

# Fecal Microbiota Transplantation for Recurrent *Clostridioides difficile* infection: The COVID-19 Era

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*Am J Gastroenterol* 2020;00:1–4. <https://doi.org/10.14309/ajg.0000000000000689>; published online XXX

Long before coronavirus disease of 2019 (COVID-19) was deemed to be a human infection, *Clostridioides difficile* infection (CDI) has been among the top 5 urgent infectious threats identified by the US Centers for Disease Control and Prevention. Management recommendations for primary CDI and first CDI recurrence includes antibiotic regimens of oral vancomycin or fidaxomicin. Recurrent CDI incidence is at an all-time high, and recurrence rates are as high as 60% after 3 or more infections (1). Fecal microbiota transplantation (FMT), although not approved by the US Food and Drug Administration (US FDA), is widely used to manage recurrent CDI and has demonstrated success rates of 90% to prevent recurrent CDI compared with 40% with antibiotic regimens (2). These therapies are dependent on the procurement of stool from well-screened healthy donors. Despite the institution of screening procedures, there have been serious adverse events reported related to FMT due to transmission of infectious agents from asymptomatic donors to recipients (3). In addition to these 2 cases of extended-spectrum beta-lactamase producing *Escherichia coli*, the US FDA has recently reported 6 patients who received FMT for recurrent CDI who developed infections after FMT, 2 with enteropathogenic *E. coli*, and 4 with Shiga toxin-producing *E. coli* (4).

COVID-19 is caused by a novel beta coronavirus believed to be originated from wild bats, with increasing reports of human-to-human community transmission. Clinical features include fever, cough, chest tightness, dyspnea, transient diarrhea, and, in severe cases, pneumonia, acute respiratory distress syndrome, intensive care admission, and death (5,6). The average incubation period is 5 days, and there is an unknown fraction of the asymptomatic population in the community carrying this novel coronavirus. Respiratory droplet transmission is the primary mode but feco-oral transmission is being emergently reported. There have been reports of prolonged shedding in the stool after recovery from respiratory illness, which is also likely contributing to community spread of COVID-19 (7).

There are several important considerations while considering FMT to prevent recurrent CDI in the era of COVID-19 to protect patients and avoid transmission of COVID-19.

## MAKE AN ACCURATE DIAGNOSIS OF RECURRENT CDI

Now, as always, an accurate diagnosis of recurrent CDI is essential because about 20% of patients develop postinfectious irritable

bowel syndrome after CDI and symptoms overlap with recurrent CDI (8). In addition, there is also a high risk of persistently positive nucleic acid–based assay after resolved CDI. To make a diagnosis of primary and recurrent CDI, there needs to be the presence of (i) risk factors for CDI, (ii) symptoms of diarrhea with or without abdominal pain, (iii) a positive nucleic acid or toxin-based assay, and (iv) a response to treatment with vancomycin or fidaxomicin (primary nonresponse is extremely rare and suggests an alternate diagnosis) (Table 1). Symptoms of CDI typically resolve while on antibiotic therapy for CDI, but symptoms recur shortly after the antibiotic is stopped. In patients who do not meet all 4 criteria above, especially #2 and/or #4, an alternate diagnosis should be considered. Patients who are diagnosed with multiply recurrent CDI (by meeting all 4 criteria above) are considered good candidates for FMT. In some instances, those with refractory or fulminant CDI also may benefit from FMT to treat acute CDI and improve mortality.

## STOOL BANKING DURING THE COVID-19 ERA

Access to FMT varies with the type of healthcare establishment and geographic location. Fresh and freeze thawed stool has shown similar efficacy for the management of recurrent CDI (9). Using standard well-screened donors who have undergone rigorous stool testing for repeated donations, and storing and banking stool makes FMT more accessible and cost-effective (10). There are commercial stool banks available, and some centers maintain their own stool banks. A typical “dose” for FMT is 50 g of donor stool mixed in a 150–250 mL diluent. One bowel movement from a donor can be split to multiple doses. Donor stool from multiple donors are not pooled at this time.

With the advent of the COVID-19 pandemic, donor stool obtained and banked before December 2019 must be stored separately from stool donated and stored after December 1, 2019. This is in accordance with recent guidance from the US FDA for studies performing FMT under an investigational new drug application (11). The shelf life of frozen donor stool is not known but viability up to 6 months has been demonstrated (12). It is unclear how many doses of FMT may be available

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**Received March 30, 2020; accepted April 13, 2020**

**Table 1. How to make an accurate diagnosis of CDI**

Criteria for an accurate diagnosis of <i>C. difficile</i> infection	
1	Assess the risk factors for CDI
2	Assess for the presence of symptoms of CDI (diarrhea with or without abdominal pain)
3	A positive nucleic acid or toxin-based assay for CDI
4	A response to treatment with vancomycin or fidaxomicin (primary nonresponse is extremely rare and suggests alternate diagnoses).

CDI, *Clostridioides difficile* infection.

that have been collected before December 2019. In the current era, stool donation can be continued only for use in very few clinical instances described below.

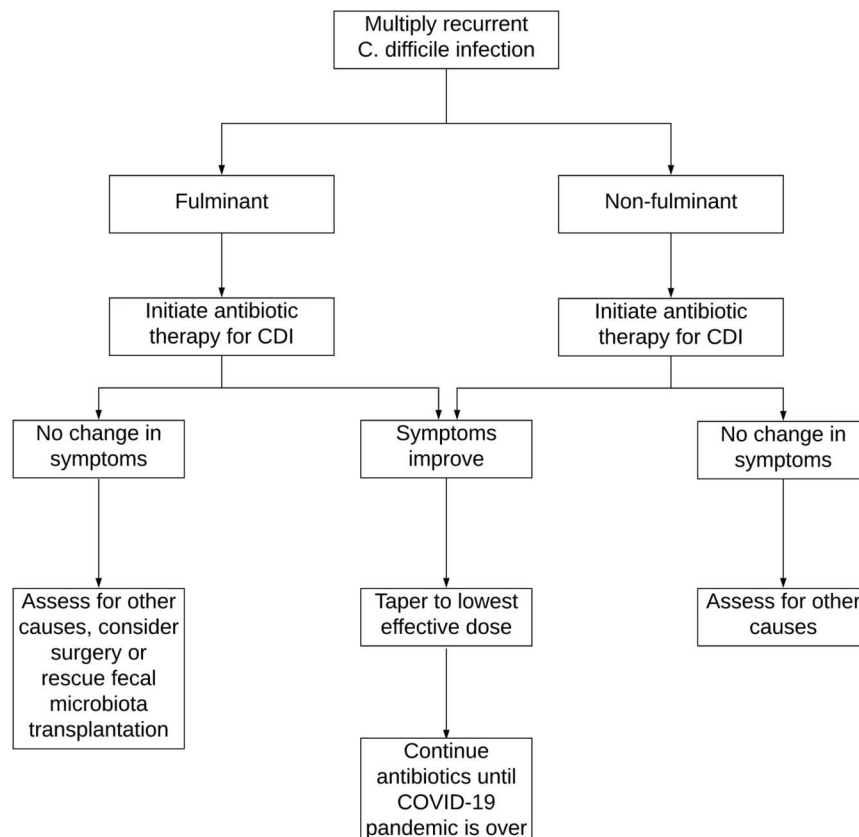
**DONOR TESTING FOR INFECTIONS AND NOVEL CORONAVIRUS**

Apart from the general health screening questions and blood tests, several stool tests are recommended for donors including those for enteric pathogens and screening for multidrug-resistant infections (13). In the era of COVID-19, with the presence of diarrhea in patients with COVID-19 and perhaps asymptomatic shedding in stool along with feco-oral transmission, virus being

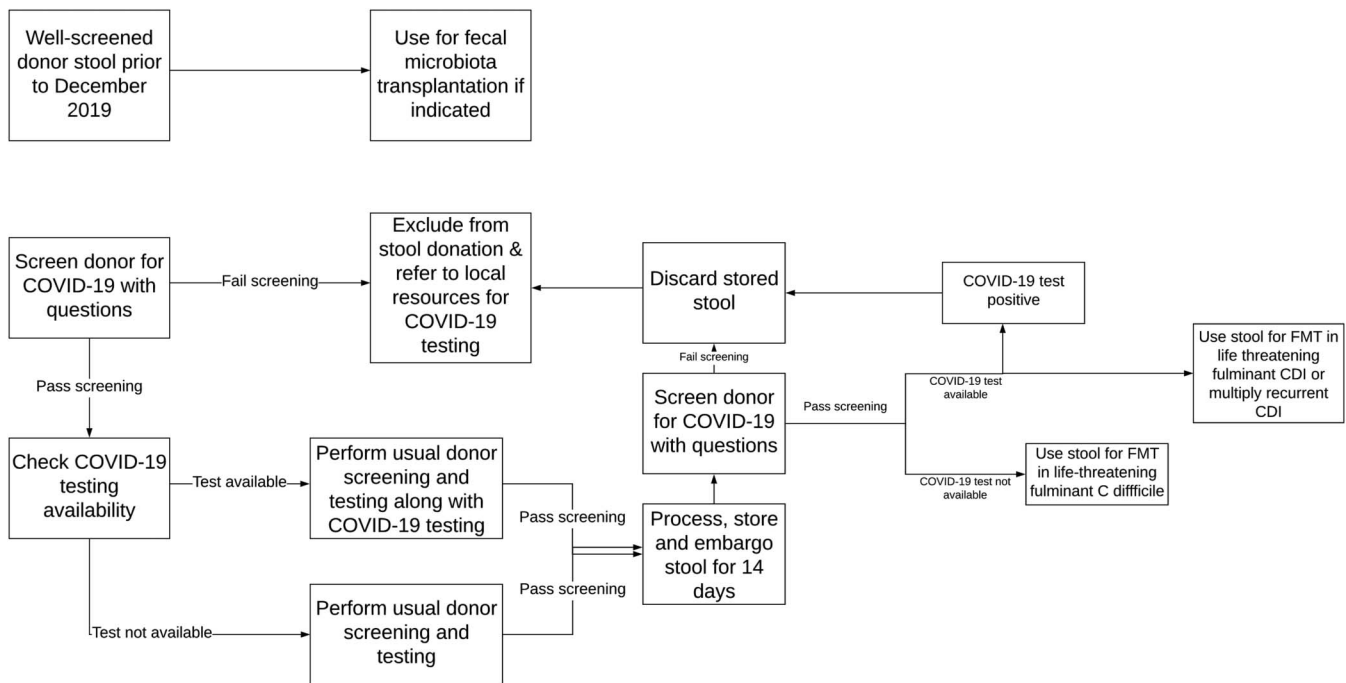
detectable in stool after being undetectable in the respiratory tract, there is definitely a need to screen donor stool for the presence of this virus (14). However, there are several challenges to this approach because there are not enough tests available to diagnose symptomatic people, respiratory swab-based tests are not validated for asymptomatic people (i.e., donors), validated stool assays for asymptomatic carriage are not available, and finally, the absence of a respiratory coronavirus in an asymptomatic person does not rule out fecal carriage and transmission.

Before every stool donation, donors should be screened for a travel history and COVID-19 symptoms and contact with patients infected with COVID-19. Donors who fail this screen should be excluded from donating stool and channeled through the local resources available for COVID-19 screening, testing, and self-isolation if applicable. Because the disease is now a pandemic worldwide, donors who pass this screen should be considered for COVID-19 testing (nasal swab or stool) if adequate numbers of test kits become available. Stool from these donors can be processed, stored, and should be embargoed for at least 14 days and donors should be rescreened with symptom questions and testing for COVID-19. If donors fail rescreening, the stool should be discarded (Figure 2).

Once tests for COVID-19 become readily available and validated for screening asymptomatic individuals, donor screening should routinely incorporate nasal swab and stool testing for COVID-19. If the testing sensitivity remains low, then multiple tests may be needed to reduce the likelihood of false negatives. As serological tests become available, an immunoglobulin G response could be used as a marker of recovery from previous



**Figure 1.** Treatment algorithm for recurrent and fulminant *Clostridioides difficile* infection in the era of COVID-19.



**Figure 2.** An algorithm for donor screening and stool banking for fecal microbiota transplantation.

COVID-19 exposure. Finally, as a vaccine becomes available, vaccination against COVID-19 would become required to qualify to be a stool donor.

### AN APPROACH TO MANAGING RECURRENT CDI IN THE COVID-19 ERA

Despite antibiotic treatment after a primary infection, the risk of recurrent CDI is 20%–30%; after a second infection, the risk of recurrence is 40%–50%; and after a third infection, the risk of recurrence over 60% after antibiotics are stopped (1). Of all patients with CDI, about 5%–10% are candidates to consider microbiome replacement therapies such as FMT. Once a patient is deemed to truly have multiply recurrent CDI, the first step is to initiate oral vancomycin therapy to treat acute diarrhea and assess response. The time to resolution of diarrhea is typically 4–5 days. Once diarrhea resolves (which happens in over 95% patients while on vancomycin), vancomycin should be tapered to the lowest effective dose, which is typically 125 mg once a day or once every other day. A commonly used taper regimen is vancomycin 125 mg 4 times a day for 2 weeks, followed by twice a day for 1 week, followed by once a day for a week and then every other day. An alternative to using vancomycin would be fidaxomicin, but its use for long-term use would be cost-prohibitive.

In the COVID-19 era, FMT for these patients should be delayed until the pandemic is better controlled (Figure 1). In patients with fulminant CDI with no response to maximal guideline-based combination therapy, surgery or rescue FMT (may be considered even during the ongoing pandemic) are options. As this pandemic progresses, access to FMT will become scarce because of the nonavailability of the stool banked before December 2019, lack of guidance, and availability of validated tests for the donor stool COVID-19 screening. If FMT is a needed treatment, consider using the banked stool

with donations before December 2019. An alternate approach would be to screen a household contact (with usual donor screening performed before COVID-19) because the COVID-19 status of household contacts will be similar because of high contagiousness of this coronavirus. A third approach would be to screen a potential recipient for COVID-19 status (with symptoms, travel history, and testing if a test is readily available), and if a recipient is positive, any otherwise well-screened donor may be used. If the recipient is negative for coronavirus, and FMT is a life-saving procedure (surgery is not an option), then banked stool before December 2019, or stool from a coronavirus-negative donor should be used (Figure 2).

If the COVID-19 pandemic persists and the novel coronavirus becomes a population-wide pathogen, in future both donors and recipients would need to be tested and matched for COVID-19 status. The future of microbiome replacement therapies include stool treated to remove viruses and bacterial pathogens and synthetically grown defined microbial consortia to avoid the risk of transmitting pathogens, including the novel coronavirus.

### CONFLICTS OF INTEREST

**Guarantor of the article:** Sahil Khanna, MBBS, MS.

**Specific author contributions:** S.K. wrote the manuscript and D.S.P. reviewed the manuscript.

**Financial support:** None to report.

**Potential competing interests:** S.K.: research grants from Rebiotix, Inc. (A Ferring company), consulting fees from Shire Plc, Premier Inc., Facile therapeutics, ProBioTech Inc., outside of the submitted work. D.S.P.: research grants from Vedanta, Seres therapeutics, 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.

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