor exposure) and was managed with vancomycin, followed by repeat FMT. Two patients had recurrent CDI after additional systemic antibiotic exposure and were managed with a standard course of oral vancomycin, with resolution of their symptoms. An alternate cause of diarrhea was identified in the remaining patients (primarily postinfection irritable bowel syndrome or active IBD), and these patients responded to appropriate therapies. There were no differences in efficacy seen in patients based on presence of underlying IBD.

Of those who underwent FMT, 1 patient developed respiratory symptoms suggestive of COVID-19 and tested negative via a nasopharyngeal swab PCR. Eleven additional patients underwent COVID-19 testing for further elective procedures or hospitalizations, and all tested negative. No COVID-19 transmission was seen. Fortunately, there has been no COVID-19 diagnosed in the health care workers and technicians involved in the FMT procedure.

### DISCUSSION

Microbiome restoration therapies, such as FMT, are the cornerstone for management of rCDI, with high rates of success, and have been deemed cost effective for CDI.<sup>18</sup> In this study, we demonstrate a robust screening program for SARS-CoV-2 from 2 academic centers, enabling the study to continue FMT during this pandemic. Donors who test positive or get exposed to SARS-CoV-2 are excluded from being stool donors. In addition, we demonstrate ongoing success of FMT for CDI and, more importantly, establish safety and efficacy of FMT in management of CDI with meticulously screening donors for COVID-19. Patients were able to undergo FMT safely, and none developed COVID-19 after FMT.

Performing FMT during a pandemic such as COVID-19 has several challenges.<sup>15</sup>

Because of concerns about patient safety and limitations of health care resources, elective procedures are usually delayed or canceled.<sup>19</sup> As most patients with rCDI have resolution of symptoms on antibiotics and can be maintained on low-dose oral vancomycin (eg, 125 mg once a day or every other day) or fidaxomicin, long term, with resolution of symptoms, FMT can be considered an elective procedure.<sup>15</sup> However, this strategy can be challenging owing to the cumulative cost and rare instances of side effects from oral vancomycin. This strategy raises even more concerns in the pediatric population, in which the long-term effects of antibiotics can affect the developing microbiome or may have other detrimental effects on health. In addition, long-term use of vancomycin may risk development of resistance in *C. difficile* and other organisms.<sup>20,21</sup>

Clinically, at times it is challenging to differentiate rCDI from other causes, such as postinfection irritable bowel syndrome. In previous studies, patients with resolved CDI and postinfection irritable bowel syndrome have been administered FMT or similar microbiome-based therapies when these therapies were not needed.<sup>22</sup> If there is primary nonresponse to oral vancomycin, one should look for alternative causes of diarrhea. For true primary nonresponse to vancomycin therapy (which is rare), fidaxomicin can be used, or one can resort to FMT (if available) to treat active CDI.<sup>23</sup> During these unprecedented times, FMT may not be readily available. Novel regimens of fidaxomicin have been shown to have a low rate of recurrence.<sup>24,25</sup> An example of such a regimen is the fidaxomicin extended protocol, in which fidaxomicin is used as 200 mg twice a day for 5 days and then every other day from day 7 through day 25. Other alternatives, such as intravenous bezlotoxumab, are available and have shown reduced rates of recurrence compared with placebo.<sup>26</sup> Patients who respond to oral vancomycin can be maintained on the lowest effective dose of oral vancomycin for control of symptoms until FMT is available. Finally, there are available clinical trials for microbiome restoration therapies that can be considered.



The availability of resources to test for COVID-19 is variable. In the United States, some centers are still struggling with adequate access to testing, and the turnaround time for symptomatic patients is longer than is practicable or clinically helpful. Access to testing is currently prioritized for symptomatic patients and patients undergoing procedures in which knowledge of infection would have an impact on the patient or health care team. Stool donors are generally considered to be of lower priority for access to testing, and these donors need repeat testing. Both Mayo Clinic in Rochester and University of Minnesota have had a standard donor program and, over the years, have maintained standard donors. Donor screening by history and for infectious agents was carried out per existing protocol. At one center, adding regular testing for SARS-CoV-2 led to attrition of 1 standard donor, whereas the other donor agreed to continue in the program to undergo symptom screening every other week and at every donation and undergo every-other-week testing for COVID-19 with antibody testing and nasopharyngeal swab for PCR testing. A new donor was recruited after starting this program to keep up with the demands of the practice. Serology testing is performed to evaluate for seroconversion over time in a known donor and enhance the ability to detect asymptomatic infection, given that PCR screening performed every other week may fail to identify asymptomatic patients with COVID-19 infection. Stool samples are kept under embargo until follow-up testing is performed. As stool is kept under embargo, and bookend testing is performed for COVID-19—including serology—and donors are screened with symptoms at every donation in between, a testing frequency of every other week seems reasonable. Two donors at 1 of the centers have tested positive; their material has not been used, and they have been excluded from being stool donors. There will continue to be logistical implications if the asymptomatic donor tests positive for COVID-19 in terms of isolation practices, testing, and information from family members and other

close contacts, and the psychological effects of a positive COVID-19 test on an otherwise asymptomatic patient. A similar donor-screening protocol has been proposed by a multicenter group.<sup>14</sup>

Moving forward, assays for detection of the SARS-CoV-2 virus in stool with a PCR-based assay would help with the logistics of FMT. If such a test is available, individual or batched stool samples from 1 donor can be checked with a stool assay. This would help with expanding the availability of FMT during this pandemic, along with donor retention. Availability of stool testing could replace serology and nasopharyngeal swabs with continuation of donor-symptom assessment. At our centers, like many others during a pandemic, the clinical and research virology laboratory has been diligently working on developing validated assays to diagnose patients. The clinical load of testing for COVID-19 for symptomatic patients during a pandemic is very high, and the majority of the testing capacity is being used to diagnose local patients and referred patient samples. These logistics have delayed the validation and implementation of a stool assay. We are hopeful that a stool assay will be available in the near future. It is very interesting to speculate that the transmissibility of the infection from a PCR-positive tested stool sample would be variable based on the viral load in the stool sample. It is still not clear if SARS-CoV-2 seen in the stool samples is living or transmissible. A cycle threshold value correlating with viral transmissibility has not yet been established, and, conceivably, a very low cycle threshold could correlate with transmissibility. It seems unlikely that FMT would lead to SARS-CoV-2 transmission and nasopharyngeal screening and serology appear to be useful until stool tests are available.

Medical centers that do not have access or resources for maintaining frozen stool may consider recruiting and screening individual donors, such as family members. Recommended donor infectious screening along with COVID-19 screening can be performed in this setting within 48 hours

of FMT procedure. It would be pertinent in this situation for the potential donor to self-quarantine to avoid COVID-19 exposure between testing and stool donation. Another option would be to screen a close household contact, such as a spouse, considering that members of a family living in close proximity would share similar COVID-19 status.

The majority of FMT done in the United States is dependent on OpenBiome, which has recently paused its operations.<sup>27</sup> Therefore, there is an unmet clinical need that has led to increased consideration of donor-directed FMT and clinical trials of microbiome restoration therapies. There have been positive phase 3 topline results, and scientific publications are awaited.<sup>28,29</sup> Until an FDA-approved product becomes widely available, it is important for us to have protocols and procedures in place to perform FMT safely.

The donor data presented in this study are from 2 centers, the experience for FMT is at a single center, and there is a rather short-term follow-up, but they provide insight and guidance as to how to perform FMT during the pandemic. The lack of availability of a validated stool assay for SARS-CoV-2 remains a limitation.

## CONCLUSIONS AND RECOMMENDATIONS

The optimal strategy to treat rCDI starts with appropriate identification of cases, including an accurate diagnosis of rCDI based on symptoms, testing, and response to antibiotic treatment. Fecal microbiota transplantation can be performed safely for rCDI during the COVID-19 pandemic, using our described donor screening and testing strategy that mitigates the risk of transmission of COVID-19. Detailed informed consent outlining risks and benefits of FMT vs alternatives, such as continued low-dose vancomycin, or immune-enhancing strategies, such as bezlotoxumab, is prudent. Donor screening for COVID-19 by history, serology, and nasopharyngeal PCR should be performed every 2 weeks, with stool donations in the interim. Processed and frozen stool should be embargoed until follow-up

testing results are negative. Development and validation of a sensitive stool assay for SARS-CoV-2 would mitigate this risk further.

## ACKNOWLEDGMENTS

S.K. and D.S.P. were responsible for the inception of this study, data abstraction, analysis, drafting, and revision of the manuscript. A.T. was responsible for the inception of the study, appraisal of the data, and critical revision of the manuscript. D.T.R., A.K., and S.A.K. were responsible for the appraisal of the data and critical revision of the manuscript. All authors have approved the final version of the manuscript.

**Abbreviations and Acronyms:** ACE = angiotensin converting enzyme; CDI = *Clostridioides difficile* infection; FDA = Food and Drug Administration; FMT = fecal microbiota transplantation; IRB = institutional review board; rCDI = recurrent *Clostridioides difficile* infection; PCR = polymerase chain reaction; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

**Potential Competing Interests:** Dr Khanna has received research grants from Rebiotix, Inc (a Ferring company), consulting fees from Shire Plc, Premier Inc, Facile Therapeutics, and ProBioTech Inc, outside of the submitted work. Dr Khoruts holds patents pertaining to preparation of fecal microbiota and a research grant from Finch Therapeutics. Dr Kahn has received research support from OpenBiome, Cures Within Reach (Pilot Grant and NIH 1R24AI118629-01A1), outside of the submitted work. Dr Pardi has received research grants from Vedanta and Seres Therapeutics and consulting fees from Assembly Biosciences, Inc; Gilead Sciences, Inc; Janssen Pharmaceuticals, Inc; Otsuka America Pharmaceutical, Inc; Pfizer Inc; Merck & Co, Inc; C3J Therapeutics, Inc; Nestlé; and Salix Pharmaceuticals, outside of the submitted work. The other authors report no competing interests.

**Correspondence:** Address to Sahil Khanna, MBBS, MS, FACC, Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN (khanna.sahil@mayo.edu; Twitter: @Khanna\_S).

## ORCID

Sahil Khanna:  <https://orcid.org/0000-0002-7619-8338>;  
Aaron Tande:  <https://orcid.org/0000-0001-9775-7082>

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