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MINIREVIEW

Fecal Microbiota Transplantation Donor Screening Updates and Research Gaps for Solid Organ Transplant Recipients

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ABSTRACT In this review, we discuss stool donor screening considerations to mitigate potential risks of pathogen transmission through fecal microbiota transplant (FMT) in solid organ transplant (SOT) recipients. SOT recipients have a higher risk for *Clostridioides difficile* infection (CDI) and are more likely to have severe CDI. FMT has been shown to be a valuable tool in the treatment of recurrent CDI (RCDI); however, guidelines for screening for opportunistic infections transmitted through FMT are underdeveloped. We review reported adverse effects of FMT as they pertain to an immunocompromised population and discuss the current understanding and recommendations for screening found in the literature while noting gaps in research. We conclude that while FMT is being performed in the SOT population, typically with positive results, there remain many unanswered questions which may have major safety implications and warrant further study.

KEYWORDS *Clostridium difficile*, fecal microbiota transplant, solid organ transplant, transplant infectious diseases

Solid organ transplant (SOT) recipients carry an increased risk of health care-associated infections as a result of frequent exposure to immunosuppressive medications, prophylactic and therapeutic antibiotics, gastric acid-suppressing agents, and recurrent hospitalizations (1). In SOT recipients, the risk of *Clostridioides difficile* infection (CDI) is up to 5 times higher than that of the general population (2). The incidence of CDI in SOT recipients is highest within the first 3 months of transplantation, likely due to the degree of immunosuppression, antibiotic exposures, and prolonged hospitalization during this period (3).

CDI is associated with significant health consequences and worse outcomes in SOT recipients, such as fulminant colitis, increased length of hospitalization, readmissions, and allograft rejection (4–6). In multiple studies of immunocompetent populations, the use of fecal microbiota transplant (FMT) for treatment of recurrent *Clostridioides difficile* infection (RCDI) has been noted to have high cure rates and relatively few adverse events (7). However, there are limited data on the use of FMT in SOT recipients, and the published evidence is almost entirely sourced from retrospective clinical reviews. Despite concerns about infectious risks of FMT in this population, the safety of FMT is supported by a growing number of studies, including two retrospective multicenter studies of FMT for RCDI in 94 SOT patients and 80 immunosuppressed patients (8–14). Importantly, no prospective clinical trials of FMT for any indication have focused on the high-risk population of SOT recipients. In this review, we will review current regulatory guidance and current screening and safety considerations for FMT in the SOT population.

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CURRENT AND LIKELY FUTURE REGULATORY APPROACH TO FMT IN THE UNITED STATES

In May 2013, the FDA announced that FMT would be regulated as an investigational new drug (IND) due to its use for the treatment of disease and the absence of phase 3 randomized, controlled studies supporting its efficacy and safety (15). However, the FDA revised its announcement and elected to exercise enforcement discretion to allow health care professionals to administer FMT without an IND for the treatment of refractory CDI or RCDI with informed consent (15). In 2016, the FDA published draft guidance indicating a potential regulatory shift that would require stool banks to submit an IND application to distribute stool to physicians; this draft guidance has not been finalized. This draft guidance also included a plan to continue to exercise enforcement discretion if stool is obtained outside a stool bank (i.e., directly by hospitals or health care providers) (16). With the near-term likelihood of an FDA-approved microbiome therapeutic and risks of potential infection after FMT, it is likely that the FDA will seek to revise its regulatory approach for FMT for RCDI.

There has also been a growing recognition of the potential infectious risks of FMT. In June 2019, the FDA recommended expanded multidrug-resistant organism (MDRO) screening criteria for potential stool donors after reported transmission of extended-spectrum β-lactamase (ESBL)-producing bacteria in immunocompromised FMT recipients (17). This was unfortunately followed by reports of transmission of *Escherichia coli* pathotypes through FMT that were associated with diarrhea, and in two cases, the association with FMT could not be determined because patients died prior to collection of specimens for confirmatory analyses (18).

The Coronavirus disease 19 (COVID-19) pandemic has been very disruptive to the use of FMT. Early studies demonstrated that rectal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) swabs remain positive even after nasopharyngeal swabs become negative (19). As a result, in March 2020, the FDA released a safety alert recommending the use of FMT material donated prior to December 2019 to mitigate potential transmission of SARS-CoV-2 through donor stool. For material donated after December 2019, the recommendation is for testing both donor nasopharyngeal and possibly donor stool for SARS-CoV-2 (20).

CURRENT SCREENING GUIDELINES

Current practices for stool donor screening and selection are largely based on expert opinion (21–23). Since there are no standardized stool donor eligibility criteria, or standardized materials and methods for stool collection and preservation, guidance on stool donor selection has been developed from joint society consensus recommendations and research protocols (23–27). Donor eligibility criteria typically include a questionnaire, physical exam, and laboratory testing (28). Specific recommendations for screening are summarized in Tables 1 to 3. While donor eligibility criteria are strict, existing guidance does not comprehensively address fecal-oral-transmitted opportunistic infections that may affect SOT recipients who are at risk for donor-to-recipient transmission.

Most recommendations, including a recent international consensus published in 2019, recommend standardized donor screening questionnaires, laboratory screening, and standardized protocols for collection, storage, and documentation of the fecal material (23) (Tables 1 to 3). In the United States, adherence to these recommendations falls on individual providers or stool banks under the current FDA policy for FMT for RCDI. This may contribute to significant heterogeneity in practices, which may have safety consequences, especially for immunocompromised FMT recipients.

LIMITATIONS OF CURRENT SCREENING RELEVANT TO FMT USE IN IC/SOT PATIENTS

Current donor screening guidance is not explicit for how to screen potential stool donor material for administration to immunosuppressed recipients beyond mention of serological screening for cytomegalovirus (CMV) IgG and IgM (26, 29). Screening practices are not standardized across sites or stool banks. In fact, the way in which this product is classified

TABLE 1 Recommended donor selection criteria based on presently published guidance and protocols[a]

Characteristic	Consistently recommended	Occasionally recommended	Case-by-case basis	Recently recommended
Relationship to patient				
Intimate, long-time partner (25, 26, 51, 52)	•			
Unknown to patient (26, 53)		•		
Inclusion criteria				
Age > 18 (25, 26, 34, 52, 53)	•			
Children with parental consent and child assent (25, 52)			•	
Negative screening questionnaire similar to those given to potential blood donors (23, 25, 26, 34, 51–53)	•			
Exclusion criteria				
Risk factors for transmittable diseases (e.g., new sexual contact in last six mo, recent needle stick accident, recent transfusion, i.v. drug use, risk for variant Creutzfeldt-Jakob disease, sex for drugs or money, homosexuality, or tattoos) (23, 24, 26, 34, 53)	•			
Travel to tropical area in last 3 mo (23, 25, 26, 34, 51, 53)	•			
Known history of tropical infection (23)				•
Employment in clinical work (23, 34, 53)				•
Use of antibiotics in the 3 mo prior to donation (23, 25, 26, 34, 51–53)	•			
Diarrhea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours (23, 34, 51, 53)		•		
Household contacts with active gastrointestinal infection (26)		•		
Abnormal blood or stool test result suggestive of active/current disease (23, 25, 26, 34, 51–53)	•			
Any gastrointestinal illness (inflammatory bowel disease, irritable bowel syndrome, gastrointestinal malignancies, or major gastrointestinal surgery) or complaints (23, 25, 26, 34, 51–53)	•			
Family history of intestinal cancer or inflammatory bowel disease (23, 34, 52)				•
Diet (51)			•	
History of autoimmune or atopic illness or ongoing immune modulating therapy (23, 25, 26, 34, 51, 53)	•			
History of chronic pain syndromes (fibromyalgia, chronic fatigue) or neurologic or neurodevelopmental disorders (25, 26, 34, 51, 53)	•			
History of psychiatric conditions (25, 34)				•
Metabolic syndrome, obesity (BMI of >30), moderate to severe undernutrition (23, 25, 26, 34, 51, 53)	•			
History of malignancy/receipt of chemotherapy (23, 25, 26, 34, 51, 53)	•			

[a]Consistently recommended, recommended in >4 guidance/protocols; occasionally recommended, recommended in some but not >4 guidance/protocols; case-by-case basis, case-by-case consideration of screening is suggested; recently recommended, recently recommended in response to reported safety concerns. i.v., intravenous; BMI, body mass index.

and, as a result, the way in which it is regulated vary widely between countries. In North America, this FMT material is classified as a biologic product, whereas in the UK, France, and Germany, it is classified as a drug product. In other parts of Europe, it is considered a human cell/tissue product (30). Such differences in classification translate to varied regulatory requirements and are a challenge in developing harmonized recommendations.

FREQUENCY OF DONOR TESTING

During the stool donation period, stool donors remain at risk for potentially transmissible infections that may be asymptomatic or only mildly symptomatic in immunocompetent hosts. It follows that repeat testing completed 2 to 4 weeks after final collection could detect infections with a "window period" that may not have been identified during early stages of infection, such as HIV or viral hepatitis. Repeat testing is particularly important for detection of opportunistic infections such as CMV and BK virus, which may not be symptomatic in immunocompetent hosts but are potentially transmissible to immunosuppressed FMT recipients. Recent retrospective studies of MDRO screening and simulation modeling studies of SARS-CoV-2 screening suggest that they greatly reduce the frequency of releasing doses that may contain pathogens (31, 32). Further work needs to be done to understand the optimal timing and frequency of

TABLE 2 Recommended blood testing for potential fecal donors based on presently published guidance and protocols[a]

Characteristic	Consistently recommended	Occasionally recommended	Case-by-case basis	Recently recommended
Bacterial tests				
Treponema pallidum serology (23–26, 34, 52)	•			
Helicobacter pylori EIA (25)			•	
Viral tests				
Cytomegalovirus serology (23, 25, 52)		•		
Epstein Barr virus serology (23, 25, 52)		•		
Hepatitis A virus IgM (23–26, 34, 52)	•			
Hepatitis B virus surface antigen (23–26, 34, 52)	•			
Hepatitis C virus antibody (23–26, 34, 52)	•			
HIV Ab/Ag including p24 (23–26, 34, 52)	•			
HTLV 1 and 2 antibodies (23, 25, 26, 34, 52)			•	
JC virus serology (25)			•	
Protozoal tests				
Entamoeba histolytica latex agglutination and dipstick (23, 25, 52)		•		
Strongyloides stercoralis serology (23, 25, 34, 52)			•	
Schistosoma spp. (25)			•	
Other blood tests				
Complete blood count (23, 26, 34)				•
Complete metabolic panel (23, 26)		•		
Liver function panel (23, 26, 34)				•
ESR and CRP (23, 26, 52)		•		

[a]Consistently recommended, recommended in >4 guidance/protocols; occasionally recommended, recommended in some but not >4 guidance/protocols; case-by-case basis, case-by-case consideration of screening is suggested; recently recommended, recently recommended in response to reported safety concerns. EIA, enzyme immunoassay; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein.

repeat blood and stool safety testing of the donor to evaluate for interim infections/exposures during the donation period. Presently, there is little standardization of these screening methods and even less consistency in screening approaches for donor screening for FMT in vulnerable hosts. Given the currently available data, it is prudent for stool donor screening programs to quarantine stool products for some period with repeat donor screening prior to use (33).

RECENT FMT DONOR-DERIVED INFECTIONS SUGGEST CURRENT SCREENING MAY BE INSUFFICIENT

Infectious complications following FMT have been reported more frequently in the past 2 years. Two cases of *E. coli* bacteremia in FMT recipients were reported at a single center, resulting in the death of one of the patients. Genomic analysis confirmed the same strain isolated from the blood and FMT capsules (17). These incidents led the FDA to recommend screening donors for risk of carrying MDROs and exclude those deemed high risk, as well as testing stool itself for MDROs prior to transplant (20). In March 2020, OpenBiome, a large stool bank, announced plans to enhance donor screening after receiving 4 reports of Shiga toxin-producing *E. coli* (STEC) and 2 reports of enteropathogenic *E. coli* (EPEC). In the case of the STEC cases, screening was done via enzyme immunoassay (EIA) prior to transplantation, but as these organisms were missed on the screening, the protocol was later updated to include nucleic acid amplification tests (NAAT) for specific pathotypes (34). Prior to these events, the majority of adverse events after FMT were directly attributable to the procedural complications rather than risk from the transplanted material itself, such as the case of fatal pneumonia due to aspiration of FMT material during esophagogastroduodenoscopy (EGD) (35).

With the emergence of SARS-CoV-2, a group from Hong Kong released a proposed protocol for screening stool for SARS-CoV-2 from their center in which they describe a reverse transcriptase PCR (RT-PCR) developed for detection of SARS-CoV-2 in the stool of donors, which appeared to be both sensitive and specific based on a small number of samples by which it was validated (36). Several other groups have also released protocols and have validated fecal SARS-CoV-2 testing (37). Given the extent of the current

TABLE 3 Recommended stool testing for potential feces donors based on presently published guidance and protocols[a]

Characteristic	Consistently recommended	Occasionally recommended	Case-by-case basis	Recently recommended
Clostridioides difficile tests[b]				
Off-label toxin PCR (23, 26, 34, 51, 52)	•			
EIA (25, 51, 52)		•		
Bacterial tests				
Enteric pathogen culture (*Salmonella, Shigella, Campylobacter*) (23, 34, 51)		•		
Shiga toxin or *E. coli* O157 culture (25, 34)		•		
Listeria spp. (23, 25)				•
H. pylori EIA (23, 25, 34)			•	
Vibrio spp. (23, 25)			•	
MRSA (23, 25)		•		
VRE culture (23, 25, 34)		•		
Viral tests				
Adenovirus EIA (34)		•		
Norovirus EIA or real-time PCR (23, 25, 26)				•
Rotavirus EIA (23, 25)			•	
Protozoal tests				
Ovum and parasite microscopic examination (23, 25, 26, 34, 51, 52)	•			
Microsporidia microscopic examination (34)		•		
Giardia fecal antigen/EIA (23, 25, 26, 34, 51)	•			
Cryptosporidium EIA (23, 25, 26, 34, 51)	•			
Isospora and *Cyclospora* microscopic examination (23, 25)			•	

[a]Consistently recommended, recommended in >4 guidance/protocols; occasionally recommended, recommended in some but not >4 guidance/protocols; case-by-case basis, case-by-case consideration of screening is suggested; recently recommended, recently recommended in response to reported safety concerns. EIA, enzyme immunoassay; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus* spp.
[b]Cammarota et al. (23) did not specify modality.

pandemic, it is anticipated that this will become a required component of donor testing in the future.

FMT-ASSOCIATED SCREENING CONSIDERATIONS IN SOT RECIPIENTS

Although there are a number of published recommendations for screening stool donors and stool for FMT for RCDI, screening stool donors prior to FMT for SOT patients warrants special attention (Table 4).

CMV. Given CMV's significance as an opportunistic pathogen in SOT recipients, as well as its immunomodulatory effects, there are specific screening issues to consider. Although CMV is known to be acquired through mucosal transmission from close contacts, the transmission risk for CMV via stool is not well described. PubMed English-language literature searches with combinations of the terms "cytomegalovirus," "CMV," "stool," and "feces" did not identify studies of CMV PCR detection in stool of healthy individuals. In one study evaluating rates of various enteropathogens in patients with ulcerative colitis, 3.2% of immunocompetent controls were found to have PCR-positive stool for CMV (38). This indicates that CMV can be detected in, and thus possibly transmitted, via fecal matter. In a multicenter study of FMT in the SOT population, 14% of patients experienced reactivation of CMV following FMT (14). An international consensus conference published in 2019 recommends against exclusion of donors based on the presence of CMV IgG given no reported cases of CMV transmission but recommends shared decision making with patients, especially those who are seronegative, and consideration of exclusion of donors with positive CMV IgM for immunocompromised recipients (23, 29).

Further study is needed to confirm the safety of FMT material obtained from donors who are CMV IgM negative but IgG positive. Negative stool CMV PCR may help delineate risk. However, stool donor screening programs may encounter logistical and performance characteristic issues with testing of CMV stool PCR. While it has shown some promise for utility in

TABLE 4 Opportunistic fecal to oral pathogen prevalence and detection frequencies in healthy adults and implications in solid organ transplant recipients[a]

	Data for viruses:			
OI epidemiology and SOT implications	**CMV**	**EBV**	**BKV**	**JCV**
Seroprevalence of virus in healthy U.S. adults (%)	30–97 (54)	90–95 (55)	82 (56)	58 (57)
Frequency of stool shedding in healthy adults (%)	Limited data (38)	Limited data (38)	8.2 (44)	9.1 (44)
Frequency of symptomatic infection in SOT recipients (%)	9–32 (58)	1–32 (57)	1–10 (59)	2–5 (60, 61)
Known cases of FMT-derived infection	Possibly (62)	No	No	No
Known cases of SOT organ donor-derived infection	Yes (63)	Yes (57)	Yes (59)	Unknown
Are SOT donors typically screened prior to transplant (64)	Yes; IgG	Yes; IgG	No	No
Are SOT recipients typically screened prior to transplant? (64)	Yes	Yes	No	No
Is antiviral prophylaxis required for viremia?	Yes	No	No	No
Current recommendations for donor screening	Serology occasionally recommended (23, 25, 52)	Serology occasionally recommended (23, 25, 52)	Serology rarely recommended (25)	No recommended screening

[a]OI, opportunistic infection; CMV, cytomegalovirus; EBV, Epstein-Barr virus; BKV, BK virus; JCV, JC virus; SOT, solid organ transplant; FMT, fecal microbiota transplant.

the inflammatory bowel disease (IBD) population (39), the performance characteristics of stool CMV PCR testing are poorly defined and not validated for asymptomatic screening purposes.

Alloimmunity following FMT has been demonstrated to change the rates of rejection of FMT in murine models (40). In the retrospective review from Cheng et al., the reactivation rate of CMV was 14% (14). All patients were seropositive for CMV prior to transplant. This group hypothesizes that decreased CD4 levels and thus lower CD8 activation may drive reactivation of CMV. Some animal models may contradict this hypothesis (41), and further study is needed, specifically to drive the need for potential CMV prophylaxis in different patient populations.

Epstein Barr virus (EBV). EBV infection, whether by new infection or reactivation of a latent infection, also carries specific risks in SOT recipients, including inducing post-transplant lymphoproliferative disorder (PTLD). Screening for EBV is required for organ donors and recipients by the United Network for Organ Sharing (UNOS) (42). However, to our knowledge, no studies have investigated or reported EBV transmission post-FMT. English PubMed literature searches with combinations of the terms "Epstein Barr virus," "EBV," "stool," and "feces" did not identify studies of EBV PCR detection in stool of healthy individuals. In one study evaluating enteropathogen detection frequencies in patients with ulcerative colitis, 25% of immunocompetent controls were found to have PCR-positive stool for EBV (38). Similar to CMV, a recently published consensus did not recommend excluding donors who are EBV IgG positive, although again, data are limited (29). Screening donors and recipients for EBV may be considered by centers performing FMTs on SOT recipients; however, the benefit of this practice is unclear and needs further study.

Polyomaviruses. The general population has widespread infection with polyomaviruses, but this carries various degrees of clinical significance in SOT patients. BK virus (BKV) nephropathy is an important cause of graft loss for renal transplant recipients, though BK-related disease is not typically seen in nonkidney solid organ transplant recipients (13). BKV has been detected in the stool of healthy individuals, though this may be more common in children than adults (43, 44). JC virus (JCV) is another clinically important polyomavirus that is the cause of progressive multifocal leukoencephalopathy (PML). JCV was detected in the stool of 9.1% of 110 adult subjects (43, 44). Long-term studies of renal transplant patients undergoing FMT or human-derived microbial therapeutics should be established to estimate rates of post-FMT BK nephropathy and PML.

Other opportunistic pathogens. Screening donors for additional viral infections such as human T-cell lymphotropic virus 1 (HTLV-1) and HTLV-2, adenovirus, human herpesvirus 6 (HHV-6) and HHV-8, and parasitic infections such as *Toxoplasma gondii*, strongyloidiasis, and *Trypanosoma cruzi* may also be important to consider. Beyond preliminary evidence, however, the fecal transmission risks, and much less, the temporal dynamics of these risks, for most of these pathogens are not well understood. Travel to areas of endemicity and clinical history of infection should guide screening for these pathogens.

FUTURE DIRECTIONS

In order to better quantify the risk of pathogenic transmission, as well as to demonstrate safety, more longitudinal studies and larger studies are needed. At present, the largest published prospective study of FMT recipients included 219 patients (45). However, only 18 of these patients were immunocompromised, and 5 were post-renal transplant status (45). In the hematopoietic stem cell transplant population, DeFilipp et al. performed an open-label single-group pilot study in the allo-hematopoietic stem cell transplant population in which a small group of patients received FMT capsules within 1 month of neutrophil engraftment to expand microbiome diversity (46). The trial demonstrated that administration of FMT soon after engraftment was safe, with no FMT-associated infections noted in the group. A similar but larger series would be helpful in the SOT population. The American Gastroenterological Association and the National Institutes of Health have announced an FMT National Registry to collect clinical and patient-reported outcomes. This registry, when results are published, will be vital in better understanding safety concerns. This registry will also collect information on other microbiota products which will be important as oral microbiota products are more widely used (47).

Different FMT delivery methods in the SOT population. Multiple sources of FMT/microbiota-restoring therapies are available at this time. These include stool banks, smaller hospital-based donor programs, and feces donors who are friends or relatives of the patient. Stool bank FMT doses may be manufactured with more standardized screening protocols than doses sourced from individuals known to the patient or health care provider. Additionally, individually sourced FMT doses may be less efficient to produce, as individual practitioners often do not have the infrastructure or workflows for screening and storage at scale (48, 49). Centralized stool banks allow for standardized, potentially tailored screening practices, which may be especially relevant for SOT recipients (49). On the other hand, production at scale carries distinct risks of contamination, which could impact larger numbers of patients, including potentially immunocompromised FMT recipients.

In some cases, patients may prefer FMT doses manufactured from a family member or friend given concern about perceived risk of infection when material is received from an anonymous donor. In this case, additional time for screening and manufacture must be considered, which may delay therapy (48). In SOT recipients, this may have significant implications given the higher risk of serious CDI.

Over the next few years, oral microbiome therapeutics are likely to obtain FDA marketing approval, which will expand nonantibiotic approaches for treatment of CDI. These oral live-bacterial product therapeutics deliver a standardized fraction of intestinal microbiota for treatment of diseases such as CDI. These products would be regulated by the FDA and manufactured with good manufacturing practices (GMP). These products are expected to carry a lower risk for pathogen transmission (50). Thus, it is likely that once available, they may have safety profiles for immunocompromised patients that are preferable to FMT.

CONCLUSIONS

Microbial therapeutics are a promising intervention for an expanding number of clinical indications, and immunosuppressed patients such as SOT recipients stand to

benefit given their increased risk for CDI, chronic MDRO colonization, and opportunistic infections. Though initial data suggest FMT is safe for SOT recipients, FMT has unique risks and potential benefits from microbiota enrichment that warrant further study. We have examined several challenges to conducting microbial therapeutic studies in immunosuppressed populations. We hope that attention to these issues will spur expanded investigation of opportunistic pathogen colonization and shedding in healthy stool donors.

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