Fecal Microbiota Transplantation: The Evolving Risk Landscape

Sanchit Gupta, MD, MS1,2, Benjamin H. Mullish, MB BChir, PhD3 and Jessica R. Allegretti, MD, MPH1,2

Fecal microbiota transplantation (FMT) has been recommended in clinical guidelines for the treatment of recurrent Clostridioides difficile infection (CDI). However, it is considered investigational by most regulatory agencies. As the adoption of FMT has increased from a small group of CDI experts alone to more widespread use, there has been a corresponding increase in concern regarding potential risk. FMT is largely considered a safe procedure although risks described range from mild gastrointestinal symptoms to serious infection. Currently, there is variability in how “FMT” is characterized specifically regarding testing approach, which, in turn, impacts the risk profile. This has been highlighted by the rare cases of multidrug-resistant organisms, Shiga toxin–producing Escherichia and enteropathogenic E. coli, recently reported, where these organisms were not screened. These cases have prompted additional screening mandates from the US Food and Drug Administration (FDA), which has maintained its policy of enforcement discretion for the use of FMT for CDI not responding to standard therapy. Here, we examine the evolving risk landscape of FMT.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B892


INTRODUCTION

Fecal microbiota transplantation (FMT) continues to be a highly effective therapeutic for Clostridioides difficile infection (CDI) not responding to standard therapy. Because the accessibility of FMT has increased, adoption in clinical practice has become more widespread. Initially, FMT use was fairly limited to centers with expertise. Each center would screen donors and CDI candidates, evaluate appropriate delivery modality, obtain a detailed informed consent, and perform close clinical follow-up. Subsequently, FMT has been recommended by multiple society treatment guidelines, stool banks have emerged, and ease of administration has become apparent (1–6). This has led to many clinicians, both gastroenterologists and infectious diseases specialists, adopting this highly effective therapy into their practice. Additionally, given the growing recognition of the potential contribution of the gut microbiome to a diverse range of diseases, interest in FMT for clinical research also continues to increase (7). Several additional potential indications for FMT have been studied with mixed results (Table 1), and at the time of writing, 316 FMT trials are currently registered on ClinicalTrials.gov. As use of FMT expands both within and beyond CDI to clinical trials, concerns regarding the potential risk and meaningful consequences on the safety profile expand as well, especially in vulnerable populations. Given this, significant focus on standardization is needed to safeguard patient

FMT: The Evolving Risk Landscape

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access to this essential therapeutic. Here, we examine the evolving risk landscape of FMT.

ESTABLISHED RISKS

Procedure risk

The administration of FMT is not technically difficult and has variable delivery modalities (colonoscopy, enema, and naso-enteric tube), allowing access to a variety of physicians with differing training (8). However, there are procedural considerations that need to be well understood by practitioners. FMT is largely believed to be a safe procedure although risks have been described (9). Inherent risks of FMT include the possibility of aspiration with upper gastrointestinal (GI) delivery or bowel perforation after a colonoscopy. A case of feculent aspiration after FMT by upper endoscopy was subsequently fatal, with a recommendation to use an antiemetic agent and avoid sedation for upper GI FMT administration (10). Additionally, large-volume FMT should not be administered into the upper GI tract by nasogastric tube or upper endoscopy (11).

One study reported a case of a superficial mucosal tear because of colonoscopy (12). One patient reportedly experienced a bowel perforation associated with FMT that appears to have been administered by nasogastric tube (13–15). It is unclear if bowel perforation in this patient was directly related to FMT. One study of FMT in severe/fulminant CDI reported a bowel perforation after FMT, although 2 patients who did not receive an FMT also experienced a bowel perforation (16). Still, FMT through the lower GI tract seems to be safe overall, and for patients with fulminant CDI, bedside flexible sigmoidoscopy with direct visualization can be used (17).

Overall, the decision to use a particular FMT procedure requires careful patient considerations including relative contraindications (e.g., stricture/altered anatomy and anesthesia-associated risks with colonoscopy), physician factors (e.g., gastroenterologists vs infectious disease specialists), and procedure-related risks (e.g., appropriateness of sedation/anesthesia). Benefits and alternatives should be communicated to patients undergoing FMT, and a shared decision-making process should be used to identify the most appropriate FMT delivery modality for each patient.

FMT material risk

Mild gastrointestinal symptoms may develop after FMT and are typically self-limiting. Symptoms reported include diarrhea, constipation, abdominal discomfort or cramping, fever, belching, bloating, flatulence, nausea, vomiting, and borborygmus (9,18). Patients who are younger or have preexisting irritable bowel syndromes or inflammatory bowel disease (IBD) are more likely to develop gastrointestinal symptoms (19). Individual cases of diverticulitis, appendicitis, and peritonitis have been reported as possibly related to FMT but may be related to underlying comorbidities (9).

The primary acute concern of FMT is the risk of infection transmission. This is of particular importance in the treatment of immunocompromised patients, who may be more vulnerable (12,20,21). Common infections such as norovirus and influenza have been reported after FMT, but these were felt to be attributable to exposure from infected staff at the center where FMT was being administered (12,22).

Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) are ubiquitous viruses that are generally not part of routine donor screening under the assumption that most donors will be positive (23). This is not felt to be clinically significant to an immunocompetent recipient. To date, no cases of EBV have been reported after FMT. Two cases of CMV colitis after FMT in patients with ulcerative colitis, a known risk factor for CMV, have been reported: one patient developed CMV colitis after performing a do-it-yourself FMT from their child’s stool, and another patient developed CMV after receiving an autologous FMT in the control arm of a randomized controlled trial (24,25). Additionally, in a retrospective study of 94 solid-organ transplant recipients, 3 patients experienced CMV reactivation after FMT although none underwent CMV seroconversion (20). Recipients who are severely immunocompromised and seronegative before FMT may be at the highest risk for CMV infection transmitted by stool, although the potential for CMV transmission or reactivation needs to be better understood (26). It is reasonable, therefore, to check CMV/EBV exposure status and for seronegative immunocompromised recipients, discuss the potential risk, benefits, and alternatives to enable complete informed consent (Table 2) (23).

There had been concerns regarding the impact of FMT on patients with preexisting IBD, specifically for higher risk of FMT failure and risk for IBD flare after FMT. A meta-analysis revealed that among all reports of FMT performed in patients with IBD, the risk of worsening underlying IBD was higher among the cohort receiving FMT for CDI whereas patients receiving FMT for the treatment of IBD had negligible rates of IBD worsening (27). In response to this concern, our group enrolled a prospective multicenter trial of 50 patients with IBD receiving FMT for the treatment of CDI (NCT03106844) (28). Only 2% (1/50) of these patients met criteria for a de novo flare (quiescent disease at FMT and a documented increase in partial Mayo score post-FMT) (29). If the patient has active IBD at the time of FMT, their IBD will likely still be active afterward and further treatment escalation should be considered.

RECENT AND EMERGING CONCERNS

In the past year, several safety reports have been filed. Initially, a US Food and Drug Administration (FDA) alert noted 2 immunocompromised patients who developed bacteremia from an extended-spectrum beta-lactamase-producing E. coli, which was traced to donor stool by genomic sequencing. Unfortunately, one of these patients died as a result (30). These patients had received FMT in clinical trials (one for hepatic encephalopathy and the other after allogeneic hematopoietic cell transplantation). In these cases, stool was manufactured at a hospital-based stool bank without screening for multidrug-resistant organisms (MDRO) such as extended-spectrum beta-lactamase organisms, methicillin-resistant Staphylococcus aureus, or carbapenem-resistant Enterobacteriaceae. It has been noted that screening for such organisms has been standard practice at a public stool bank (OpenBiome, Cambridge, MA) since 2016 (31). Consequently, the US FDA released a list of minimum screening requirements that included enhanced donor screening for potential MDRO colonization and MDRO testing of donor stool as of July 2019 (32,33). These cases highlight variability in FMT testing approaches and the need for standardized donor screening, especially when treating vulnerable and immunocompromised patient populations. Notably, there is growing interest in the use of FMT as a possible means of decolonizing MDROs from the gut (34,35).

In March 2020, infections caused by Shiga toxin-producing E. coli (STEC) were reported post-FMT (36–39). Four patients developed a self-limited diarrheal illness associated with a positive STEC test from a single donor. The donor involved had previously screened negative for Shiga-like toxin through
<table>
<thead>
<tr>
<th>Category</th>
<th>Specific indication</th>
<th>Discussion</th>
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| **Gastrointestinal luminal disease** | Inflammatory bowel disease | - Four RCTs collectively suggest FMT may be more effective than placebo in induction of remission of ulcerative colitis. However, marked heterogeneity in patient selection and FMT administration protocols means that further studies are required to define these factors; no current data exist for FMT being effective in maintaining FMT remission (25,104–106).
- No evidence of improved rates of remission after FMT in small randomized study (n = 17) in patients with Crohn's disease given FMT vs sham FMT by colonoscopy soon after steroid-induced remission from flare (107). |
| **Irritable bowel syndrome** | | - Variable outcome data from different RCTs, which again may reflect different administration strategies, patient selection factors, and multiple syndrome phenotypes. Increased level of efficacy seen in study using single "super donor" (108–114). |
| **Liver disease** | Hepatic encephalopathy | - Both enema and capsule FMT reduced burden of HE in patients treated in RCTs including a placebo-controlled trial (115,116). |
| **Primary sclerosing cholangitis** | | - Improvement in ALP of > 50% observed in 3/10 patients treated with FMT as treatment of PSC and concurrent IBD, with ALP levels correlating with abundance of bacterial engraftment (117). |
| **Nonalcoholic fatty liver disease** | | - In a pilot RCT, thin-donor/healthy-donor FMT by duodenoscopy was associated with reduction in intestinal permeability at 6 weeks in patients with NAFLD and elevated gut permeability at baseline. However, no changes in liver fat and/or insulin resistance were observed (118). |

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<tr>
<td>Alcohol dependence</td>
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<td>- In a pilot study, reduced alcohol craving (along with improved cognition and psychosocial quality of life) was observed in 10 patients with alcohol-related cirrhosis given FMT by enema vs placebo</td>
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<tr>
<td>Alcoholic hepatitis</td>
<td></td>
<td>- Cohort studies describe a potential mortality benefit of healthy-donor FMT administered by nasoduodenal tube in patients with severe alcoholic hepatitis ineligible for treatment with steroids (119,120).</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td></td>
<td>- In a pilot nonrandomized study, FMT by gastroduodenoscopy along with antiviral treatment was potentially effective in HBeAg clearance (n = 2/12) (121).</td>
</tr>
</tbody>
</table>
| Metabolic disorders | Obesity, type 2 diabetes, and metabolic syndrome | - In 2 RCTs, including 56 white obese males, an improvement in peripheral insulin sensitivity was observed at 6 weeks post-upper GI FMT, but no other metabolic improvements were seen, and improved insulin sensitivity was lost by beyond 6 weeks (122,123).
- In a randomized study of 22 obese patients (but without other features of metabolic syndrome), lean-donor FMT using capsule was associated with gut microbiome and bile acid changes, but no changes in weight were seen compared with placebo-treated patients (95).
- In a further study of 24 obese adults with insulin resistance, 6 weekly capsules of lean-donor FMT resulted in no changes compared with placebo (124).
- One RCT of 22 patients who received FMT through duodenal tube from donors with metabolic syndrome vs donors post-Roux-en-Y gastric bypass found decreased insulin sensitivity after FMT from donors with metabolic syndrome (125). |
enzyme immunoassay (EIA) testing as recommended by Centers for Disease Control and Prevention guidelines but subsequently tested positive by stool nucleic acid amplification testing (NAAT), which is more sensitive for detection (40,41). Carriers of STEC may be asymptomatic, and therefore, EIA testing may be insufficient compared with NAAT for donor screening (42–45). The US FDA has subsequently required NAAT testing moving forward. This case highlights that the risk profile for FMT changes based on the screening test type and the limits of detection.

Infections caused by enteropathogenic E. coli (EPEC) were also reported (36–38). Two patients who received FMT material from different donors tested positive for EPEC by NAAT. One patient was hospitalized for an illness attributed to EPEC that ultimately resolved. However, CDC and Health Canada state that it is not known if EPEC is a pathogen, and data suggest it may be part of a healthy gut microbiome (46,47). Additionally, standard FMT screening guidelines do not include recommendations to test for EPEC (23,48,49). Although EPEC can cause diarrheal illness in children or severely immunocompromised patients, most are asymptomatic carriers or those with noninfectious diarrhea.

### Table 1. (continued)

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<th>Category</th>
<th>Specific indication</th>
<th>Discussion</th>
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<tbody>
<tr>
<td>Oncologic disorders</td>
<td>Allogenic hematopoietic stem cell transplant</td>
<td>• In an RCT, autologous FMT given after antibiotics during allogenic hematopoietic stem cell transplantation restored pretreatment gut microbiota composition and diversity (126).</td>
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<tr>
<td>Graft-vs-host disease</td>
<td></td>
<td>• A pilot study of healthy-donor FMT by nasoduodenal tube for intestinal graft-vs-host disease demonstrated clinical response, increased gut microbiota diversity, and improved survival (127).</td>
</tr>
<tr>
<td>Chemotherapy-induced diarrhea</td>
<td></td>
<td>• One RCT of 20 patients with metastatic renal cell carcinoma demonstrated benefit of FMT by colonoscopy over placebo for tyrosine kinase inhibitor–induced diarrhea (128).</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor colitis</td>
<td></td>
<td>• A case series of 2 patients demonstrated resolution of immune checkpoint inhibitor colitis refractory to steroids and biologics after healthy-donor FMT (129).</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>Autism spectrum disorders</td>
<td>• One open-label trial in a pediatric population with autism spectrum disorders and gastrointestinal symptoms that underwent treatment with vancomycin, bowel preparation, and FMT for 7–8 weeks, with subsequent improvement in gastrointestinal and behavioral symptoms maintained 8 weeks after treatment; improvements in findings were sustained in a 2-year follow-up study (130,131).</td>
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<tr>
<td>Parkinson’s disease</td>
<td></td>
<td>• A pilot study of FMT by colonoscopy and nasojejunal tube in 15 patients with Parkinson’s disease found a potential improvement in both motor and nonmotor symptoms assessed by multiple scoring systems (132).</td>
</tr>
<tr>
<td>Other</td>
<td>Decolonization of intestinal multidrug-resistant organisms</td>
<td>• No evidence of higher rates of intestinal decolonization of multidrug-resistant bacteria (ESBL-producing Enterobacteriaceae and/or carbapenemase-producing Enterobacteriaceae) in patients treated with 5 days of oral antibiotics before healthy-donor FMT, but small study with heterogenous cohort. Additional study suggests that although FMT may not lead to MDRO decolonization, there may be an associated reduction in bacteremia, carbapenem use, and hospital length of stay (34,35).</td>
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<tr>
<td>Systemic sclerosis</td>
<td></td>
<td>• An RCT of a commercial anaerobic culture of healthy-donor stool vs placebo by gastroduodenoscopy in patients with gastrointestinal involvement of systemic sclerosis led to improvement in bloating, diarrhea, and fecal incontinence (133).</td>
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ALP, alkaline phosphatase; CDI, Clostridioides difficile infection; ESBL, extended spectrum beta-lactamase; FMT, fecal microbiota transplantation; HBeAg, hepatitis B e-antigen; IBD, inflammatory bowel disease; MDRO, multidrug-resistant organisms; NAFLD, nonalcoholic fatty liver disease; PSC, primary sclerosing cholangitis; RCT, randomized clinical trial.
Emerging concerns

The COVID-19 pandemic has raised concerns regarding the impact of the SARS-CoV-2 virus on FMT. SARS-CoV-2 genetic material, including live virus, has been detected in stool even after resolution of respiratory symptoms (63–67). FMT could potentially transmit SARS-CoV-2, although no cases of actual transmission have been reported. Expert panels have advocated for screening of donors for symptoms of or possible exposure to SARS-CoV-2, testing donors as possible, and quarantining stool to monitor donors for development of findings consistent with COVID-19 disease (68–71). Stool testing for SARS-CoV-2 is not currently widely available. The US FDA guidance initially required that stool used for FMT should have been donated before December 1, 2019, unless protocols include screening questionnaires to exclude donors with suspected or confirmed infection and testing of stool for SARS-CoV-2 genetic material (72,73). OpenBiome, the largest universal stool bank, continued to ship FMT material collected before December 1, 2019, for clinical trials and scheduled CDI patients while SARS-CoV-2 testing protocols were being implemented, with nasopharyngeal swab testing of donors at a minimum of every 30 days; assessment of symptoms, exposure, and travel; and a plan to quarantine all newly collected material for the time being (74). However, as of July 23, 2020, the US FDA has required a clinical hold on all investigational new drug applications (IND) for FMT using stool bank (OpenBiome) material and stool banks have temporarily halted shipments, leaving clinicians and patients considering alternatives such as a regression to the less ideal patient-directed donation, which is more cumbersome, time-consuming, and overall costly to the system (31,75,76).

Longer quarantine periods for material may help mitigate risk, especially in situations where new pathogens emerge. This will allow older “pathogen-free” material to be stockpiled for use and provide time to develop assays to test for new pathogens to ensure that material moving forward is pathogen-free.

LONG-TERM AND THEORETICAL RISKS

Long-term risks of FMT have not been established, although theoretical concerns linked to diseases associated with perturbation of the gut microbiome, including autoimmune diseases and metabolic syndrome, have been postulated. Although retrospective data regarding FMT suggest a favorable long-term safety profile to date, the quantity of long-term follow-up data is relatively limited and is further confounded by variable material testing methods, delivery modalities, and patient populations (77–86). Additionally, because recurrent CDI patients tend to be older with multiple medical comorbidities, determining causality from open-label studies is challenging. Case reports of autoimmune diseases including peripheral neuropathy, rheumatoid/psoriatic arthritis, idiopathic thrombocytopenic purpura, and mastocytosis have been diagnosed after FMT and are likely not related to FMT (77,78). Jalanka and colleagues conducted a long-term safety study of CDI patients comparing FMT (n = 45) vs antibiotics alone (n = 39) and report no increased risk of autoimmune diseases, IBD, cancer, allergy, neurological disease, or obesity over a mean follow-up of 3.8 years (86). The American Gastroenterological Association FMT National Registry is ongoing and currently collecting data on long-term safety and efficacy with up to 10-year follow-up of patients treated with FMT (87). Initial 6-month analysis on available registry data reported 2 new cases of ulcerative colitis (88). This stresses the importance of appropriate follow-up after FMT.

(50–57). EPEC may be an “innocent bystander,” raising questions of appropriateness of screening FMT donors for EPEC, impacts of additional testing on cost-effectiveness of FMT because it is commonly detected in healthy individuals, and further limiting a highly selective donor population. Programs in other countries are not currently screening for EPEC because it is generally not considered a pathogen. Nevertheless, the US FDA has mandated NAAT testing for EPEC in addition to STEC to better screen for these pathogens and prevent future possible transmission, particularly in immunocompromised individuals (58).

These concerns highlight the importance of pathogen testing and the possible limitations of bookend screening that is currently used, where stool donors are tested periodically (Figure 1) (23,31). It has been shown that MDROs’ intestinal carriage may be transient and therefore missed with bookend screening (59–62). Appropriate patient consent regarding what is and is not being screened for is very critical (Table 2). The safety of the procedure and risks may differ with testing every sample vs bookend screening (as in the case with MDROs) and using EIA testing vs NAAT (i.e., with STEC) as reviewed above. Longer quarantine periods may help mitigate these uncertainties, especially in cases where new pathogens emerge.

Table 2. Considerations for informed consent when discussing FMT

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<td>Cramping/discomfort</td>
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<td>Borborygmus</td>
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<td>Fever of unknown origin</td>
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<td>Infection risks</td>
<td>Life-threatening sepsis</td>
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<td>Antibiotic-resistant infections</td>
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<td>Blastocystis spp</td>
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<td>CMV/EBV infection in immunocompromised patients</td>
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<td>Limited evidence on long-term safety outcomes</td>
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</table>

CMV, cytomegalovirus; EBV, Epstein–Barr virus; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.
Practitioners who perform FMT in clinical practice need to implement follow-up programs to assess patients for potential short- and long-term adverse events.

The possibility of phenotype transfer by FMT has been supported by rodent studies, where many findings are purported to represent causal inferences for human disease but are limited by definitions of phenotypes, outcomes, and insufficient mechanistic analyses (89). For example, mouse models suggested a role of the gut microbiome in obesity, including after transfer of human stool into mice (90–92). A case report described marked weight gain after FMT for CDI in a patient who received stool from her overweight daughter, raising interest in the transferability of obesity as a trait related to gut microbiota in humans (93). However, this observation was not replicated in larger cohorts where stool donor body mass index (BMI) did not affect recipient weight after FMT for CDI and FMT derived from a lean donor did not reduce BMI in obese patients (94,95).

At the same time, some health benefits after FMT for CDI have been observed compared with patients treated with antibiotics alone. Self-reported mental health after FMT for CDI was improved compared with patients who received antibiotics for CDI (86,96). FMT for CDI has been associated with fewer future bloodstream infections and decreased mortality compared with patients receiving antibiotics (97,98).

Evolving Definition of FMT and the Effect on Safety

FMT is certainly not a new therapy; however, its use for the treatment of CDI not responding to standard care began to increase in 2012–2013. The US FDA initially required an IND for FMT in May 2013. In these early days, access was limited to large academic centers with experts in the field. After concerns regarding patient access to an efficacious therapy began to rise, the US FDA amended this policy in July 2013 to allow enforcement discretion for FMT used to treat CDI not responsive to standard therapies. Before the rise of stool banks, clinicians using FMT to treat patients with CDI were using patient-directed donors. Given the lack of guidance regarding donor screening protocols initially, FMT was still limited to expert centers, making the procedure very safe but less accessible.

Stool banks emerged to address the issue of accessibility and undertook coordinating donations, screening, and sourcing of FMT material. At a public stool bank, only 2.5% of prospective donors ultimately qualified (31). Harmonizing the logistics and coordination like a blood bank allowed for CDI experts to move away from patient-directed donors. History and data from blood transfusions suggest that universal donors may be safer than patient-directed donors (99,100). The initial increased access and standardized screening provided by stool banks allowed this procedure to be both safe and accessible.

Through 2019, OpenBiome provided 53,461 FMT preparations to more than 1,250 providers (101). However, because access has become nearly universal, we may be seeing a slight shift in the safety profile. The nuances of selecting appropriate patients for this therapy and providing critical follow-up may be lost. Unlike European stool banks (who typically work directly with the treating physician to assess if FMT is indicated), the US stool bank model has adopted a different approach, in which FMT material can be purchased by treating facilities without required clinical discussion with the stool bank or justification for use. Given that FMT remains an unapproved product, consideration should be given to adoption of a center of excellence model, as is done in other countries. This model would limit widespread use but may overall increase the safety of this treatment, so a balance between access and safety is clearly needed.

Until there is an approved product, the current policy of enforcement discretion states that FMT can be used only for CDI without an IND in an effort to maintain treatment accessibility. The US FDA is still debating a possible IND requirement, which could improve safety profiles but make FMT pragmatically challenging for use by many health centers and may limit use to expert centers (102). Restricted access may lead individual patients to revert to a do-it-yourself approach in the absence of physician supervision, which is certainly not advisable, and treatment of fulminant CDI will not be possible because IND requirements may preclude timely use in a critically ill patient population (103). There clearly needs to be a balance between safety and accessibility that we are still seeking to strike.

Conclusions

The recent cases of MDRO, STEC, and EPEC and theoretical transmission of SARS-CoV-2 have shed an appropriate spotlight on the risk profile associated with FMT. The regulatory consequences remain in flux at the time of writing, with OpenBiome...
shipsments currently halted. From a clinical perspective, appropriate patient selection, standardized and rigorous donor screening, detailed informed consent, and close follow-up are needed to safeguard patient care. However, until there is an approved product enabling patient access, FMT is an essential therapeutic despite its intrinsic testing/manufacturing variability and pragmatic limitations.

CONFLICTS OF INTEREST

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Specific author contributions: S.G.: drafting of the manuscript.
B.H.M., J.R.A.: critical revision of the manuscript.

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