

# Allogeneic Hematopoietic Stem Cell Transplantation

Subjects: **Oncology**

Contributor: Davide Leardini

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a well-established treatment for a variety of hematologic malignancies, immune disorders and metabolic diseases. Allo-HSCT often represents the only possible curative therapy, however it is hampered by high morbidity and mortality rates for an array of complications, including bloodstream infection and graft-versus-host disease (GvHD).

gut microbiome

hematopoietic stem cell transplantation

## 1. Introduction

Recently, the gut microbiome (GM) has emerged as a major contributor to the genesis of the complications of Allo-HSCT and to transplant outcomes [1][2][3]. While this relationship has been extensively studied in terms of clinical correlations, the underlying biological processes still remain poorly understood [4]. A growing body of evidence is now focused on the role of metabolomics in the immune response regulation and in other host biochemical processes [5]. Interestingly, among the factors that modify fecal, plasmatic and urinary metabolites, the GM, alongside with diet, have emerged as the major determinants [6]. Analogously, metabolic activities of GM are affected by environmental factors and host activities. The latter include a complex crosstalk taking place in the intestinal mucosa, with the secretion of mucus, secretory IgA, antibacterial peptides and microRNA [7]. Hence it has been suggested that microbiome-derived metabolites could provide some insights in the complex relationship between the GM, immune system and intestinal microenvironment, particularly in the HSCT setting [8]. To address this issue, we conducted a narrative literature review of studies addressing the role of gut microbiota derived metabolites in allo-HSCT. Electronic databases, including PubMed, Google Scholar and EMBASE, were searched to identify relevant studies published up to December 2020. The search was restricted to English-language studies involving both humans, mice and pre-clinical models. Papers were selected independently by two authors independently, and a third author supervised the selection. Herein, we provide a comprehensive overview on the current knowledge of gut microbiome-derived metabolites and their role in determining relevant biological processes in HSCT (Table 1 and Table 2).

**Table 1.** Summary of studies investigating the role of microbiome-derived metabolites in HSCT setting in mouse model.

Metabolites	Results	References
Fiber-Derived Metabolites—Short-Chain Fatty Acids		
Butyrate	Butyrate can improve IEC integrity, decrease apoptosis and mitigate GvHD. Administration of Clostridiales strain leads to higher butyrate levels.	[9]
Butyrate	Post-transplant enterococcal domination and loss of Clostridiales were associated with a reduction in butyrate in mice developing GvHD.	[10]
Butyrate, propionate	Butyrate and propionate improve GvHD in mouse model. This effect is dependent on the presence of SCFA receptor GRP43.	[11]
Amino Acid-Derived Metabolites		
Tryptophan-derived AhR ligand		
Indoles and derivatives	GM derivatives, such as indole, limit intestinal inflammation and damage associated with myeloablative chemotherapy or radiation exposure and acute GvHD. Treatment with indole-3-carboxaldehyde can protect from gut damage in HSCT recipients.	[12]
Tyrosine-derived metabolites		
Tyrosine	Mice with aGvHD present lower levels of tyrosine. Oral administration of tyrosine can ameliorate aGvHD and modify GM configuration.	[13]
Choline-derived metabolites		
TMAO	TMAO augments allo-reactive T-cell proliferation and Th1 subtype differentiation mediated by the polarized M1 macrophages. This results in higher severity of GvHD.	[14]
Bile Acids		
Tauroursodeoxycholic acid (TUDCA)	BAs were altered after HSCT. Administration of exogenous TUDCA protects intestinal epithelium by inflammatory cytokines. TUDCA did not influence GM composition.	[15]

**Table 2.** Summary of studies investigating the role of microbiome-derived metabolites in HSCT setting in human.

Metabolites	Study Design	Results	References
Fiber-Derived Metabolites—Short-Chain Fatty Acids			
Butyrate	1325 allo-HSCT adult patients	Post-transplant enterococcal domination and loss of Clostridiales were associated with a reduction in butyrate in patients developing GvHD.	[10]

Metabolites	Study Design	Results	References
Butyrate, propionate, acetate	35 allo-HSCT adult aGvHD patients	Butyrate, propionate and acetate levels were lower in patients experiencing GvHD 2–3 compared to the control. Butyrate was low even in patients with GvHD 1.	[16]
Butyrate, propionate, acetate, formate	42 allo-HSCT pediatric patients	Butyrate, propionate, acetate decrease within the first 14 days after HSCT and are lower in patients developing GvHD. Formate is a possible marker for the <i>Enterobacteriaceae</i> family. Expression of butyrate transporters in GvHD is altered. Greater number of days of antibiotic was associated with lower levels of butyrate and propionate.	[17]
Butyrate, propionate, hexanoate, isobutyrate	10 allo-HSCT adult cGvHD patients	Plasma concentration of SCFAs reflects fecal content. Patients developing cGvHD present lower plasma concentration of butyrate, propionate, hexanoate, isobutyrate.	[18]
Butyrate	44 allo-HSCT adult patients	Butyrate levels were correlated with Shannon index and were low in patients experiencing bloodstream infections within 30 days after HSCT.	[19]
Butyrate, propionate, acetate, desaminotyrosine	360 allo-HSCT adult patients	Butyrate-producing bacteria and fecal SCFAs were associated with a protection from viral lower respiratory tract infections	[20]
Butyrate	99 allo-HSCT adult patients	Oral supplementation with resistant starch and commercially available prebiotic mixture, GFO, resulted in higher post-HSCT butyrate-producing bacteria and a maintained or increased fecal butyrate concentration.	[21]
Butyrate, propionate, acetate	20 allo-HSCT pediatric patients	Enteral nutrition resulted in higher fecal concentration of butyrate, propionate and acetate.	[22]
Amino Acid-Derived Metabolites			
Tryptophan-derived AhR ligand			
3-IS	131 allo-HSCT adult patients	Lower 3-IS urinary levels are associated with higher transplant-related mortality and worse outcome. 3-IS urinary levels are correlated with GM diversity and with a higher presence of <i>Eubacterium rectale</i> and <i>Ruminococcaceae</i> .	[23]
3-IS	13 allo-HSCT adult patients	FMT results in higher 3-IS urinary levels.	[24]

Metabolites	Study Design	Results	References
	receiving FMT		
Indoxyl sulfate	Two cohort of 43 and 56 allo-HSCT adult patients	Tryptophan-derived AhR ligand 3-indoxyl sulfate was involved in the GvHD-related metabolic alterations.	[25]
Tyrosine-derived metabolites			
Tyrosine	86 allo- HSCT adult patients	In patients who develop aGvHD tyrosine metabolism was found to be altered. Other microbiome-derived metabolites (tryptophan, lysine, phenylalanine and secondary bile acids) were altered.	[26]
Riboflavin (Vitamin B2)-Derived Metabolites			
Riboflavin	121 allo- HSCT adult patients receiving CBT	Patients with post-HSCT MAIT cells reconstitution had a GM with higher expression of genes involved in the riboflavin synthesis pathway.	[27]
Polyamines and Breath Metabolites			
N-acetylputrescine, agmatine	184 allo- HSCT adult patients	Salivary metabolic profile of HSCT patients with and without severe oral mucositis (grade 0–1 vs. 3–4) was found to be different. Metabolites such as urea, 5- aminovalerate, N-acetylputrescine and agmatine, also show differences between the pre-transplant and the time of mucositis onset.	[28]
2-propanol, acetaldehyde, dimethyl sulfide, isoprene, and 1-decene	19 allo- HSCT adult patients	Comparing patients with and without GI GvHD, the former show modification in the levels of volatile organic compounds, namely 2-propanol, acetaldehyde, dimethyl sulfide, isoprene, and 1- decene.	[29]

## 2. Microbiome-Derived Metabolites in Allogeneic Hematopoietic Stem Cell Transplantation

GM-derived metabolites have emerged as crucial players in mediating crosstalk between GM and host in allo-HSCT recipients. Several questions should still be addressed in the upcoming studies. Firstly, the different metabolic profiles should be more precisely characterized and the relationship between specific bacterial strains and derived metabolites should be investigated. These data should be accomplished with ‘-omics’ approaches, including metabolomics, metagenomics and metatranscriptomics. Alongside with the aforementioned metabolites, many others have been demonstrated to have a role in human homeostasis and should thus be investigated in the

HSCT setting [8][30]. Future collaborative studies on larger cohorts will also clarify whether specific metabolic profiles could be associated with allo-HSCT outcomes as it has been demonstrated for GM diversity [1]. Lastly, the different metabolic patterns between children and adults should be directly addressed, considering the differences in GM configuration [31] and HSCT outcomes [32]. Certainly, these data pose a new intriguing field of research and substantial opportunities for the near future. GM-derived metabolites might serve as a feasible surrogate marker for microbiome characterization that may be clinically useful to predict HSCT-related risk [23]. Furthermore, the modulation of GM-derived metabolites should also appear as a target for therapeutic interventions. These should include diet, which is known to represent the main strategy to modulate microbial products m[8], emphasizing the importance of nutritional support during HSCT [22][33][34][35]. Other strategies should also be tested in order to modulate metabolites, such as probiotics, prebiotics and other oral supplements alongside FMT. In conclusion, GM-derived metabolites have proven to be an important field of research in the HSCT setting, also appearing as a promising therapeutic target for the nearfuture.

## References

1. Peled, J.U.; Gomes, A.L.C.; Devlin, S.M.; Littmann, E.R.; Taur, Y.; Sung, A.D.; Weber, D.; Hashimoto, D.; Slingerland, A.E.; Slingerland, J.B.; et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N. Engl. J. Med.* 2020, 382, 822–834.
2. Zama, D.; Biagi, E.; Masetti, R.; Gasperini, P.; Prete, A.; Candela, M.; Brigidi, P.; Pession, A. Gut microbiota and hematopoietic stem cell transplantation: Where do we stand? *Bone Marrow Transplant.* 2017, 52, 7–14.
3. Biagi, E.; Zama, D.; Rampelli, S.; Turroni, S.; Brigidi, P.; Consolandi, C.; Severgnini, M.; Picotti, E.; Gasperini, P.; Merli, P.; et al. Early gut microbiota signature of aGvHD in children given allogeneic hematopoietic cell transplantation for hematological disorders. *BMC Med. Genom.* 2019, 12, 1–11.
4. Andermann, T.M.; Peled, J.U.; Ho, C.; Reddy, P.; Riches, M.; Storb, R.; Teshima, T.; van den Brink, M.R.M.; Alousi, A.; Balderman, S.; et al. The Microbiome and Hematopoietic Cell Transplantation: Past, Present, and Future. *Biol. Blood Marrow Transplant.* 2018, 24, 1322–1340.
5. Zmora, N.; Bashiardes, S.; Levy, M.; Elinav, E. The Role of the Immune System in Metabolic Health and Disease. *Cell Metab.* 2017, 25, 506–521.
6. Bar, N.; Korem, T.; Weissbrod, O.; Zeevi, D.; Rothschild, D.; Leviatan, S.; Kosower, N.; Lotan-Pompan, M.; Weinberger, A.; Le Roy, C.I.; et al. A reference map of potential determinants for the human serum metabolome. *Nature* 2020, 588, 135–140.
7. Gopalakrishnan, V.; Helmink, B.A.; Spencer, C.N.; Reuben, A.; Wargo, J.A. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. *Cancer Cell* 2018, 33, 570–580.

8. Postler, T.S.; Ghosh, S. Understanding the Holobiont: How Microbial Metabolites Affect Human Health and Shape the Immune System. *Cell Metab.* 2017, 26, 110–130.
9. Mathewson, N.D.; Jenq, R.; Mathew, A.V.; Koenigsknecht, M.; Hanash, A.; Toubai, T.; Oravecz-Wilson, K.; Wu, S.-R.; Sun, Y.; Rossi, C.; et al. Gut microbiome–derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat. Immunol.* 2016, 17, 505–513.
10. Stein-Thoeringer, C.K.; Nichols, K.B.; Lazrak, A.; Docampo, M.D.; Slingerland, A.E.; Slingerland, J.B.; Clurman, A.G.; Armijo, G.; Gomes, A.L.C.; Shono, Y.; et al. Lactose drives *Enterococcus* expansion to promote graft-versus-host disease. *Science* 2019, 366, 1143–1149.
11. Fujiwara, H.; Docampo, M.D.; Riwes, M.; Peltier, D.; Toubai, T.; Henig, I.; Wu, S.J.; Kim, S.; Taylor, A.; Brabbs, S.; et al. Microbial metabolite sensor GPR43 controls severity of experimental GVHD. *Nat. Commun.* 2018, 9, 1–15.
12. Swimm, A.; Giver, C.R.; DeFilipp, Z.; Rangaraju, S.; Sharma, A.; Ulezko Antonova, A.; Sonowal, R.; Capaldo, C.; Powell, D.; Qayed, M.; et al. Indoles derived from intestinal microbiota act via type I interferon signaling to limit graft-versus-host disease. *Blood* 2018, 132, 2506–2519.
13. Li, X.; Lin, Y.; Li, X.; Xu, X.; Zhao, Y.; Xu, L.; Gao, Y.; Li, Y.; Tan, Y.; Qian, P.; et al. Tyrosine supplement ameliorates murine aGVHD by modulation of gut microbiome and metabolome. *EBioMedicine* 2020, 61, 103048.
14. Wu, K.; Yuan, Y.; Yu, H.; Dai, X.; Wang, S.; Sun, Z.; Wang, F.; Fei, H.; Lin, Q.; Jiang, H.; et al. The gut microbial metabolite trimethylamine N-oxide aggravates GVHD by inducing M1 macrophage polarization in mice. *Blood* 2020, 136, 501–515.
15. Haring, E.; Uhl, F.M.; Andrieux, G.; Proietti, M.; Bulashevska, A.; Sauer, B.; Braun, L.M.; de Vega Gomez, E.; Esser, P.R.; Martin, S.F.; et al. Bile acids regulate intestinal antigen presentation and reduce graft-versus-host disease without impairing the graft-versus-leukemia effect. *Haematologica* 2020.
16. Payen, M.; Nicolis, I.; Robin, M.; Michonneau, D.; Delannoye, J.; Mayeur, C.; Kapel, N.; Berçot, B.; Butel, M.J.; Le Goff, J.; et al. Functional and phylogenetic alterations in gut microbiome are linked to graft-versus-host disease severity. *Blood Adv.* 2020, 4, 1824–1832.
17. Romick-Rosendale, L.E.; Haslam, D.B.; Lane, A.; Denson, L.; Lake, K.; Wilkey, A.; Watanabe, M.; Bauer, S.; Litts, B.; Luebbering, N.; et al. Antibiotic Exposure and Reduced Short Chain Fatty Acid Production after Hematopoietic Stem Cell Transplant. *Biol. Blood Marrow Transplant.* 2018, 24, 2418–2424.
18. Markey, K.A.; Schluter, J.; Gomes, A.L.C.; Littmann, E.R.; Pickard, A.J.; Taylor, B.P.; Giardina, P.A.; Weber, D.; Dai, A.; Docampo, M.D.; et al. The microbe-derived short-chain fatty acids

butyrate and propionate are associated with protection from chronic GVHD. *Blood* 2020, **136**, 130–136.

19. Galloway-Peña, J.R.; Peterson, C.B.; Malik, F.; Sahasrabhojane, P.V.; Shah, D.P.; Brumlow, C.E.; Carlin, L.G.; Chemaly, R.F.; Im, J.S.; Rondon, G.; et al. Fecal microbiome, metabolites, and stem cell transplant outcomes: A single-center pilot study. *Open Forum Infect. Dis.* 2019, **6**, 1–10.

20. Haak, B.W.; Littmann, E.R.; Chaubard, J.L.; Pickard, A.J.; Fontana, E.; Adhi, F.; Gyaltshen, Y.; Ling, L.; Morjaria, S.M.; Peled, J.U.; et al. Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following allo-HCT. *Blood* 2018, **131**, 2978–2986.

21. Yoshifuji, K.; Inamoto, K.; Kiridoshi, Y.; Takeshita, K.; Sasajima, S.; Shiraishi, Y.; Yamashita, Y.; Nisaka, Y.; Ogura, Y.; Takeuchi, R.; et al. Prebiotics protect against acute graft-versus-host disease and preserve the gut microbiota in stem cell transplantation. *Blood Adv.* 2020, **4**, 4607–4617.

22. D’Amico, F.; Biagi, E.; Rampelli, S.; Fiori, J.; Zama, D.; Soverini, M.; Barone, M.; Leardini, D.; Muratore, E.; Prete, A.; et al. Enteral Nutrition in Pediatric Patients Undergoing Hematopoietic SCT Promotes the Recovery of Gut Microbiome Homeostasis. *Nutrients* 2019, **11**, 2958.

23. Weber, D.; Oefner, P.J.; Hiergeist, A.; Koestler, J.; Gessner, A.; Weber, M.; Hahn, J.; Wolff, D.; Stammler, F.; Spang, R.; 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.

24. DeFilipp, Z.; Peled, J.U.; Li, S.; Mahabamunuge, J.; Dagher, Z.; Slingerland, A.E.; Del Rio, C.; Valles, B.; Kempner, M.E.; Smith, M.; et al. Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity. *Blood Adv.* 2018, **2**, 745–753.

25. Michonneau, D.; Latis, E.; Curis, E.; Dubouchet, L.; Ramamoorthy, S.; Ingram, B.; de Latour, R.P.; Robin, M.; de Fontbrune, F.S.; Chevret, S.; et al. Metabolomics analysis of human acute graft-versus-host disease reveals changes in host and microbiota-derived metabolites. *Nat. Commun.* 2019, **10**, 1–15.

26. Reikvam, H.; Hatfield, K.; Bruserud, Ø. The pretransplant systemic metabolic profile reflects a risk of acute graft versus host disease after allogeneic stem cell transplantation. *Metabolomics* 2016, **12**, 1–11.

27. Konuma, T.; Kohara, C.; Watanabe, E.; Takahashi, S.; Ozawa, G.; Suzuki, K.; Mizukami, M.; Nagai, E.; Jimbo, K.; Kaito, Y.; et al. Reconstitution of Circulating Mucosal-Associated Invariant T Cells after Allogeneic Hematopoietic Cell Transplantation: Its Association with the Riboflavin Synthetic Pathway of Gut Microbiota in Cord Blood Transplant Recipients. *J. Immunol.* 2020, **204**, 1462–1473.

28. Shouval, R.; Eshel, A.; Dubovski, B.; Kuperman, A.A.; Danylesko, I.; Fein, J.A.; Fried, S.; Geva, M.; Kouniavski, E.; Neuman, H.; et al. Patterns of salivary microbiota injury and oral mucositis in

recipients of allogeneic hematopoietic stem cell transplantation. *Blood Adv.* 2020, 4, 2912–2917.

29. Hamilton, B.K.; Rybicki, L.A.; Grove, D.; Ferraro, C.; Starn, J.; Hodgeman, B.; Elberson, J.; Winslow, V.; Corrigan, D.; Gerds, A.T.; et al. Breath analysis in gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Blood Adv.* 2019, 3, 2732–2737.

30. Köhler, N.; Zeiser, R. Intestinal microbiota influence immune tolerance post allogeneic hematopoietic cell transplantation and intestinal GVHD. *Front. Immunol.* 2019, 10, 1–9.

31. Masetti, R.; Zama, D.; Leardini, D.; Muratore, E.; Turroni, S.; Prete, A.; Brigidi, P.; Pession, A. The gut microbiome in pediatric patients undergoing allogeneic hematopoietic stem cell transplantation. *Pediatric Blood Cancer* 2020, 67, e28711. Available online: <http://www.ncbi.nlm.nih.gov/pubmed/32939928> (accessed on 2 January 2021).

32. Dini, G.; Zecca, M.; Balduzzi, A.; Messina, C.; Masetti, R.; Fagioli, F.; Favre, C.; Rabusin, M.; Porta, F.; Biral, E.; et al. No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission. *Blood* 2011, 118, 6683–6690.

33. Zama, D.; Bossù, G.; Leardini, D.; Muratore, E.; Biagi, E.; Prete, A.; Pession, A.; Masetti, R. Insights into the role of intestinal microbiota in hematopoietic stem-cell transplantation. *Ther. Adv. Hematol.* 2020, 11, 204062071989696.

34. Zama, D.; Gori, D.; Muratore, E.; Leardini, D.; Rallo, F.; Turroni, S.; Prete, A.; Brigidi, P.; Pession, A.; Masetti, R. Enteral versus Parenteral Nutrition as Nutritional Support after Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis. *Transplant. Cell. Ther.* 2020, in press.

35. Zama, D.; Muratore, E.; Biagi, E.; Forchielli, M.L.; Rondelli, R.; Candela, M.; Prete, A.; Pession, A.; Masetti, R. Enteral nutrition protects children undergoing allogeneic hematopoietic stem cell transplantation from blood stream infections. *Nutr. J.* 2020, 19, 29.

Retrieved from <https://encyclopedia.pub/entry/history/show/17518>