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Fecal Microbiota Transfer in Acute Graft-versus-Host Disease following Allogeneic Stem Cell Transplantation

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Abstract
Background: Acute graft-versus-host disease (GvHD) is a major and sometimes lethal complication following allogeneic stem cell transplantation (aSCT). In the last 10 years, a massive loss of microbiota diversity with suppression of commensal bacteria and their protective metabolites has been identified as a major risk factor of GvHD. ***Summary:*** Since 2018, several studies have been published showing some efficacy of fecal microbiota transfer (FMT) in aSCT patients. FMT was used (1) to eliminate antibiotic resistant bacteria, (2) to restore microbiota diversity after hematopoietic recovery, or (3) in most cases to treat steroid-resistant GvHD. Overall response rates between 30 and 50% have been reported, but randomized trials are still pending. Newer approaches try to evaluate the role of prophylactic FMT in order to prevent GvHD and other complications. Although aSCT patients are heavily immunosuppressed, no major safety concerns regarding FMT have been reported so far. ***Key Message:*** FMT is a promising approach for modulation of GvHD after aSCT and should be further explored in randomized trials.

Introduction

Allogeneic stem cell transplantation (aSCT) is a significant treatment modality in hematological malignancies that cannot be controlled or cured by classical chemotherapy, antibodies, or small molecule inhibitors such as acute leukemias and myelodysplastic syndromes. The significant chance of cure in aSCT is counteracted by the high risk of immunological complications resulting in substantial long-term morbidity and a treatment related mortality of 10–30% depending on the stage of disease at the time of aSCT. Acute graft-versus-host disease (aGvHD) is the primary cause of these complications. It is induced by immunological attack of donor cells against recipient target tissues such as the skin, the gastrointestinal (GI) tract, or the liver. Until now, the major challenge in prophylaxis and treatment is to suppress deleterious immune reactions while maintaining the beneficial graft-versus-leukemia effects [1, 2]. aGvHD of the lower GI tract presenting with severe enteritis with diarrhea, abdominal pain or even bleeding is the most deleterious manifestation and results in a treatment-related mortality of 60–80% if more severe.

From a pathophysiological aspect, exposure and interaction with microbiota may explain the high susceptibility of the GI tract and skin for GvHD. In the early 70s, the costimulation of alloreaction by bacteria was in the focus, as experimental studies showed almost absence of GvHD in

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germfree animals [3]. These results prompted clinical translation to strict decontamination and prophylaxis against infection, especially in the early period of neutropenia before engraftment of donor hematopoiesis [4]. With the breakthrough in microbiota ribosomal sequencing, it soon became apparent, that these procedures result in severe dysbiosis which enhances the risk of aGvHD and results in inferior outcome. This was first described in early single-center reports [5, 6] but later on confirmed by multicenter studies [7, 8]: In these studies, the massive exposure to antibiotics in the early posttransplant period overcomes potential nutritional and ethnical differences between centers and explains the uniform occurrence of dysbiosis in aSCT patients worldwide.

Fecal Microbiota Transfer in Allogeneic SCT

As in other diseases associated with dysbiosis, such as inflammatory bowel disease, the logical next step was the hypothesis that preventing or correcting in dysbiosis might help reduce and fight against severe GvHD, especially in patients with GI GvHD. Antibiotic stewardship on the one side and fecal microbiota transfer (FMT) from healthy donors on the other side were the most feasible and direct approaches [9], but further options such as pre- and postbiotics are also currently evaluated. 3 major applications of FMT in SCT patients are currently investigated and will be discussed here.

FMT to Correct Colonization with Antibiotic and Multidrug Resistant Bacteria and GI-Related Infections

FMT was first introduced to treat recurrent *Clostridium difficile* infections (CDI) in non-hematology patients. Thereafter, first reports on FMT to treat immunocompromised and SCT patients with CDI suggested that CDI can be successfully eliminated also in this vulnerable patients group without an excess risk of complications. In 2016, Webb et al. [10] reported a 6/7 cure rate in patients with CDI after SCT and recovery from neutropenia. In 2017, Bilinski et al. [11] reported 20 hematological patients including 6 patients after allogeneic SCT who received FMT to eliminate antibiotic resistant bacteria (mainly different β-lactamase resistant strains and VRE) with a response rate in 75% of these patients. In Battipaglia et al.'s [12] report decolonization of carbapenem – resistant bacteria and VRE was achieved in 7/10 patients (including 6 SCT patients) without major side effects. Several further reports confirmed these results [13, 14] making FMT an interesting and in CDI, widely used approach as opposed to repeated antibiotic treatments. Interestingly, in a trial on prophylactic autologous FMT in acute leukemia patients aiming to restore loss of diversity after chemotherapy and treatment of neutropenic infections the rapid increase of *ABR* genes during neutropenia could be corrected by FMT in the majority of patients [15].

Prevention and Treatment of Dysbiosis following aSCT

In 2018, Taur et al. [16] used autologous fecal material collected prior to transplantation to restore microbiota after engraftment in patients with reduced copy numbers in Bacteroidetes PCR after engraftment: 15 patients received autologous FMT and were compared against 11 patients in the control arm. The beneficial effect of FMT was highly significant also after correction for dietary impact and application of growth factors, both in 16 s rRNA and metagenomic analysis. However, a limitation of this approach is the lack of suitable autologous FMT products in a large number of patients due to preexisting microbiota damage by antibiotic exposure during previous antileukemic treatment episodes.

DeFilipp et al. [17] applied in a single arm study 3rd party donor FMT capsules in patients recovering from neutropenia following aSCT. FMT could be performed in 13/18 planned (5 patients had to be excluded due to early GI GvHD or other GI toxicity) patients as indicated: In these 13 patients, they observed restoration of diversity associated with expansion of donor microbiota. Overall, only 2 patients developed subsequently GI GvHD, and treatment-related mortality was as low as 8% in the cohort with almost no severe toxicity.

The first randomized study on FMT in HSCT patients used oral encapsulated FMT to restore microbiota diversity after recovery from neutropenia and was presented in 2023 [18]. Although the overall infection frequencies in the first 4 month after FMT was not significantly reduced with a ratio of 0.83 (FMT vs. control), FMT improved recovery of dysbiosis and reduced the abundance of expanded pathobionts like *Enterococci* and others. In a subanalysis of this trial, authors report lower preFMT diversity in patients with more severe aGvHD suggesting potential benefits of FMT in these patients [19].

Treatment of GvHD

Based on the clear association of dysbiosis and acute GvHD, treatment of steroid refractory aGvHD was in the focus of the earliest pilot studies reported since 2018: Kakihana et al. (2016 [20]) and Spindelboeck et al. (2017 [21]) treated 4 and 3 patients, respectively, with steroid-resistant or dependent GI-GvHD with related or unrelated donor FMT by endoscopic application or via nasoduodenal tube: Most of these patients required repeated applications of FMT before improvement, and none of them developed any infectious complications in spite of far advanced and severe aGvHD. Both groups reported an increase in the T reg/CD8 ratio in blood and GI biopsies of patients who responded to FMT [20, 22]. Following these pilots, multiple small reports (see Table 1) as well as more extensive studies confirmed response in about half of the patients. In van Lier's study, 10/15 patients responded and showed improved survival after 24 months [23]. Goeser et al. [24] published 11 patients

Table 1. Summary of published reports on FMT in allogeneic SCT

Author	Type of FMT	Time point	*n* treated	*n* control	Results
Kakihana 2016 [20]	Allog	SR/SD GvHD	4	–	3 CR/1 PR
Spindelboeck 2017 [21]	Allog	SR GvHD	3	–	2 CR/1 PR
Bilinski 2017 [11]	Allog	ABR colonized	20	–	Decolonization in 75%, ABX: less response
Taur 2018 [16]	Autolog	after engraftment	14	11	Restoration of diversity
Kaito 2018 [27]	Allog	SR GvHD	1	–	Less diarrhea
DeFilipp 2018 [17]	Allog	after engraftment	13	–	Restoration of diversity, low TRM of 8%
Battipaglia 2019 [12]	Allog	ABR colonized	10	–	Decolonization in 7/10
Goloshchapov 2020 [28]	Allog	SR GvHD	19	8	OR in FMT d30 $n = 8$, D90 $n = 16$, only in 1 control
Mao 2020 [29]	Allog	SR GvHD	1	–	Response
Biernat 2020 [30]	Allog	SR GvHD	2	–	CR in 1 patient
Van Lier 2020 [23]	Allog	SR/SD GvHD	15	–	CCR in 10/15
Zhao 2021 [31]	Allog	SR/SD GvHD	23	18	Survival better in FMT group ($p = 0.02$)
Su 2021 [14]	Allog	ABR colonized	1		Decolonization
Spindelboeck 2021 [22]	Allog	SR GvHD	9	–	OR in 4/9, ABX prevented response
Goeser 2021 [24]	Allog	SR GvHD	11		Reduction of diarrhea
Innes 2021 [13]	Allog	ABR colonized	10		Decolonization in 25%, improved outcome
Liu 2022 [32]	Allog + Ruxo	SR GvHD	21	–	Response in 71%, CCR in 10/21
Zheng 2023 [25]	Allog	SR/SD GvHD	19	10	CR in 10/19 versus 2/10
Rashidi 2023 [18]	Allog	after engraftment	50	24	No significant reduction of infections
Malard 2023 [26]	Allog	SR GVHD	24/52	–	ORR 38%/58%

Allog, FMT from allogeneic donors; SR/SD GvHD, steroid-resistant/dependent GvHD; ABR colonized, patients colonized with bacteria bearing antibiotic-resistance genes; CR, complete response; CCR, continuous CR; PR, partial response; ABX, antibiotics; TRM, treatment-related mortality.

with SR GvHD treated with various modes of FMT; they showed significant improvement of stool volume and severity of GvHD in some patients but pointed to the need of prospective trials. Some groups [25] included control groups with data suggesting superiority of FMT. By far the largest group of FMT-treated refractory aGvHD was included in the prospective Heracles trial published by Malard et al. in 2023 [26]. Patients were treated with MAAT013, a highly diverse multidonor FMT product manufactured by Maat Pharma. In the 24 patients included in the trial, the overall GI response rate was 38%, and in further 52 patients treated in a French early access program, ORR was even 58% with a 12 months survival of about 1/3 of FMT treated patients. As a caveat, in 5 of the treated patients, severe infectious complications could not be excluded to be related to the study intervention, but in none of these infections bacteria derived from the donor product could be detected.

Pitfalls of the Currently Published Trials

A major concern in severely immunosuppressed patients like SCT patients is the extreme susceptibility to bacterial infections, especially if the GI tract is damaged by conditioning associated mucositis or GvHD itself and therefore highly vulnerable for bacterial translocation; simultaneous presence of severe neutropenia like it occurs early after transplantation potentiates the risk of bacteremia and sepsis. For this reason, all reported applications of FMT in SCT patients were therefore administered once the patients had recovered from neutropenia. In these patients, FMT was in general safe, but the occurrence of clear transmission of multidrug resistant bacteria by a FMT donor to a single HSCT recipient has been reported [33]. This patient received FMT capsules for prevention of GvHD and bacteremia occurred during the neutropenic period highlighting the extreme vulnerability in this phase early after SCT.

The pre- and early posttransplant period in SCT patients sees the frequent application of prophylactic or therapeutic antibiotics; indeed, antibiotics are frequently continued or given in the early postengraftment period when aGvHD occurs. Thus in almost all trials FMT had to be applied in antibiotics exposed patients, and several reports stressed the inferior response to FMT in these patients. Several strategies have been used to overcome this hurdle like short term (12 h) interruption of systemic antibiotics during application of FMT, postponement of FMT until antibiotics have been stopped and most frequently repeated administration of FMT beyond the cessation of antibiotics. Thus standardization of conditions for FMT in these patients remains tricky and therefore, comparisons between different reports are limited. So far, antibiotic stewardship should be strictly applied, e.g., avoiding antibiotics in patients with a high likelihood of cytokine release syndrome [34], but this may be feasible only in a minority of patients. Inactivation of antibiotics selectively in the GI tract may be an alternative approach but has not been applied in the setting of aSCT to date [35].

Given the fact that treatment of steroid resistant GvHD with FMT may be ineffective in already irreversible damage, actual approaches are designed to prevent microbiota damage. This approach is based on more recent studies indicating that pretransplant loss of diversity is already a risk factor for poor posttransplant outcome [8, 36]. Several ongoing trials (including the Phoebus Phase IIb trial by Maat Pharma) will see application of FMT prior to conditioning and occurrence of neutropenia, interrupt treatment in the critical neutropenic period, and restart long-term prevention after engraftment. Alternatively, FMT should be applied earlier in the course of GvHD based on biomarkers capable of identifying patients at higher risk of poor outcome.

Another area of improvement is the need for prospective randomized trials. Several randomized trials are now underway but will not be completed before 2026 or beyond.

Discussion and Future Directions

Although these many reports strongly support the development of FMT in the setting of aSCT, it is unlikely that FMT alone will cure GvHD based on our current understanding of its pathophysiology. Alloreactive donor T lymphocytes are the primary cause of GvHD, whereas microbiota shape the threshold for T-cell activation and affect tissue tolerance and regeneration as suggested by Wu and Reddy [37]. In a recent study combining single cell sequencing, advanced staining technologies as well as microbiota analysis in tissue biopsies from SCT patients, we demonstrate, that commensal bacteria and their metabolites control regulatory T-cell function. In addition, we showed that FMT contributes to a stronger interaction between regulatory T cells and effector CD8 cells by bringing them into closer proximity [38]. Thus, FMT can be seen as a robust ancillary approach to dampen or modulate T cell-mediated diseases. Whether antibacterial T-cell responses contribute to the pathophysiology of GvHD itself is currently under active investigation.

As in other indications of FMT, the exact mechanisms how it modulates immune system mediated diseases is still poorly understood. Currently, restoration of beneficial metabolites such as SCFAs and indoles is the best explanation, as also shown in a recent paper by our group [39]. If this holds, consortia selected on optimized metabolite production or even metabolite cocktails might be safer approaches in SCT patients in the future.

Finally, the resolution of microbiota and their host interaction at a deeper level must be pursued. Species specific beneficial as well as detrimental effects on host tissues need to be considered as well as the impact of transkingdom interactions, especially with regard to bacteriophages. This is highlighted by several recent studies. While enterococci are in general considered to worsen outcome of SCT patient, Rashidi et al. [40] reported protection by *E. casseliflavus* and linked this to specific production of tryptophan metabolites. Likewise, our study's association of bacteriophages with protective signatures revealed auxiliary metabolic genes [39] as a potential modulator of bacterial metabolism, indicating cross-kingdom interaction. In immunotherapy, certain enterococcal-specific phages induce expression of immunogenic peptides cross reactive with tumor antigens thus enhancing specific T-cell responses [41], and similar effects might be seen in the setting of allogeneic SCT and graft-versus-leukemia effects in the future.

Conflict of Interest Statement

E. Holler is member of the Scientific Advisory Board of Maat Pharma, Lyon, and Pharmabiome, Zürich.

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Author Contributions

D.W. and E.H. wrote the manuscript. E.M., H.P., E.T.O., A.G., and A.H. contributed to research and discussed and corrected the manuscript with substantial input.

References

1 Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550–61. doi: 10.1016/S0140-6736(09)60237-3.

2 Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. Nat Rev Dis Primers. 2023;9(1):27. doi: 10.1038/s41572-023-00438-1.

3 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(2):401–4. doi: 10.1093/jnci/52.2.401.

4 Vossen JM, Guiot HF, Lankester AC, Vossen AC, Bredius RG, Wolterbeek R, et al. Complete suppression of the gut microbiome prevents acute graft-versus-host disease following allogeneic bone marrow transplantation. PLoS One. 2014;9(9):e105706. doi: 10.1371/journal.pone.0105706.

5 Jenq RR, Ubeda C, Taur Y, Menezes CC, Khanin R, Dudakov JA, et al. Regulation of intestinal inflammation by microbiota following allogeneic bone marrow transplantation. J Exp Med. 2012;209(5):903–11. doi: 10.1084/jem.20112408.

6 Holler E, Butzhammer P, Schmid K, Hundsrucker C, Koestler J, Peter K, et al. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-versus-host disease. Biol Blood Marrow Transpl. 2014;20(5):640–5. doi: 10.1016/j.bbmt.2014.01.030.
7 Stein-Thoeringer CK, Nichols KB, Lazrak A, Docampo MD, Slingerland AE, Slingerland JB, et al. Lactose drives Enterococcus expansion to promote graft-versus-host disease. Science. 2019;366(6469):1143–9. doi: 10.1126/science.aax3760.
8 Peled JU, Gomes ALC, Devlin SM, Littmann ER, Taur Y, Sung AD, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. N Engl J Med. 2020;382(9):822–34. doi: 10.1056/NEJMoa1900623.
9 Peled JU, Jenq RR, Holler E, van den Brink MR. Role of gut flora after bone marrow transplantation. Nat Microbiol. 2016;1:16036. doi: 10.1038/nmicrobiol.2016.36.
10 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(4):628–33. doi: 10.1111/tid.12550.
11 Bilinski J, Grzesiowski P, Sorensen N, Madry K, Muszynski J, Robak K, 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(3):364–70. doi: 10.1093/cid/cix252.
12 Battipaglia G, Malard F, Rubio MT, Ruggeri A, Mamez AC, Brissot E, et al. Fecal microbiota transplantation before or after allogeneic hematopoietic transplantation in patients with hematologic malignancies carrying multidrug-resistance bacteria. Haematologica. 2019;104(8):1682–8. doi: 10.3324/haematol.2018.198549.
13 Innes AJ, Mullish BH, Ghani R, Szydlo RM, Apperley JF, Olavarria E, et al. Fecal microbiota transplant mitigates adverse outcomes seen in patients colonized with multidrug-resistant organisms undergoing allogeneic hematopoietic cell transplantation. Front Cel Infect Microbiol. 2021;11:684659. doi: 10.3389/fcimb.2021.684659.
14 Su F, Luo Y, Yu J, Shi J, Zhao Y, Yan M, et al. Tandem fecal microbiota transplantation cycles in an allogeneic hematopoietic stem cell transplant recipient targeting carbapenem-resistant Enterobacteriaceae colonization: a case report and literature review. Eur J Med Res. 2021;26(1):37. doi: 10.1186/s40001-021-00508-8.
15 Malard F, Vekhoff A, Lapusan S, Isnard F, D'Incan-Corda E, Rey J, et al. Gut microbiota diversity after autologous fecal microbiota transfer in acute myeloid leukemia patients. Nat Commun. 2021;12(1):3084. doi: 10.1038/s41467-021-23376-6.
16 Taur Y, Coyte K, Schluter J, Robilotti E, Figueroa C, Gjonbalaj M, et al. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. Sci Transl Med. 2018;10(460):eaap9489. doi: 10.1126/scitranslmed.aap9489.
17 DeFilipp Z, Peled JU, Li S, Mahabamunuge J, Dagher Z, Slingerland AE, et al. Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity. Blood Adv. 2018;2(7):745–53. doi: 10.1182/bloodadvances.2018017731.
18 Rashidi A, Ebadi M, Rehman TU, Elhusseini H, Kazadi D, Halaweish H, et al. Randomized double-blind phase II trial of fecal microbiota transplantation versus placebo in allogeneic hematopoietic cell transplantation and AML. J Clin Oncol. 2023;41(34):5306–19. doi: 10.1200/JCO.22.02366.
19 Rashidi A, Ebadi M, Rehman TU, Elhusseini H, Kazadi D, Halaweish H, et al. Potential of fecal microbiota transplantation to prevent acute GVHD: analysis from a phase II trial. Clin Cancer Res. 2023;29(23):4920–9. doi: 10.1158/1078-0432.CCR-23-2369.
20 Kakihana K, Fujioka Y, Suda W, Najima Y, Kuwata G, Sasajima S, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. Blood. 2016;128(16):2083–8. doi: 10.1182/blood-2016-05-717652.
21 Spindelboeck W, Schulz E, Uhl B, Kashofer K, Aigelsreiter A, Zinke-Cerwenka W, 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(5):e210–3. doi: 10.3324/haematol.2016.154351.
22 Spindelboeck W, Halwachs B, Bayer N, Huber-Krassnitzer B, Schulz E, Uhl B, et al. Antibiotic use and ileocolonic immune cells in patients receiving fecal microbiota transplantation for refractory intestinal GvHD: a prospective cohort study. Ther Adv Hematol. 2021;12:20406207211058333. doi: 10.1177/20406207211058333.
23 van Lier YF, Davids M, Haverkate NJE, de Groot PF, Donker ML, Meijer E, et al. Donor fecal microbiota transplantation ameliorates intestinal graft-versus-host disease in allogeneic hematopoietic cell transplant recipients. Sci Transl Med. 2020;12(556):eaaz8926. doi: 10.1126/scitranslmed.aaz8926.
24 Goeser F, Sifft B, Stein-Thoeringer C, Farowski F, Strassburg CP, Brossart P, et al. Fecal microbiota transfer for refractory intestinal graft-versus-host disease: experience from two German tertiary centers. Eur J Haematol. 2021;107(2):229–45. doi: 10.1111/ejh.13642.
25 Zheng YY, Yang XT, Lin GQ, Bian MR, Si YJ, Zhang XX, et al. [Clinical study of 19 cases of steroid-refractory gastrointestinal acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation with fecal microbiota transplantation]. Zhonghua Xue Ye Xue Za Zhi. 2023;44(5):401–7. doi: 10.3760/cma.j.issn.0253-2727.2023.05.008.
26 Malard F, Loschi M, Huynh A, Cluzeau T, Guenounou S, Legrand F, et al. Pooled allogeneic faecal microbiota MaaT013 for steroid-resistant gastrointestinal acute graft-versus-host disease: a single-arm, multicentre phase 2 trial. EClinicalMedicine. 2023;62:102111. doi: 10.1016/j.eclinm.2023.102111.
27 Kaito S, Toya T, Yoshifuji K, Kurosawa S, Inamoto K, Takeshita K, et al. Fecal microbiota transplantation with frozen capsules for a patient with refractory acute gut graft-versus-host disease. Blood Adv. 2018;2(22):3097–101. doi: 10.1182/bloodadvances.2018024968.
28 Goloshchapov OV, Chukhlovin AB, Bakin EA, Stanevich OV, Klementeva RV, Shcherbakov AA, et al. [Fecal microbiota transplantation for graft-versus-host disease in children and adults: methods, clinical effects, safety]. Ter Arkh. 2020;92(7):43–54. doi: 10.26442/00403660.2020.07.000773.
29 Mao D, Jiang Q, Sun Y, Mao Y, Guo L, Zhang Y, et al. Treatment of intestinal graft-versus-host disease with unrelated donor fecal microbiota transplantation capsules: a case report. Medicine. 2020;99(38):e22129. doi: 10.1097/MD.0000000000022129.
30 Biernat MM, Urbaniak-Kujda D, Dybko J, Kapelko-Slowik K, Prajs I, Wrobel T. Fecal microbiota transplantation in the treatment of intestinal steroid-resistant graft-versus-host disease: two case reports and a review of the literature. J Int Med Res. 2020;48(6):300060520925693. doi: 10.1177/0300060520925693.
31 Zhao Y, Li X, Zhou Y, Gao J, Jiao Y, Zhu B, et al. Safety and efficacy of fecal microbiota transplantation for grade IV steroid refractory GI-GvHD patients: interim results from FMT2017002 trial. Front Immunol. 2021;12:678476. doi: 10.3389/fimmu.2021.678476.
32 Liu Y, Zhao Y, Qi J, Ma X, Qi X, Wu D, et al. Fecal microbiota transplantation combined with ruxolitinib as a salvage treatment for intestinal steroid-refractory acute GVHD. Exp Hematol Oncol. 2022;11(1):96. doi: 10.1186/s40164-022-00350-6.
33 DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, et al. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. N Engl J Med. 2019;381(21):2043–50. doi: 10.1056/NEJMoa1910437.
34 Weber D, Hiergeist A, Weber M, Ghimire S, Salzberger B, Wolff D, et al. Restrictive versus permissive use of broad-spectrum antibiotics in patients receiving allogeneic stem cell transplantation and with early fever due to cytokine release syndrome: evidence for beneficial microbiota protection without increase in infectious complications. Clin Infect Dis. 2023;77(10):1432–9. doi: 10.1093/cid/ciad389.
35 Vehreschild M, Ducher A, Louie T, Cornely OA, Feger C, Dane A, et al. An open randomized multicentre Phase 2 trial to assess the safety of DAV132 and its efficacy to protect gut microbiota diversity in hospitalized patients treated with fluoroquinolones. J Antimicrob Chemother. 2022;77(4):1155–65. doi: 10.1093/jac/dkab474.
36 Masetti R, Leardini D, Muratore E, Fabbrini M, D'Amico F, Zama D, et al. Gut microbiota diversity before allogeneic hematopoietic stem cell transplantation as a predictor of mortality in children. Blood. 2023;142(16):1387–98. doi: 10.1182/blood.2023020026.

37 Wu SR, Reddy P. Tissue tolerance: a distinct concept to control acute GVHD severity. Blood. 2017;129(13):1747–52. doi: 10.1182/blood-2016-09-740431.
38 Jarosch S, Kohlen J, Ghimire S, Orberg ET, Hammel M, Gaag D, et al. Multimodal immune cell phenotyping in GI biopsies reveals microbiome-related T cell modulations in human GvHD. Cell Rep Med. 2023;4(7):101125. doi: 10.1016/j.xcrm.2023.101125.
39 Thiele Orberg E, Meedt E, Hiergeist A, Xue J, Heinrich P, Ru J, et al. Bacteria and bacteriophage consortia are associated with protective intestinal metabolites in patients receiving stem cell transplantation. Nat Cancer. 2024;5(1):187–208. doi: 10.1038/s43018-023-00669-x.
40 Rashidi A, Ebadi M, Shields-Cutler RR, Kruziki K, Manias DA, Barnes AMT, et al. Early E. casseliflavus gut colonization and outcomes of allogeneic hematopoietic cell transplantation. PLoS One. 2019;14(8):e0220850. doi: 10.1371/journal.pone.0220850.
41 Fluckiger A, Daillere R, Sassi M, Sixt BS, Liu P, Loos F, et al. Cross-reactivity between tumor MHC class I-restricted antigens and an enterococcal bacteriophage. Science. 2020;369(6506):936–42. doi: 10.1126/science.aax0701.