Biol Blood Marrow Transplant 25 (2019) e17–e22

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Fecal Microbiota Transplantation: Restoring the Injured Microbiome after Allogeneic Hematopoietic Cell Transplantation

Zachariah DeFilipp[1,*], Elizabeth Hohmann[2], Robert R. Jenq[3,4], Yi-Bin Chen[1]

[1] *Blood and Marrow Transplant Program, Massachusetts General Hospital, Boston, Massachusetts*
[2] *Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts*
[3] *Genomic Medicine Department, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas*
[4] *Stem Cell Transplantation and Cellular Therapy Department, Division of Cancer Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas*

Article history:
Received 30 August 2018
Accepted 24 October 2018

Key Words:
Microbiome
Fecal microbiota transplantation
Allogeneic hematopoietic cell transplantation
Graft-versus-host disease
Clostridium difficile infection

A B S T R A C T

Disruption of the intestinal microbiome early after allogeneic hematopoietic cell transplantation (allo-HCT) has been linked to adverse outcomes in transplant recipients. To date, whether microbiome-directed interventions will be able to impact important clinical endpoints remains unknown. Fecal microbiota transplantation (FMT) is a compelling intervention to restore healthy diversity to the intestinal microenvironment after allo-HCT, but currently has no established role in transplant recipients. In this review, we examine the use of FMT as treatment for *Clostridium difficile* infection and acute graft-versus-host disease, and also as a restorative intervention early after allo-HCT. Ongoing and planned studies will help determine the ultimate role of FMT in allo-HCT recipients.

© 2018 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for malignant and nonmalignant hematologic disorders. Numerous patient-, donor-, disease-, and transplant-related factors are known to impact clinical outcomes after allo-HCT. Decades after early studies identified a potential association between the microbiome and graft-versus-host disease (GVHD) [1,2], the composition of the recipient microbiome has reemerged as a possible contributor to allo-HCT outcomes. With significant advances in sequencing techniques, we are beginning to better understand the composition of the host intestinal microbiome and how it changes after receipt of allo-HCT [3].

Significant evidence suggests that patterns of microbiome changes are associated with clinical allo-HCT outcomes. Analysis of stool specimens from allo-HCT recipients collected at the time of stem cell engraftment has demonstrated that lower diversity is associated with worse overall survival and increased nonrelapse mortality [4]. In addition, the presence and absence of specific bacterial species are associated with the development of acute GVHD and disease relapse, respectively. Increased bacterial diversity early after allo-HCT has been associated with reduced GVHD lethality, and an abundance of bacteria from the genus *Blautia* has been associated with less GVHD-related mortality and improved overall survival [5]. Although overall intestinal diversity has not been associated with the risk of relapse or disease progression [4], a higher abundance of a bacterial group composed mostly of *Eubacterium limosum* has been associated with a decreased risk of disease relapse [6]. Furthermore, the administration of broad-spectrum antibiotics that are active against commensal organisms likely contributes to both microbiome changes (eg, lower fecal abundance of commensal Clostridiales) and higher rates of transplantation-related mortality [7].

It remains uncertain whether these associative relationships are in any way causative and will result in potential targets for meaningful clinical interventions. Currently, there is great interest in investigating interventions that can restore microbiome diversity in allo-HCT recipients. Fecal microbiota transplantation (FMT) refers to the administration of fecal matter from a healthy donor into a recipient with the intent of directly modifying the recipient's intestinal microbiome composition [8]. After showing success in the treatment of recurrent *Clostridium difficile* infection (rCDI) [9], FMT has been proposed as a potentially advantageous intervention for other conditions, including inflammatory bowel disease and metabolic syndrome [10–12]. There are multiple ongoing and planned clinical investigations of FMT in allo-HCT recipients. In this review, we examine the use and future direction of FMT as treatment for rCDI, therapy for acute GVHD, and as a microbial restorative intervention early after transplantation in allo-HCT recipients.

Financial disclosure: See Acknowledgments on page e21.
* Correspondence and reprint requests: Zachariah DeFilipp, MD, 55 Fruit Street, Boston, MA 02114.
E-mail address: zdefilipp@mgh.harvard.edu (Z. DeFilipp).

https://doi.org/10.1016/j.bbmt.2018.10.022
1083-8791/© 2018 American Society for Blood and Marrow Transplantation.

POTENTIAL MECHANISMS OF CLINICAL BENEFITS

The mechanisms by which FMT can mediate clinical benefits are multiple (Figure 1) and have been best studied in the context of rCDI [13]. FMT primarily restores the intestinal microenvironment through replacement of a contracted, low-diversity microbiome with a rich, diverse microbiome from a healthy donor source. In the clinical context of rCDI, FMT restores communities of Firmicutes and Bacteroidetes and decreases Proteobacteria to favor outcompeting *C difficile* for nutrients and creation of an environment that is unfavorable for its sustenance and growth [14,15]. In the setting of allo-HCT, the restoration of diverse healthy commensal communities likely modifies the intestinal microenvironment in a similar manner, eliminating what has been described as "microbial domination" by potentially inflammatory bacteria (eg, gram-negative Proteobacteria, *Enterococcus* spp, *C difficile*, and others.). The efficacy of FMT for rCDI is also thought to be influenced by its ability to restore secondary bile acid metabolism and sialic acid utilization in the colon [16,17]. Whether these mechanisms are important in settings other than rCDI (eg, acute GVHD) is unclear, however.

Of particular interest for allo-HCT recipients, FMT may modulate repair of the intestinal mucosal barrier via immune-mediated pathways. Continuous signaling from native microbiota is required to maintain the optimal structure and function of the intestinal mucosal barrier, which serves to prevent autoimmunity and exclude pathogens [18]. Numerous important epithelial cell populations located in the intestinal mucosa (eg, enterocytes, goblet cells, Paneth cells, intestinal stem cells) can be adversely affected by the conditioning regimen and/or acute GVHD [3]. Furthermore, regulatory T cells and innate lymphoid cells (ILCs), which produce Th17 family cytokines, including IL-22, are abundant within the intestinal tract. ILCs are important components of the recovery and regeneration of the damaged tissue, but their actions can be limited by ongoing insults [19]. For example, recipient-derived IL-22 can limit the severity of intestinal pathology resulting from GVHD, although the signal can be lost with GVHD-mediated damage to ILCs [20]. Similar to GVHD, ongoing exposure to *C difficile* toxins can persistently activate inflammatory signals (eg, IL-1, IL-18) and FMT can potentially provide the necessary tonic signals for epithelial regeneration and production of mucins and antimicrobial peptides [13]. It can be hypothesized that a similar mechanism is operative when FMT is used to correct the dysbiosis seen after allo-HCT and treat GVHD. FMT also has been associated with restoration of short-chain fatty acids (eg, butyrate, acetate, propionate) in patients with rCDI [21]. This may be important for allo-HCT recipients, given that butyrate has recently been identified as a potentially important microbial metabolite with beneficial effects on immune and epithelial cells that mitigate GVHD severity [22]. However, with FMT still at its infancy in the realm of allo-HCT, these immune-mediated mechanisms are currently not established and will need to be further investigated through future studies.

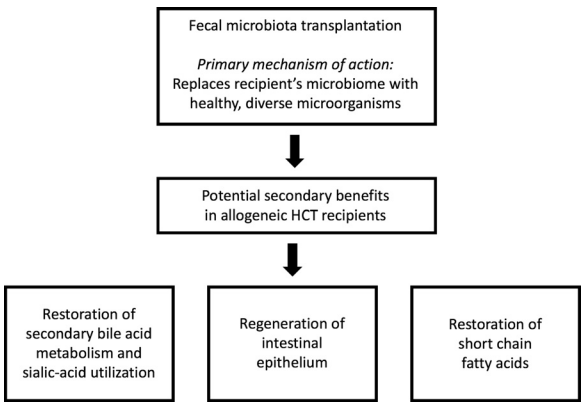

Figure 1. Potential mechanisms of clinical benefit for FMT in allogeneic HCT recipients.

GENERAL FACTORS

Multiple practical and microbiological issues arise when contemplating FMT in allo-HCT recipients (Table 1). First, the clinical indication can be classified as either therapeutic (GVHD or rCDI) or empiric/restorative. Restorative goals could include general well-being and microbial diversity, as well as prevention of such clinical outcomes as GVHD, bacteremia, or *C difficile* infections. The indication for FMT may impact decisions regarding the clinical evaluation of responses. Acute GVHD and rCDI may be evaluated clinically, whereas FMT performed to correct dysbiosis will require serial stool analyses to assess response. In addition, the clinical indication also may influence the number (single or multiple) and frequency of doses given.

Second, the source of the FMT must be considered, which can be the patient (previously collected and stored autologous FMT) or a healthy donor (related or unrelated). For patients receiving autologous FMT, stool samples should be collected at a time of relatively good health and tested to ensure acceptable microbial diversity and the absence of infectious pathogens. For patients receiving FMT from a donor, it is important to consider the possibility that because of genetic and/or environmental factors, a related FMT donor may have a microorganism composition closer to that of the recipient (at baseline health) compared with an unrelated donor. One potential advantage of using unrelated healthy FMT donors is that inocula can be collected and stored frozen, allowing for immediate "off-the-shelf" administration of FMT when clinically indicated.

Third, multiple routes of administration exist. Traditionally, liquid fecal material has been administered via endoscopy (nasoduodenal/nasojejunal tube or colonoscope). However, FMT also can be administered via oral capsules, eliminating the need for an invasive procedure [23,24].

Additional factors to consider include the exposure to systemic antibiotics, both before and after FMT, and the risk of pathogen transmission with FMT. Treatment of infection in immunocompromised hosts is essential, and antibiotic therapy

Table 1
Factors to Consider in the Administration of FMT to Allo-HCT Recipients

Indication	• Restorative/preventative (restore microbiome diversity, prevent GVHD, prevent infection) • Active GVHD • Active infection
FMT donor source	• Self • Family member • Unrelated volunteer
Route of administration	• Capsule • Nasogastric or nasoduodenal tube • Endoscope
Other	• Dose and timing of administration • Antibiotic exposure (previous, ongoing, or future) • Risk for transmitted infection from FMT

should not be withheld in consideration of any potential impact on the microbiome. If a prolonged course of antibiotic therapy is anticipated, this may adversely affect an FMT inoculum and influence decisions regarding the timing and frequency of FMT. The necessary temporal distance from antibiotic therapy for successful engraftment of a new, intentionally administered microbiome is unknown, however. There is also a concern regarding the potential for transmitting bloodstream infections from the FMT when administered to immunosuppressed allo-HCT recipients, although this has not been reported in the published literature to date. All of these factors are important to consider when designing, conducting, and evaluating studies of FMT in allo-HCT recipients.

FMT FOR TREATING rCDI

Following the establishment of FMT as treatment for rCDI [25], case reports emerged reporting the use of FMT for rCDI in allo-HCT recipients [26,27]. Subsequently, 3 small case series have reported the use of FMT for rCDI in this population (Table 2). In one series of 7 patients with rCDI, 5 of the patients (71.4%) were receiving systemic immunosuppressive therapy at the time of treatment. FMT was administered via the nasojejunal route in 6 of the 7 patients. No serious adverse events were noted. Six of the 7 patients (85.7%) had no recurrence of CDI; 1 patient experienced recurrence at day 156 post-FMT after receipt of an oral antibiotic and required repeat FMT, after which no recurrence was observed [28]. In another series, 8 allo-HCT recipients were treated for rCDI with capsule-based FMT from unrelated volunteer donors [29]. Six of these 8 patients underwent FMT from the same donor. No significant side effects or CDI relapses were reported. Strain-level metagenomic sequencing of 2 recipients before and after FMT showed significant divergence from the same donor over time. In a third series, FMT was administered for CDI in 3 pediatric allo-HCT recipients [30]. Fecal material was collected from either a family member or an unrelated donor and administered by gastric tube or colonoscopy. All 3 children tolerated the procedure without adverse events or invasive infection; however, 2 of the patients experienced rCDI after FMT.

Taken together, these early experiences suggest that FMT for rCDI in allo-HCT recipients is safe and efficacious, and that multiple routes of administration are possible. The decision to use FMT in allo-HCT recipients for CDI should follow established infectious disease guidelines [31]. Nonetheless, this remains an individualized decision that may be influenced by the availability of a fecal donor, the presence of concurrent infections requiring antibiotic administration, and the presence of gastrointestinal (GI) GVHD.

FMT FOR TREATING ACUTE GVHD

To date, there have been 2 reports of FMT for the treatment of steroid-refractory acute GVHD of the GI tract (Table 2). In a pilot study of 4 patients with steroid-refractory or steroid-dependent GVHD, FMT inocula were collected from the patient's spouse or a relative and administered via a nasoduodenal tube for a maximum of 2 treatments. There were no severe AEs attributed to FMT. Clinical improvements were observed in all patients (3 complete responses and 1 partial response). At the time of clinical response, the patients' microbiota composition was dominated by bacterial species generally considered beneficial (*Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* spp) in the 3 complete responders, whereas *Escherichia* species were increased in the patient with a partial response. In addition, the number of peripheral circulating regulatory T cells increased during the

Table 2
Review of Published Studies of FMT in Allo-HCT Recipients

Study	Study Type	Primary Reason for FMT	Number of Patients Receiving FMT	FMT Donor	Route of Administration	Primary Clinical Outcome	Serious Adverse Events
FMT for rCDI in recipients of allo-HCT							
Webb et al., 2016 [28]	Retrospective, case series	rCDI	7	Relative or unrelated volunteer	Nasojejunal tube or colonoscopy	6 patients without rCDI	None
Moss et al., 2017 [29]	Retrospective, case series	rCDI	8	Unrelated volunteer	Oral capsule	All patients with resolution of rCDI	None
Bluestone et al., 2018 [30]	Retrospective, case series	rCDI	3	Relative or unrelated volunteer	Gastric tube or colonoscopy	1 patient without rCDI	None
FMT for treatment of acute GI GVHD							
Kakihana et al., 2016 [32]	Prospective, pilot	Steroid-refractory/ dependent GVHD	4	Spouse or relative	Nasoduodenal tube	3 patients with CR; 1 patient with PR	None
Spindelboeck et al., 2017 [33]	Retrospective, case series	Steroid-refractory GVHD	3	Relative or unrelated volunteer	Endoscopically (colonoscope)	2 patients with CR; 1 patient with PR	None
FMT as a restorative approach after allo-HCT							
Bilinski et al., 2017 [35]	Prospective, single arm	ARB colonization	20 (all with blood disorders and/or HCT recipients)	Unrelated volunteer	Nasoduodenal tube	15 patients with complete ARB decolonization	None
DeFilipp et al., 2018 [34]	Prospective, single arm	Microbiome diversity	13 (all HCT recipients)	Unrelated volunteer	Oral capsule	All patients met feasibility endpoint	Severe abdominal pain (n = 1)

CR indicates complete response; PR, partial response.

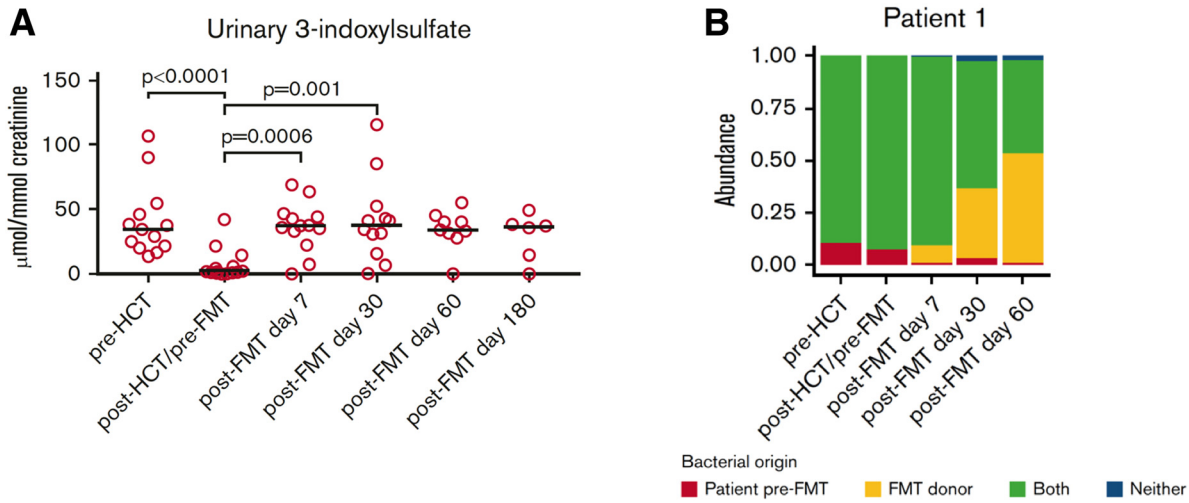

Figure 2. (A) Longitudinal changes in urinary 3-indoxylsulfate levels from a pilot study of empiric FMT early post-transplantation demonstrating improvement in microbiome diversity within 1 week after FMT administration. (B) Longitudinal changes in the origin of operational taxonomic units in a sample patient, as determined by 16S rRNA sequencing of stool specimens. (Adapted with permission [35].)

clinical response after FMT. This increase may reflect improving GI GVHD, but also suggests that the immunologic effects of FMT may reach beyond the intestinal microenvironment [32]. In another case series, 3 patients with acute GI GVHD underwent repeated (up to 6 times) FMT via a colonoscope [33]. Donor stool samples were collected from either a relative or an unrelated adult. Two patients achieved a complete remission of GVHD symptoms, and a third patient experienced transient improvement in diarrhea. No cases of bacteremia or systemic infection occurred immediately after FMT. 16S rRNA gene analysis of stool specimens suggested that multiple FMTs were required to achieve successful donor microbiome engraftment [33].

These reports provide preliminary data and proof of concept regarding the safety and feasibility of FMT administration to treat GI GVHD, although efficacy certainly remains to be evaluated in larger prospective trials. Currently, multiple prospective clinical studies investigating FMT for treating acute GI GVHD are planned. Of note, a multicenter study (goal accrual, 32 participants) investigating oral third-party FMT capsules for steroid-refractory GI GVHD) is currently underway in Europe (ClinicalTrials.gov identifier NCT03359980). In addition, a prospective evaluation (goal accrual, 70 participants) of autologous FMT collected before allo-HCT and subsequently administered in the setting of GI GVHD is also underway (ClinicalTrials.gov identifier NCT03492502).

FMT AS AN EMPIRIC INTERVENTION IN ALLO-HCT RECIPIENTS

Given the adverse association between contracted microbiome diversity and clinical outcomes after allo-HCT, FMT represents a microbiome-directed intervention that may be able to improve intestinal diversity and potentially prevent certain adverse complications. To date, a limited number of studies have investigated the administration of FMT for preventative reasons (Table 2). We conducted an open-label, single-arm pilot study to administer oral, third-party, previously collected FMT capsules to patients early after allo-HCT. FMT capsules were administered no later than 4 weeks after neutrophil engraftment, and systemic antibiotics were not allowed within 48 hours before FMT. Eighteen patients were enrolled. Five patients did not receive FMT owing to the development of early acute GI GVHD before FMT (n = 3), persistent HCT-associated GI toxicity (n = 1), or patient decision (n = 1). Thirteen patients received FMT at a median of 27 days (range, 19 to 45 days) after HCT. Participants were able to swallow and tolerate all FMT capsules (30 capsules over 2 days), meeting the primary study endpoint of feasibility. FMT was well tolerated, with only 1 treatment-related significant adverse event (abdominal pain). Two patients subsequently developed acute GI GVHD, 1 of whom with concurrent bacteremia. We did not observe transmission of any infectious organisms from the FMT capsules. Low urinary concentrations of 3-indoxyl sulfate (3-IS) after allo-HCT are indicative of significant and clinically relevant intestinal microbiota disruption [34]. Analysis of urine 3-IS concentrations indicated improvement in intestinal microbiome diversity after FMT. In addition, 16S ribosomal sequencing of stool specimens revealed expansion of FMT donor-only operational taxonomic units in recipients, strongly suggesting engraftment of the FMT product (Figure 2). These results indicate that empiric third-party FMT following allo-HCT appears to be feasible, safe, and associated with expansion of recipient microbiome diversity [35].

In a separate prospective study, FMT was administered to patients with blood disorders (including some HCT recipients) to inhibit gut colonization with antibiotic-resistant bacteria (ARB). Participants colonized with ARB were treated with intraduodenal FMT collected from a healthy volunteer donor. Twenty-five FMTs were performed in 20 participants (including 40% with neutropenia) who were colonized by a median of 2 (range, 1 to 4) strains of ARB. There were no severe adverse events. Complete ARB decolonization—the primary endpoint—was achieved in 15 of the 25 FMTs (60%) and more frequently in cases with no periprocedural use of antibiotics (79% versus 36%; $P < .05$). Fifteen of the 20 participants (75%) experienced complete ARB decolonization [36].

Given the wide range of indications, numerous avenues for restorative and preventative FMT administration in HCT recipients exist. An ongoing phase II study (goal accrual 59 participants) is randomizing patients undergoing allo-HCT to receive autologous FMT (collected before HCT and stored) or treatment according to the standard of care, with a primary efficacy endpoint of CDI evaluated 1 year after randomization (ClinicalTrials.gov identifier NCT02269150). We are planning a randomized, placebo-controlled single-center phase II study of third-party FMT capsules to be administered in the pre-HCT and early post-HCT periods (goal accrual, 48 participants). The primary

endpoint of the study will be to assess microbiome diversity at 1 month after post-HCT FMT administration, as measured by urinary 3-IS level. 16S sequencing of stool specimens will characterize changes in microbiome composition.

FUTURE DIRECTIONS

There are several broad questions regarding the use of microbiome-directed interventions, including FMT.

Are Microbiome-Directed Interventions Clinically Impactful? What Endpoints Should Be Used in This Assessment?

As reviewed earlier, changes in the intestinal composition early after allo-HCT have been associated with distinct patterns of survival, GVHD, and disease relapse. Whether these associations are causative, and whether interventions directed at the microbiome will affect these outcomes, remain unclear, however. Ongoing and future prospective trials will begin to clarify the validity of the microbiome as an interventional target. For studies investigating FMT to treat GI GVHD, a clinical endpoint of GVHD response is easily agreed upon. When it comes to the preventive indications, a primary clinical endpoint will be required to show actual benefit, compared with a correlative microbiome-related endpoint. What this endpoint should be is unclear and merits much discussion.

Who Should Receive a Microbiome-Directed Intervention? Should the Choice Be FMT?

These same future studies will also start to clarify clinical indications for interventions. Currently, FMT is the only microbiome intervention being investigated as therapeutic (for GVHD). However, multiple ongoing clinical trials are investigating antibiotic administration (ClinicalTrials.gov identifiers NCT02641236 and NCT03078010) and prebiotic/probiotic administration (ClinicalTrials.gov identifiers NCT02805075 and NCT03057054) as preventative intervention early after allo-HCT. Results of these studies, as well as additional preventative studies with FMT, will begin to inform us as to whether other microbiome-directed interventions could achieve similar clinical outcomes as FMT.

How Would a Large, Multicenter FMT Study Be Conducted?

If initial trials with FMT in allo-HCT recipients produce positive results, then larger multicenter studies will be warranted. The use of oral FMT capsules previously collected from unrelated, volunteer donors allows for immediate administration and the potential for scaling up to meet the needs of a multicenter studies. There has traditionally been little industry support for FMT, given the lack of a propriety product. However, this may be changing, beginning with the ongoing industry-sponsored trial in Europe for steroid-refractory GI GVHD (ClinicalTrials.gov identifier NCT03359980). We also encourage pursuing such trials through large grants or existing collaborative groups or consortia.

CONCLUSION

Preliminary reports and studies of FMT in allo-HCT recipients suggest that it is safe, feasible, and associated with promising efficacy in multiple clinical settings. Future studies will further elucidate the multiple mechanisms by with FMT can reset the intestinal microenvironment after allo-HCT and provide clarity regarding the appropriate clinical indications for FMT in this specific population.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported by the National Heart, Lung, and Blood Institute (Grant R01 HL124112) and the Cancer Prevention and Research Institute of Texas Recruitment of Rising Stars (R.R.J.).

Conflict of interest statement: Z.D. has no conflicts of interest to report. E.H. receives research support from Seres Therapeutics. R.R.J serves on the board of directors and an advisory committee for Seres Therapeutics, has consulted for Ziopharm Oncology, and holds patents with and receives royalties from Seres Therapeutics. Y.-B.C. has received consulting fees from Takeda, Magenta, and Incyte.

REFERENCES

1. Jones JM, Wilson R, Bealmear PM. Mortality and gross pathology of secondary disease in germfree mouse radiation chimeras. *Radiat Res*. 1971;45:577–588.
2. van Bekkum DW, Roodenburg J, Heidt PJ, van der Waaij D. Mitigation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora. *J Natl Cancer Inst*. 1974;52:401–404.
3. Peled JU, Hanash AM, Jenq RR. Role of the intestinal mucosa in acute gastrointestinal GVHD. *Blood*. 2016;128:2395–2402.
4. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. *Blood*. 2014;124:1174–1182.
5. Jenq RR, Taur Y, Devlin SM, et al. Intestinal blautia is associated with reduced death from graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:1373–1383.
6. Peled JU, Devlin SM, Staffas A, et al. Intestinal microbiota and relapse after hematopoietic-cell transplantation. *J Clin Oncol*. 2017;35:1650–1659.
7. Weber D, Jenq RR, Peled JU, et al. Microbiota disruption induced by early use of broad-spectrum antibiotics is an independent risk factor of outcome after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23:845–852.
8. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 2017;66:569–580.
9. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368:407–415.
10. Gupta S, Allen-Vercoe E, Petrof EO. Fecal microbiota transplantation: in perspective. *Therap Adv Gastroenterol*. 2016;9:229–239.
11. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis*. 2014;8:1569–1581.
12. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012;143:913–916. e917.
13. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol*. 2016;13:508–516.
14. Shahinas D, Silverman M, Sittler T, et al. Toward an understanding of changes in diversity associated with fecal microbiome transplantation based on 16S rRNA gene deep sequencing. *MBio*. 2012;3:e00312–e00338.
15. Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. *Gastroenterology*. 2015;149:223–237.
16. Weingarden AR, Chen C, Bobr A, et al. Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection. *Am J Physiol Gastrointest Liver Physiol*. 2014;306:G310–G319.
17. Ng KM, Ferreyra JA, Higginbottom SK, et al. Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens. *Nature*. 2013;502:96–99.
18. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157:121–141.
19. Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat Immunol*. 2016;17:765–774.
20. Hanash AM, Dudakov JA, Hua G, et al. Interleukin-22 protects intestinal stem cells from immune-mediated tissue damage and regulates sensitivity to graft versus host disease. *Immunity*. 2012;37:339–350.
21. Seekatz AM, Theriot CM, Rao K, et al. Restoration of short chain fatty acid and bile acid metabolism following fecal microbiota transplantation in patients with recurrent *Clostridium difficile* infection [e-pub ahead of print]. *Anaerobe*. https://doi.org/10.1016/j.anaerobe.2018.04.001. accessed August 2018 .
22. Mathewson ND, Jenq R, Mathew AV, et al. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat Immunol*. 2016;17:505–513.
23. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis*. 2014;58:1515–1522.

24. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA*. 2014;312:1772–1778.
25. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol*. 2011;9:1044–1049.
26. Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient. *Transpl Infect Dis*. 2012;14:E161–E165.
27. de Castro Jr CG, Ganc AJ, Ganc RL, Petrolli MS, Hamerschlack N. Fecal microbiota transplant after hematopoietic SCT: report of a successful case. Bone Marrow Transplant. 2015;50:145.
28. Webb BJ, Brunner A, Ford CD, Gazdik MA, Petersen FB, Hoda D. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection in hematopoietic stem cell transplant recipients. *Transpl Infect Dis*. 2016;18:628–633.
29. Moss EL, Falconer SB, Tkachenko E, et al. Long-term taxonomic and functional divergence from donor bacterial strains following fecal microbiota transplantation in immunocompromised patients. *PLoS One*. 2017;12 e0182585.
30. Bluestone H, Kronman MP, Suskind DL. Fecal microbiota transplantation for recurrent *Clostridium difficile* infections in pediatric hematopoietic stem cell transplant recipients. *J Pediatric Infect Dis Soc*. 2018;7:e6–e8.
31. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66:987–994.
32. Kakihana K, Fujioka Y, Suda W, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. *Blood*. 2016;128:2083–2088.
33. Spindelboeck W, Schulz E, Uhl B, et al. Repeated fecal microbiota transplantations attenuate diarrhea and lead to sustained changes in the fecal microbiota in acute, refractory gastrointestinal graft-versus-host-disease. *Haematologica*. 2017;102:e210–e213.
34. Weber D, Oefner PJ, Hiergeist A, et al. Low urinary indoxyl sulfate levels early after transplantation reflect a disrupted microbiome and are associated with poor outcome. *Blood*. 2015;126:1723–1728.
35. DeFilipp Z, Peled JU, Li S, et al. Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity. *Blood Adv*. 2018;2:745–753.
36. Bilinski J, Grzesiowski P, Sorensen N, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. *Clin Infect Dis*. 2017;65:364–370.