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The Gut Microbiota in Transplant Patients

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Abstract

Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients are at increased risk for developing infections due to underlying immunosuppression. Antibiotic use, and in HSCT recipients, the use of preparative regimens prior to transplantation can deplete gut commensal bacteria, resulting in intestinal dysbiosis. Emerging evidence in transplant patients, particularly HSCT, suggest that disturbances in gut microbiota populations are associated with a number of adverse outcomes. Here, we review the outcomes of HSCT and SOT recipients with gut microbiota imbalance or dysbiosis, explore the nascent field of gut microbiome therapeutic approaches including fecal microbiota transplantation and the use of precision probiotics in HSCT and SOT recipients.

Keywords

gut microbiome; microbiota; transplant; fecal microbiota transplant; colonization resistance

1. Introduction

The gut microbiome is the collective community of microorganisms in the gastrointestinal tract and the genes that they harbor. Gut microbiota refer to the intestinal microbes.(1) Commensal bacteria provide benefit to the human host,(2) though historically an understanding of the mechanisms by which they confer benefit to the host had been

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hampered by culture-dependent methods.(3) Advances in culture-independent molecular biology-based methods, particularly the advent of next-generation sequencing approaches, have led to an explosion of microbiome research centered on understanding the role of gut microbiota in specific disease processes, and in the best cases defining underlying mechanisms and establishing causality.(3)

In health, the human gastrointestinal tract is inhabited by highly diverse microbial communities consisting of mostly bacteria especially anaerobic Firmicutes and Bacteroidetes, fungi, archaea, and eukaryotes with a density of 10^{13} to 10^{14} cells/g fecal matter.(4-6) While the variance in intestinal commensal bacterial diversity is high between individuals (with only approximately one-third of bacterial species being common between any 2 individuals), the gut microbiome tends to remain relatively stable over time in healthy individuals,(7, 8) except during the early acquisition and development of the infant gut microbiome.(9) The intestinal microbiota maintains intestinal homeostasis and epithelial integrity, modulates host inflammation, inhibits colonization and infection of pathogenic microbes, and provide nutritional benefits to the human host.

Transplant patients are more prone to develop infections compared to healthy hosts due to underlying immunosuppression. Infections in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients occur more frequently and are often more severe leading to significant morbidity and mortality. For example, in patients who underwent allogeneic HSCT from 2014 to 2015, 20% of deaths within the first 100 days post-transplant was attributed to infections. (10) Though antibiotics have undoubtedly mitigated the risk of adverse outcomes attributed to infections, recent studies suggest that early broad-spectrum antibiotic use is an independent risk factor for increased mortality in allogeneic HSCT (allo-HSCT) recipients.(4, 5, 11) Whether this relationship is causal remains to be determined.

Disruptions of gut homeostasis may occur in SOT and HSCT recipients secondary to antibiotic use, whether for prophylaxis or treatment. Further, in HSCT recipients, the standard preparative conditioning regimens consisting of chemotherapy and/or radiation can also have a significant impact on gut microbiota populations.(12, 13) Emerging evidence in HSCT recipients suggest that disturbances in gut microbiota populations are associated with a number of adverse outcomes. Here, we will review available data on outcomes of HSCT and SOT recipients with gut microbiota imbalance or dysbiosis, with a focus on HSCT recipients. Then we will explore the nascent field of gut microbiome therapeutic approaches, comparing fecal microbiota transplantation (FMT) and the use of precision probiotics.

2. Gut Microbiota Dysbiosis in HSCT Recipients

Majority of studies exploring the role of the gut microbiome and transplant patients have concentrated on the HSCT population (see the following review articles for further details. (14-16) Briefly, during the process of HSCT, the intestinal mucosa is damaged from intensive chemotherapy and/or radiation preparative regimens. The resultant injury of the gastrointestinal epithelial barrier along with the use of antibiotics, particularly those that deplete commensal anaerobic gut microbiota (i.e. piperacillin-tazobactam, imipenem-

cilastatin, metronidazole and oral vancomycin) leads to gut microbiota dysbiosis allowing for intestinal domination with gut microbiota species typically low in abundance, such as *Enterococcus*, *Streptococcus* and various Enterobacteriaceae species.(11, 17) Fluoroquinolone use in allo-HSCT recipients is significantly associated with decreased intestinal domination by Proteobacteria (HR: 0.09; p = 0.02) but not associated with *Enterococcus* domination (HR: 1.09; p=0.832).(17) Intestinal domination has been defined as gut colonization with a predominating bacterial taxon representing at least 30% relative abundance and often precedes bacteremia by the same bacterial organism in HSCT recipients.(17, 18)

Gut microbiota disruption has been associated with negative outcomes in allo-HSCT recipients. Recent data has shown that gut microbiota dysbiosis is associated with data demonstrating poorer survival, increased risk of graft-versus-host disease (GVHD) and GVHD-associated mortality, and higher rates of bacteremia in patients with low intestinal microbial diversity at the time of neutrophilic engraftment.(11, 19) The overall survival at 3 years from time of HSCT in patients with low, intermediate and high intestinal diversity was 36%, 60% and 67% respectively (p = 0.019).(11) The effect of low intestinal diversity persisted even after adjustment for other clinical predictors for transplant-related mortality in a multivariable model. Similarly, transplant-related mortality at three years differed between diversity groups: 9%, 23% and 53% (p = 0.003) in high, intermediate and low diversity groups respectively.(11)

Similarly, preservation of specific commensal members of the human intestinal microbiota is associated with survival in allo-HSCT recipients. Lachnospiraceae family were observed in greater relative abundance in allo-HSCT recipients who were alive,(11) while loss of *Clostridiales* during allo-HSCT was associated with increased transplanted-related mortality. (20) In pre-clinical studies, loss of Lachnospiraceae is associated with an increased risk for *Clostridium difficile* infection.(21, 22) A deficit in either Lachnospiraceae alone, or in combination with Bacteroidaceae in HSCT recipients is also associated with an increased risk of Grade 3 to 4 acute gastrointestinal GVHD.(19) Abundance of gram-positive, oral bacteria such as *Rothia mucilaginosa*, *Solobacterium moorei* and *Veillonella parvula* were positively correlated with the development of severe acute GVHD, while members of the *Bacteroides* genus such as *B. thetaiotaomicron*, *B. ovatus* and *B. caccae* were negatively correlated with subsequent acute severe GVHD.

Many of these studies are descriptive in nature and, as with many microbiome studies, the question of causality needs to be addressed. In some studies, supplementation with specific consortia of gut microbiota found to be associated with clinical benefit can mitigate disease severity in preclinical models of GVHD.(4, 20, 23) FMT has been used in human patients, and we will discuss those findings later in this review.

3. The Gut Microbiome and SOT Recipients

Studies characterizing changes in gut microbiota populations, the resulting physiologic impact and associated outcomes in SOT patients remain very limited. While there have been several studies examining the role of gut microbiota in specific disease states such as liver

cirrhosis and cardiovascular diseases, only a few studies characterizing intestinal microbiome changes peri-transplantation have been performed in liver, (24, 25) kidney,(26) and small intestinal transplant recipients.(27) (Table 1) and none in thoracic transplant recipients.

Intestinal dysbiosis has been described in patients with liver cirrhosis, (28, 29) especially in those who have decompensated cirrhosis and hepatic encephalopathy. (29) Furthermore, there are data suggesting that liver transplantation may be associated with improvement in intestinal dysbiosis. (24, 25) In a study of 40 liver transplant recipients, gut microbiota diversity (as determined by Shannon microbial diversity index) was significantly higher after liver transplant (assessed at 7 ± 3 months post-transplant), compared to pre-transplant (Shannon Diversity Index 2.1 ± 0.7 vs. 1.6 ± 0.7; p = 0.001).(25) During the post-transplant period, the relative abundance of potentially pathogenic taxa such as *Enterobacteriaceae* (*Escherichia*, *Shigella*, *Salmonella*) was reduced, while the relative abundance of potentially beneficial commensals *Lachnospiraceae* and *Ruminococcaceae* were increased. (25)

In another study, liver transplant recipients whose cognitive function did not improve post-transplantation were found to have significantly increased relative abundance of *Proteobacteria* and *Enterobactericeae* (median pre-liver transplant vs. post-liver transplant groups 0% vs. 12%; p = 0.04) and reduced relative abundance of Firmicutes. (24) While mechanisms driving these observations need to be defined, one potential explanation may involve bile acids. (30) Bile acids are critical for maintaining colonization resistance against pathobionts and pathogens.(31-34). Liver dysfunction has been shown to adversely affect bile acid metabolism and production which could have a significant impact on gut microbiota populations. Additionally, patients with liver cirrhosis often have increased intestinal permeability, which in turn could lead to bacterial translocation and translocation of metabolites such as indoles. (35) For example, cirrhotic patients with alcoholic hepatitis have significantly lower total fecal bile acids (2.4 vs. 11.3 μmol/L; p = 0.01) and secondary bile acids (0.7 vs. 10.7 μmol/L; p <0.01), compared to cirrhotic patients without alcoholic hepatitis. (30) Further, hyperammonemia associated with liver disease can also impact gut microbiota populations.(36, 37) Additional preclinical and clinical studies will need to be conducted, however, to establish causality.

In a study looking at kidney transplant recipients (n=26), those who developed diarrhea (n=6) during the first 90 days post-transplantation had lower gut microbiota diversity compared to time-matched kidney transplant recipients without diarrhea (n=9) (2.5 ± 0.3 vs. 3.4 ± 0.8; p = 0.02), (26) an association since confirmed in other studies. (38, 39) Kidney transplant recipients without diarrhea were noted to have higher abundance of the phylum Bacteroidetes phylum, especially the genera *Ruminococcus*, *Coprococcus* and *Dorea*. Kidney transplant recipients who developed urinary tract infections (UTI) due to *Enterococcus* had higher median *Enterococcus* fecal abundance compared to those who did not develop Enterococcal UTI (24% vs. 0%; p = 0.005),(26) suggesting that there may be an association between gut microbiota with UTI in kidney transplant recipients.

Oh et al. reported that the ileal microbiota in 19 intestinal transplant recipients had a significant increase in the relative abundance of Proteobacteria (16% to 61%; p<0.01),

primarily due to an expansion in *E. coli* and *Klebsiella pneumoniae* species and a reduction in the relative abundance of Firmicutes (81% to 29%; $p<0.001$) during episodes of acute graft rejection. (27) Ileal microbial diversity as measured by both Shannon and Simpson indices were not different. (27) Whether the observed increase in Proteobacteria/Firmicutes ratio is a cause, or a consequence of allograft rejection is unclear.

With SOT patients, the importance and impact of the microbiome will likely be highly variable and may be organ specific. For instance, in liver transplant patients, improved liver function may directly impact gut microbiota populations and *vice versa* whereas a cardiac transplant patient may only be impacted by the gut microbiome in its effect on the adaptive immune response and thus the risk of organ rejection. Lung transplant patients, however, may be impacted by both the lung microbiome (direct effect on lung functionality) and the gut microbiome (adaptive immune response for organ rejection). Thus, further studies in SOT patients will be needed to address these questions, and only then will begin to unravel the intricacies of how the microbiome and host interact in the setting of SOT.

4. Reconstitution of Gut Microbiota in HSCT Recipients

Because gut microbiota disruption has been shown to negatively impact allo-HSCT recipients, including poorer survival, higher rates of bacteremia and increased risk of GVHD and GVHD-associated mortality,(11, 19) FMT has been studied as a potential strategy to reconstitute gut microbiota in allo-HSCT recipients. (40) In a randomized controlled trial, autologously-derived FMT (auto-FMT), where a patient's own feces was collected and archived prior to transplant, was administered post-HSCT after immune reconstitution and successfully restored important commensals and members of a healthy gut microbiota, including members of the Lachnospiraceae and Ruminococcaceae families and Bacteroidetes phylum, that had been lost during the HSCT process.(40) Auto-FMT was also demonstrated to be safe and feasible in this study. (40)

In another study, the safety and feasibility of administering FMT capsules were assessed in adult patients undergoing first allo-HSCT.(41) Among the 13 patients included, there was a single case of *Klebsiella pneumoniae* bacteremia in a study participant who developed severe gastrointestinal GVHD 20 days post-FMT. (41) There was no transmission of infectious organisms from FMT capsules reported in this study. In this study neither powered to investigate the effectiveness of FMT in restoring intestinal microbial diversity nor the effect of FMT on clinical outcomes after allo-HSCT, the intestinal microbiome alpha-diversity was not found to be significantly different between the pre-HSCT and post-HSCT/pre-FMT or post-FMT specimens.(41) However, the authors found a significant decrease in the median urinary 3-indoxyl sulfate (3-IS), a tryptophan metabolite used as a surrogate marker for intestinal microbiota disruption when comparing the pre-HSCT with the post-HSCT/pre-FMT urine specimens (34.59 μmol/mmol creatinine vs. 4.36; $p \leq 0.0001$),(41) and significant increases in 3-IS in urine samples collected 1 week and 1 month post-FMT respectively, when compared with the post-HSCT/pre-FMT sample.(41)

5. Fecal Microbiota Transplantation and Colonization Resistance

The intestinal microbiome serves as a reservoir for multi-drug resistant organisms (MDROs) such as extended-spectrum β-lactamase-producing *Enterobactericeae* (ESBL), carbapenem-resistant *Enterobactericeae* (CRE), vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).(42, 43) The healthy microbiome prevents colonization of gastrointestinal niches by pathogens, a phenomenon known as colonization resistance. This defense mechanism may be impaired due to chemotherapy and antibiotics, resulting in the establishment of colonization by MDROs.(44)

Interestingly, mice with intact gut microbiota rapidly eliminate VRE from the gut, whereas antibiotic-mediated disruption of microbiota enabled VRE to expand and achieved a state of intestinal dominance, accounting for ~99% of gut microbiota.(45, 46) Further, gut microbiota-derived metabolites, namely short-chain fatty acids, can promote colonization resistance to multi-drug resistance Enterobacteriaceae via intracellular acidification of the pathogenic microbes and subsequent growth inhibition.(47) Thus, there may be a therapeutic role for FMT or precision probiotics to eradicate gut colonization by MDROs, especially in transplant patients who are frequently exposed to antibiotics.(42, 48-50) Evidence supporting this is currently limited to case reports in SOT and HSCT recipients.(48, 51, 52) Furthermore, long term follow-up data on the safety and effectiveness of FMT for eradication of MDROs in transplant patients is currently unknown, though several clinical trials are underway.(53, 54)

6. *Clostridium difficile* Infections in Transplant Recipients

Clostridium difficile infection (CDI) is the most common infectious cause of healthcare-associated diarrhea. Based on a large, longitudinal study, approximately 453,000 incident CDI and 29,000 deaths were attributable to CDI in the general U.S. population in 2011.(55) In SOT recipients, the risk of developing CDI is five times higher compared to the general population with an estimated annual of CDI post-transplant to range from 2.5% to 22.9%, (56) and even higher in HSCT recipients with CDI incidence rates reported to range from 12.1 to 37.8 per 100 allogeneic transplants.(57) Even after appropriate antibiotic treatment, CDI may recur in some patients, with recurrence rates estimated to be 20.9% and 13.5% in health care- and community-associated CDI respectively.(55) rCDI is associated with a 33% increased risk of mortality at 180 days, compared to those who do not suffer a recurrence. (58)

Based on the premise of reversing underlying intestinal dysbiosis and restoring intestinal microbial homeostasis, FMT has been successfully used in the past decade for treatment of rCDI. FMT is currently recommended for patients with rCDI only after 3 or more recurrences of infection.(59) The 2017 Update by the IDSA and SHEA Clinical Practice Guidelines for CDI currently recommends treating the first recurrence of CDI with either oral vancomycin as a pulsed and tapered regimen (weak recommendation, low quality of evidence), or a 10-day treatment course with fidaxomicin (weak recommendation, moderate quality of evidence). (59) Unfortunately, 25% patients treated with oral vancomycin for CDI experience had at least one additional episode of infection post-treatment.(60, 61) It has

been hypothesized that antibiotic treatment of CDI itself could result in intestinal dysbiosis, which could then lead to decreased colonization resistance to enteric pathogens including *C. difficile*. Oral vancomycin has been shown to induce drastic changes in human gut microbiota, specifically by significantly decreasing the relative abundance of Bacteroidetes ($p<0.01$) while concomitantly increasing the relative abundance of Proteobacteria ($p<0.01$) in patients with rheumatoid arthritis without CDI.(62) This antibiotic-induced dysbiosis effect persisted for up to 22 weeks in these patients.(62) The impact of fidaxomicin on gut microbiota remains largely undefined. In a multicenter, open-label trial, patients with CDI randomized to receive extended-pulsed fidaxomicin treatment had significantly higher mean Shannon α diversity index than those randomized to the oral vancomycin arm (1.08 vs. −0.29; $p = 0.0015$).(63) The effect of fidaxomicin on gut microbiota composition has not been studied.

The success rates of FMT in treating rCDI vary with the method of feces instillation and number of FMT treatments. In the general population, success rates of FMT administered via colonoscopy are estimated to range from 80% to 100%,(64-68) and with nasoduodenal administration to be between 77% to 94%.(69, 70) Potential post-FMT adverse events include physical complications from the instillation, such as colon perforation during colonoscopy and upper gastrointestinal bleeding from nasogastric tube insertion. Additionally, norovirus gastroenteritis have been reported in 2 patients post-FMT though neither case was proven to be donor-derived.(71) But overall the incidence of adverse effects after FMT are low and typically not severe.

Studies evaluating the safety and effectiveness of FMT in adult and pediatric HSCT recipients are limited to case series (72, 73) and case reports.(74-76) These studies demonstrate that FMT is generally safe and effective in treating rCDI in both patient populations. Up until recently, adverse events reported had been comparable to those in the immunocompetent population, and mostly included mild and transient gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea post-FMT.(77) The Food and Drug Administration issued a safety alert for the investigational use of FMT in June 2019, after two immunocompromised adults developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *E. coli* from use of FMT from the same donor, who was not screened prior to stool collection.(78)

The largest cohort of adult SOTR who received FMT for treatment of rCDI is a multicenter retrospective study, which included 94 patients.(79) Following a single FMT, the primary cure rate, defined as resolution of diarrhea or a negative stool *C. difficile* toxin or PCR assay was 63.8% (60/94) at 1 month and 58.7% (54/92) at 3 months post-FMT.(79) The effectiveness rate of single FMT in SOTR reported by Cheng et al. is comparable to reports from other studies, estimated to range from 50% to 70%.(2, 80) Risk factors associated with increased risk for FMT failure were assessed using a multivariable logistic regression model, which include use of non-CDI antibiotics at time of FMT (OR: 3.34, 95% CI: 1.07 – 10.38; $p = 0.037$), patients who received fresh stool FMT from a patient-directed donor compared to those who received frozen stool from a universal donor (OR: 4.12, 95% CI: 1.15 – 14.76; $p = 0.03$), those with severe or fulminant CDI (OR: 4.69, 95% CI: 1.28 – 17.24; $p = 0.02$)

and presence of colonic pseudomembranes at the time of FMT (OR: 6.76, 95% CI: 1.39 – 32.82; p = 0.018).(79)

In the largest case series of 7 adult allo-HSCT recipients, the median time from HSCT to FMT was 635 days (IQR: 38 − 791).(73) The most common route of FMT administration was nasoduodenal (6 of 7, 85.7%).(73) With a median follow-up of 265 days (IQR 51 − 288), all-cause mortality was 0% and no major adverse events were reported.(73) Mild, self-limited gastrointestinal discomfort or bloating was reported in 2 patients (28.6%).(73) Most (6 of 7, 85.7%) had no CDI recurrence during the follow-up period.(73) One HSCT recipient developed CDI recurrence at day 156 post-FMT after receiving a third-generation cephalosporin and underwent a repeat FMT with no further recurrences.

7. Precision Microbiome Reconstitution

While FMT effectively prevents development of rCDI by reconstituting microbiota complexity, development of microbiota-based therapies has largely been hampered by undefined microbiome-encoded genes and gene clusters critical for infection resistance to *C. difficile*. In a study of allo-HSCT recipients, presence of either one of the 3 bacterial taxa: Bacteroidetes, Lachnospiraceae and Ruminococcaceae at engraftment was significantly associated with 60% reduced risk of CDI post-engraftment.(81)

Clostridium scindens has been significantly correlated with resistance to CDI.(33) In this study by Buffie et al., the authors utilized an integrated approach when evaluating probiotic candidates. A representative consortium of four intestinal bacterial isolates with species-level 16s ribosomal RNA similar to operational taxonomic units (OTUs) found to be conserved and associated with *C. difficile* inhibition in the murine model was identified, upon which a human-derived *C. scindens* isolate was then adoptively transferred to mice.(33) Adoptive oral transfer of the consortium or *C. scindens* alone, but not transfer of the other three isolates individually significantly ameliorated murine CDI and CDI-attributed mortality compared to controls.(33) The mechanism of *C. scindens*-mediated *C. difficile* inhibition is postulated to derive from its expression of enzymes crucial for synthesis of secondary bile acids such as deoxycholate and lithocholate. The relative abundance of secondary bile acids was restored by the administration of either bacterial suspension containing the consortium or *C. scindens* alone, both of which inhibited *C. difficile* in a dose-dependent fashion.(33) Thus, study results suggest that the precise transfer and engraftment of *C. scindens* could restore physiological levels of secondary bile acid synthesis in antibiotic-exposed animals.(33)

Studies have generally, though not universally demonstrated probiotic supplements to be safe. A case of fatal gastrointestinal mucormycosis was reported in a preterm infant who was administered a dietary supplement for probiotic effects.(82) Autopsy showed angioinvasion of the cecum by *Rhizopus oryzae*, also recovered from the unopened dietary supplement.(82) Cases of probiotic strain-derived bacteremias, most commonly due to *Lactobacillus spp*. have also been reported in HSCT recipients. (83-85)

8. Conclusion

SOT and HSCT recipients are immunosuppressed, at increased risk for developing infections and are more likely to receive prophylactic and/or treatment antibiotics.Unfortunately, the resultant intestinal dysbiosis has been linked to negative clinical outcomes including poorer survival in allo-HSCT recipients. While evidence supporting the importance of the gut microbiome in the health of HSCT patients has been accumulating, it is unclear if these findings will also be applicable to SOT recipients. Allo-HSCT patients undergo a complete transplantation of their immune system, and as the gut microbiome has been shown to be critical for shaping both host innate and adaptive immune responses, it is not surprising that the gut microbiome appears to have an important role in modulating host immune response. SOT recipients, on the other hand, are more anatomically heterogeneous, and thus the impact of intestinal dysbiosis may vary across organ groups.

There is significant interest in the scientific and clinical communities regarding the use of FMT in reversing intestinal dysbiosis, and in turn its impact on patient outcomes. Preliminary studies have demonstrated FMT as a safe and effective treatment modality in reconstituting gut microbiota. Currently, FMT is used in standard clinical practice to treat rCDI. Whether it has the potential to improve clinical outcomes, and whether auto-FMT will be used routinely in all transplant recipients, or for eradication of MDRO gut colonization in transplant patients in the future requires confirmation by additional studies.

9. Future Considerations

To determine if FMT should be part of standard of care in patients undergoing allo-HSCT, a clinical trial randomizing allo-HSCT recipients to heterologous, autologous versus no FMT treatment needs to be performed. In addition to safety and effectiveness, the impact of FMT on clinically meaningful endpoints such as patient survival, disease relapse and GVHD rates should be evaluated. Determinants of an optimally effective FMT treatment in restoring gut microbiota diversity and composition in allo-HSCT recipients such as dose, frequency, timing, route, and FMT constituents need to be ascertained.

In SOT recipients, gut microbiota diversity and composition changes that occur peri-transplantation needs to be characterized. Then, the impact of gut microbiota changes on patient and graft survival should be examined. In preclinical studies, differences in gut microbiota composition have been associated with skin graft rejection,(86, 87) and murine cardiac allograft survival. (88) It is currently unknown if these results are applicable to SOT recipients. The relationship(s) between gut microbiota and pharmacokinetics of immunosuppressive medications deserve further exploration. In mice, high dose tacrolimus altered the composition and taxa of the gut microbiota,(10) and mycophenolate mofetil resulted in gut expansion of Proteobacteria. (89) Kidney transplant recipients who required a 50% increase in their tacrolimus dosing during the first month transplantation had a higher relative abundance of *Faecalibacterium praunsnitzii* compared to those who did not require an increase (11.8% vs. 0.8%; $p = 0.002$).(90) The significance and mechanisms of these observations deserve further clarification.

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Practice Points

- Low microbial diversity at the time of neutrophilic engraftment is associated with poorer survival, increased risk of GVHD and GVHD-associated mortality, and higher rates of bacteremia in allo-HSCT recipients.
- Studies have shown that FMT is safe and effective in treating rCDI in HSCT and SOT recipients.
- Auto-FMT was demonstrated to be safe, feasible and effective in restoring gut microbiota diversity and composition to pre-transplant states in a pilot study in allo-HSCT recipients.

Research Agenda

- Evaluate impact of FMT on clinical outcomes (overall and graft survival, graft rejection) in HSCT and SOT recipients.
- Characterize changes in gut microbiota peri-transplantation in various organ groups in SOT recipients.
- Determine characteristics of the gut microbiota that contribute to the effectiveness of FMT in both allo-HSCT and SOT recipients.
- Perform a randomized controlled trial to compare the safety and effectiveness of heterologous versus auto-FMT in restoring gut microbiota diversity and composition in allo-HSCT recipients.

Table 1.

Summary of Studies on Gut Microbiome in Solid Organ Transplant Recipients

Study	Study Characteristics	Key Findings of the Study
Bajaj et al.[22] (n = 40)	Liver Transplant Prospective design	**1** Shannon microbial diversity index significantly higher after LT, compared to pre-transplant (2.1 ± 0.7 vs. 1.6 ± 0.7; p = 0.001) **2** Relative abundance of potentially pathogenic family *Enterobacteriaceae* was significantly reduced post-LT **3** Relative abundance of potentially beneficial gut microbiota families *Ruminococcaceae* and *Lachnospiraceae* significantly increased post-LT
Lee et al.[23] (n = 26)	Kidney Transplant Prospective design	**1** Shannon microbial diversity index significantly lower in KT recipients with diarrhea, compared to those without diarrhea (2.5 ± 0.3 vs. 3.4 ± 0.8; p = 0.02) **2** KT recipients without diarrhea had higher abundance of the phylum Bacteroidetes (esp. genera *Ruminococcus*, *Coprococcus* and *Dorea*) **3** Higher median *Enterococcus* fecal abundance in KT recipients who developed Enterococcal UTI, vs. those without Enterococcal UTI (24% vs. 0%; p = 0.005)
Oh et al.[27] (n = 19)	Intestinal Transplant Convenience Samples	**1** Ileal microbial diversity as measured by both Shannon and Simpson indices were not different between IT patients with and without allograft rejection **2** IT recipients with acute graft rejection had significantly higher relative abundance of Proteobacteria (16% to 61%; p<0.01) **3** IT recipients with acute graft rejection had significantly reduced relative abundance of Firmicutes (81% to 29%; p<0.001)

Abbreviations: IT, intestinal transplant; KT, kidney transplant; LT, liver transplant; UTI, urinary tract infection.