HHS Public Access

Author manuscript

Semin Hematol. Author manuscript; available in PMC 2022 August 18.

Published in final edited form as:

Semin Hematol. 2020 January ; 57(1): 1–6. doi:10.1053/j.seminhematol.2020.06.001.

Short chain fatty acids: Postbiotics/ Metabolites and Graft Versus Host Disease Colitis

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Abstract

Acute Graft versus host disease (GVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo HSCT), a potent form of cellular therapy that has the potential to cure malignant and benign hematological conditions. Gastrointestinal (GI) GVHD is the principal cause of non-relapse mortality (NRM) after allo HSCT. Allo HSCT alters the intestinal microbiota and recent research uncovered a microbiome-metabolome axis that can affect intestinal homeostasis and mitigate the severity of experimental GI GVHD. This axis can potentially be manipulated via dietary intervention or through probiotics or postbiotics or antibiotics in humans. In this review we summarize major findings of how microbial metabolites and particularly short chain fatty acids (SCFAs) could impact acute GI GVHD.

Acute GVHD results from an allo-immune response driven by donor T cells causing tissue damage in target organs such as in the GI tract[1]. Significant improvements in understanding the role of donor and host immune cells, with better conditioning and supportive care regimens, have resulted in reduction of transplant-related NRM after allo HSCT[2]. However, despite major strides in understanding the pathogenesis of acute GVHD and the development of novel immunosuppressants, GI GVHD related NRM remains significant [3].

Recent studies have brought into focus the potential role played by the host microbiome on GVHD outcomes[4]. The intestinal microbiota interacts with the host intestinal immune and non-immune cells and contributes to a broad range of functions in the host, including, digestion of nutrients, production of microbial metabolites and maintenance of the intestinal homeostasis[5]. Emerging data have demonstrated a strong correlation between aberrant shifts in intestinal microbiota composition and several disease processes including autoimmune, metabolic diseases, cancer, and acute GI GVHD after allo HSCT [4, 6]. Several clinical strategies (Figure 1), such as diet and prebiotics, antibiotics, probiotics, and

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Declarations of interest for Mary Riwes and Pavan Reddy: None

fecal microbiota transplantation (FMT), can be employed to manipulate the architecture of the intestinal microbiota [7]. The mechanisms by which the intestinal microbiota modulates acute GI GVHD remain poorly understood[8]. One mechanism could be related to the ability of the intestinal microbiota to produce beneficial or harmful metabolites by breaking down host nutrients[7]. Recent evidence has brought into play the role of microbial metabolites, specifically SCFAs, in the severity of acute GI GVHD[9, 10]. In this review, we summarize data investigating the roles that microbial metabolites, and in particular SCFAs, play in impacting host intestinal immune and non-immune cells, and how these metabolites may regulate acute GI GVHD.

Immune biology of GVHD and the role of the microbiota in intestinal homeostasis

GVHD is a complex interaction between the innate and adaptive immune systems of the host and donor in allo HSCT[1]. In allo HSCT, conditioning regimens are used for facilitating engraftment of donor hematopoietic cells and eliminating residual malignant cells[11]. These regimens cause host tissue injuries which release “danger signals” including pathogen-associated molecular patters (PAMPs) and damage-associated molecular patters (DAMPs). “Danger signals” activate host or donor antigen presenting cells (APCs) which is amplified by microbial stimulation[12]. APCs present allo-antigens to donor T cells via major histocompatibility complex (MHC) class I or class II and further escalate the inflammatory response by producing T-cell stimulating cytokines[13]. Stimulated donor T cells expand and differentiate into effector T cells and these migrate into and damage GVHD target organs such as the GI tract[3]. GI tract cells such as intestinal epithelial cells (IECs), intestinal stem cells (ISCs), and paneth cells, are targeted in GI GVHD[14]. Thus, GVHD is an immunologically mediated process and GI tract damage with subsequent disruptions in intestinal homeostasis, which are further compounded by the use of broad-spectrum antibiotics and alterations in nutrition that occur during the process of allo HSCT, play important roles in augmenting GVHD.

Maintenance of intestinal homeostasis is in part regulated by the intestinal microbiota and its interactions with the host immune system[15–17]. The host immune system has been shown to modulate the intestinal microbiota and its disturbances result in intestinal microbiota dysbiosis. For example, retinoic acid receptor-related orphan receptor- γt (RORγt)+ group 3 innate lymphoid cells (ILC3s) regulate intestinal bacteria by limiting local and systemic inflammation[16] and the absence of intestinal immune cells, particularly isolated lymphoid follicles (ILFs), has been shown to result in alteration of the intestinal microbiota of mice by over representation of gram negative bacteria[18]. The intestinal microbiota also modulates host immune responses. Germ free mice developed an increase in interferon-γ (IFN-γ) after colonization with *Escherichia coli* (*E. coli*)[19]. In another study, germ free mice colonized with conventional intestinal microbiota developed structural changes with increase in the depth of the intestinal epithelial crypts as well as expansion in the lamina propria with an increase in immune cells within four days after exposure to intestinal bacteria[20]. Multiple studies linked the intestinal microbiota to regulation of T cells. In one study, it was shown that colonization of mice with segmented filamentous bacteria (SFB) induces CD4(+) T

helper cells in the lamina propria[21]. In other studies, several intestinal microbes have been shown to induce forkhead box protein (Foxp3)- expressing regulatory T cells (Tregs)[22–25]. Furthermore, interactions between the intestinal microbiota and the host promote the functions of non-immune cells such as IECs and goblet cells which play important roles in regulating the barrier function of the GI tract[26, 27]. Thus, the intestinal microbiota plays an important role in intestinal homeostasis.

Microbial changes in acute GVHD

Allo HSCT alters the diversity and composition of the intestinal microbiota[28]. There is loss of diversity after allo HSCT with a shift towards *Enterococci* and a decrease in the obligate anaerobic bacteria, such as those from the phylum *Frimicutes*[29]. This was more pronounced with the use of antibiotics and the development of GVHD[29]. Acute GVHD has been associated with major fluctuations in the intestinal microbiota including a general loss of diversity and expansion of *Enterobacteriales* (including *Escherichia, Klebsiella*, and *Enterobacter*), *Lactobacillales* (including *Lactobacillus*, *Enterococcus*, and *Streptococcus*), *Proteobacteria* and *Akkermansia*[4]. This expansion is accompanied with loss of obligate anaerobic bacteria from the phylum Firmicutes (including *Clostridia* and *Blautia*)[30, 31]. Paneth cell loss in experimental GVHD results in decreased secretion of α-defensins leading to intestinal dysbiosis and that loss of paneth cells and dysbiosis were associated with nonrelapse mortality (NRM) in clinical GVHD[14, 32, 33]. A similar shift post allo HSCT was noted in three more studies[14, 34, 35]. One identified vancomycin-resistent *eterococcus* (VRE) dominance following antibiotic treatment as a predictor of bacteremia[34]. The second showed that GVHD was associated with a shift towards *E. coli*[14]. The third study showed expansion of *Enterococcus*, *Streptococcus* and various *Proteobacteria* after allo-HSCT[35]. This study noted that expansion of these bacteria often preceded bloodstream infections by the same organisms, and identified treatment with the antibiotic metronidazole as a risk factor for enterococcal expansion[35]. The intestinal microbiota can also modulate acute GVHD severity. In 1970s, investigators found less GVHD in mice transplanted in germ-free conditions or receiving gut decontamination antibiotics[36, 37]. These studies have not been confirmed in modern day germ-free mice facilities. However, early clinical studies also showed similar beneficial effects of bacterial decontamination in allo HSCT patients[38, 39]. But subsequent studies did not replicate these benefits[40–42]. More recent research made major strides in investigating the specific alterations in the composition of the intestinal mcirobiota and their association with acute GVHD. In one clinical cohort study, high intestinal abundance of the anaerobic bactreria *Blautia* was correlated with lower rates of GVHD and improved survival[43]. Loss of diversity of the inetstinal microbiota was associated with increased mortality in allo HSCT patients which was attributed to increased death due to GVHD or infection rather than relapse[44]. Another study showed associations between the expansion of certain bacteria *Lactobacillales* as well as general loss of diversity and acute GVHD severity[30]. This study also showed that expansion of *Lactobacillales* was not the cause for the development of GVHD since eliminating *Lactobacillales* from the intestinal flora in mice before allo HSCT caused more severe GVHD and reintroducing *Lactobacillales* alleviated this effect[30]. But another study found that that modifying the intestinal mcirobiota using the probiotic

microorganism *Lactobacillus rhamnosus GG* reduced experimental GVHD[45]. Similarly, administration of a cocktail of 17 species of *Clostridia* reduced experimental GVHD and improved survival[9]. These data suggest that probiotic therapy can be used in ameliorating GVHD. As such, limited published early clinical experiences explored the use of probiotics, including via FMT in allo HSCT patients[46, 47].However, such approaches face concerns of safety in an immunocompromised population, as well as challenges related to scalability for widespread application, and large prospective trials evaluating feasibility, safety, and efficacy in allo HSCT patients are needed. A recent study described two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* (*E. coli*) bacteremia occurred after they had undergone FMT in two independent clinical trials; one of these patients was an allo HSCT recipient who died from severe sepsis[48].

Use of antibiotics

A recent retrospective study showed that broad spectrum antibiotic treatment with imipenem-cilastatin and piperacillin-tazobactam was associated with increased GVHD related mortality in patients and that treatment with imipenem-cilastatin was associated with loss of the protective mucus lining of the colon and a shift towards *Akkermansia* in mice[49]. Antibiotic agents with more limited spectra of activity such as rifaximin, cefepime and aztreonam were associated with reduced GVHD severity[49, 50]. The use of rifaximin correlated with a lower enterococcal load after allo HSCT and the use of cefepime and aztreonam correlated with less alterations to the composition of the intestinal microbiota post allo-HSCT when compared with broader spectrum antibiotics with increased anaerobic activity[49, 50]. An ongoing prospective clinical study is investigating the best antibiotic choices in protecting the integrity of the intestinal microbiota in patients undergoing allo HSCT (NCT03078010).

Introduction to microbial metabolites in acute GVHD

The intestinal mcirobiota metabolize nutrients ingested by the host and produce microbial metabolites which play critical roles in the microbiota's interactions with the host and in maintaining intestinal homeostasis[51]. Microbial metabolites include essential fatty acids and amino acids for the host[52]. SCFAs are the most studied microbial metabolites[53]. Examples of other mcirobial metabolites are bile acids, polyamines, and aryl hydrocarbon receptor (AhR) ligands[52]. These metabolites impact both non-immune and immune intestinal cells as well as the microbiome and have varying functions in maintaining the barrier surface of the GI tract, as well as modulating the innate and adaptive host immune responses[51]. There is scarcity of data on microbial metabolites in acute GVHD (Table 1).Herein, we will focus on SCFAs and their roles in acute GVHD.

Short chain fatty acids

A. Effects of SCFAs on intestinal homeostasis

SCFAs (e.g., butyrate, proprionate and acetate) are produced from fermentation of indigestible carbohydrates by intestinal anaerobic commensal bacteria such as *Clostridia* species and impact both non-immune as well as immune intestinal cells[53]. SCFAs serve

as an energy source for the intestinal microbiota as well as the IECs[53]. In the study by Donohoe et al, IECs from germ-free mice were in an energy-deprived state leading to autophagy where the cells degraded their own components for energy and this was reversed by butyrate supplementation[54]. SCFAs also maintain the integrity of the intestinal mucosal barrier. Goblet cells up-regulated their expression of mucin genes in response to SCFAs[55, 56] and inoculating germ-free rats with SCFA-producing *Bacteroides thetaiotaomicron* or *Faecalibacterium prausnitzii* induced goblet cell differentiation and mucus production[57]. Furthermore, colonization with *Bifidobacterium longum* protected mice against death induced by a lethal infection by increasing production of SCFA acetate which maintained the barrier integrity of IECs and inhibited translocation of the *E. coli* O157:H7 Shiga toxin from the gut lumen into the blood[58]. SCFAs play an important part in innate immunity as they are histone deacetylase (HDAC) inhibitors with anti-inflammatory effects[53]. In the study by Vinolo et al, the exposure of rat neutrophils to SCFAs inhibited HDAC activity which resulted in inactivation of nuclear factor κB (NF-κB) and suppression of nitric oxide (NO) and the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and cytokine-induced neutrophil chemoattractant-2 (CINC-2αβ)[59]. Similarly, exposure of human peripheral blood mononuclear cells to SCFAs and trichostatin A (TSA), a typical HDAC inhibitor, lead to inactivation of NF-κB and down-regulation of TNF-α via prostaglandin E(2) (PGE(2)) secretion[60]. SCFAs also resulted in HDAC inhibition and anti-inflammatory effects in macrophages and dendritic cells (DCs)[61, 62]. In another study, a high fiber diet or treatment with the SCFA acetate in mice increased inflammasome activation and increased levels of IL-18 which promoted epithelial repair[63]. SCFAs play a role in adaptive intestinal immunity as well[53]. They were shown to promote Treg differentiation and anti-inflammatory responses thereby mitigating the severity of colitis[22]. SCFAs butyrate, acetate, and proprionate administration to germ-free mice increased the expression of anti-inflammatory IL-10 producing Foxp3-expressing Tregs through HDAC inhibition[64]. Moreover, Butyrate increased IL-18 expression in epithelial cells, increased IL-10 expression in DCs and macrophages and enabled them to induce the differentiation of Tregs, and protected against colitis[65]. Thus, SCFAs affect both non-immune as well as immune intestinal cells and modulate intestinal homeostasis.

B. Dietary resistant starch and SCFAs

One potential approach for stimulating SCFA production could be via dietary supplementation with carbohydrates that are resistant to degradation by human enzymes but can be metabolized by select microbes in the gut. Multiple studies have reported increased fecal SCFAs, particularly butyrate, by dietary supplementation with different formulations of resistant starch (RS)[66–68]. Another study showed that one such RS prepared from potatoes (RPS) is more potent at increasing average fecal butyrate levels compared to other RS formulations[69]. Butyrate production from RS is a complex multistep process and understanding all the gut microbes involved in this process is an ongoing challenge[69, 70]. Only a limited number of gut bacteria can degrade RS, however, most primary RS degraders are not among the known butyrate producers[71]. Thus, in order for dietary supplementation with RS to stimulate butyrate production, the activities of secondary fermenters are required. These secondary fermenters capture degradation and fermentation products from primary degraders and metabolize them into new molecules, including

butyrate[72]. Known primary RS degraders include *Ruminococcus bromii*, *R. lactaris*, *R. gnavus*, and *Bifidobacterium spp* and known butyrate producers (secondary fermenters) include *Roseburia spp*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Anaerostipes spp*[69].

C. SCFA and acute GVHD

A recent murine study explored the role of microbial metabolites, specifically SCFAs, in acute GVHD severity and found that the SCFA butyrate was significantly decreased in the IECs of mice experiencing acute GVHD[9]. Restoring butyrate levels, either by direct administration of butyrate or by increasing intestinal butyrate-producing bacteria, reduced acute GVHD. Two SCFAs, butyrate and propionate, were shown to directly protect IECs and reduce acute GVHD severity in mice[9, 10]. A small clinical study found that fecal butyrate and propionate levels are decreased in patients after allo HSCT and are lower with anti-anaerobic antibiotic exposure[73]. Another recent clinical study examined fecal SCFA concentrations after allo HSCT and found that higher levels of butyrate and other SCFAs correlated with abundance of butyrate producing organisms in the intestinal microbiota and this abundance was associated with resistance against lower tract respiratory infections[74].However, the impact of SCFA levels on acute GVHD has yet to be examined in patients post allo HSCT.

D. Dietary manipulation of the microbiome-metabolome axis and acute GVHD

Diet affects the composition of the intestinal mcirobiome and the associated metabolome is correspondingly altered[75, 76]. In one study, high protein and low carbohydrate diet was associated with loss of members of *Clostridiales*, including *Roseburia*, *Faecalibacterium*, *Ruminococcus*, and *Blautia*[77]. Similar patterns were seen with diets derived entirely from animal products[75].

Turnbaugh et al showed that changes in diet from a low-fat, plant polysaccharide-rich diet to a high- fat, high-sugar diet in mice that were colonized with human feces altered the intestinal microbiota composition and this was accompanied by changes in the metabolic milieu[78]. In two other studies, researchers showed that total parenteral nutrition resulted in a pro-inflammatory pattern of immune responses in mice and humans[79, 80]. These data suggest that diet can alter the intestinal microbiota as well as the metabolome and thereby regulate intestinal homeostasis.

Specific elements of the diet called prebiotics, which usually refer to indigestible carbohydrates that are metabolized by the intestinal microbiota to produce SCFAs, are particularly influential in modulating the structure and function of the intestinal microbiota[53]. There is lack of published clinical data on the effect of prebiotics in acute GVHD. However, several studies showed that the prebiotics inulin and fructo-oligosaccharides increased intestinal microbiota diversity and decreased disease activity in inflammatory bowel disease patients[81, 82]. These studies along with the evidence that SCFAs protect IECs and reduce experimental acute GVHD severity[9, 10], provide a compelling rationale for studies of dietary manipulation of the microbiome-metabolome axis using prebiotics to mitigate acute GVHD in patients receiving allo HSCT. Of interest,

a small study showed that RPS induced the production of the SCFA butyrate from the intestinal microbiota of healthy volunteers[66]. Importantly, an abstract presented at the American Society of Hematology (ASH) conference in 2019 reported that RPS administration is feasible and safe and increased fecal RPS-degrading and butyrate-producing bacteria with a concomitant increase in butyrate levels in a pilot study in allo HSCT recipients[83]. As such, a prospective phase II clinical trial to determine whether nutritional modulation of the microbiome-metabolome axis using RPS can reduce acute GVHD, is currently underway (www.clinicaltrials.gov: NCT02763033). Similarly, a trial of Fructooligosaccharides, to assess this prebiotic's safety and tolerability in allo HSCT patients is undergoing (NCT02805075). Notably, a recent study showed that a diet free of the disaccharide lactose, a carbohydrate source for the growth and expansion of *Enterococcus faecalis* and Enterococcus *faecium*, decreased the *Enterococcus* bloom observed by this group in GVHD and attenuated GVHD in mice after allo HSCT[84]. This study also describes a high incidence of enterococcal expansion in allo HSCT patients which was associated with GVHD and mortality[84].Furthermore, patients in this study who were carriers of lactose-nonabsorber genotypes showed compromised clearance of post-antibiotic Enterococcus domination[84]. However, this study did not report whether there was an association between these lactose-nonabsorber genotypes and GVHD and mortality in patients and did not investigate the effect of a lactose free diet on GVHD in patients[84].

Other microbial metabolites in acute GVHD

The bile acid metabolite, taurine, has been shown to contribute to the mechanism of NLRP6-mediated GVHD toxicity in mice post allo HSCT[54]. AhR has been shown to be necessary for expansion of IL-22 producing ILCs needed for the clearance of Citrobacter rodentium infection[55]. In allo HSCT, IL-22 producing ILCs were depleted in the intestines of mice with acute GVHD, and treatment with IL-22 enhanced the recovery of intestinal stem cells (ISCs), increased epithelial regeneration, and reduced acute GVHD[56]. However, the role that AhR plays in modulating IL-22 producing ILCs in acute GVHD and whether dietary ligands can modulate that role are yet to be investigated. One clinical study showed that lower levels of urine 3-indoxyl sulfate, an AhR ligand, were associated with higher treatment related mortality and lower overall survival in allo HSCT patients[57].

Future perspectives

Growing evidence suggests the importance of the microbiome-metabolome axis in mitigating acute GVHD[9, 10]. Clinical approaches to rationally alter this axis in allo HSCT patients are needed. As such, dietary manipulation using RPS is currently being tested in this population (www.clinicaltrials.gov: NCT02763033). If the primary endpoint of reducing clinical acute GVHD is met, then follow-up multi-institutional prospective randomized trials will be warranted. Other dietary interventions such as lactose free diet which has been recently shown to ameliorate GVHD in mice[84], need to be investigated in allo HSCT patients. Combining dietary interventions with other approaches such as probiotics, modifications of antibiotic strategies, or FMT can also be explored in this allo HSCT population. However, exploring the safety of FMT in this immunocompromised population needs to be exercised with caution, especially in light of the recent report of

an allo HSCT recipient in whom ESBL–producing *E. coli* bacteremia and death occurred after undergoing FMT[48]. Additionally, more mechanistic studies of microbial metabolite mediated protection in acute GVHD are needed. One tactic is to better understand host metabolism and its impact on the microbiome and subsequent effect on GVHD. Another is to understand microbial metabolism and its impact on host metabolism and GVHD. Notably, a recent study in mice showed the importance of a host-microbial biliary network interaction, which was manipulated by diet, in modulating a specific colonic Treg cell population and ameliorating inflammatory colitis via the resulting gut bile acid pool[85]. This highlights the need for further investigations of the role of other microbial metabolites besides SCFAs, such as bile acids, in acute GVHD. Furthermore, the role of microbial and metabolite geographical variation (small or large bowel) and its impact on GVHD colitis needs to be explored.

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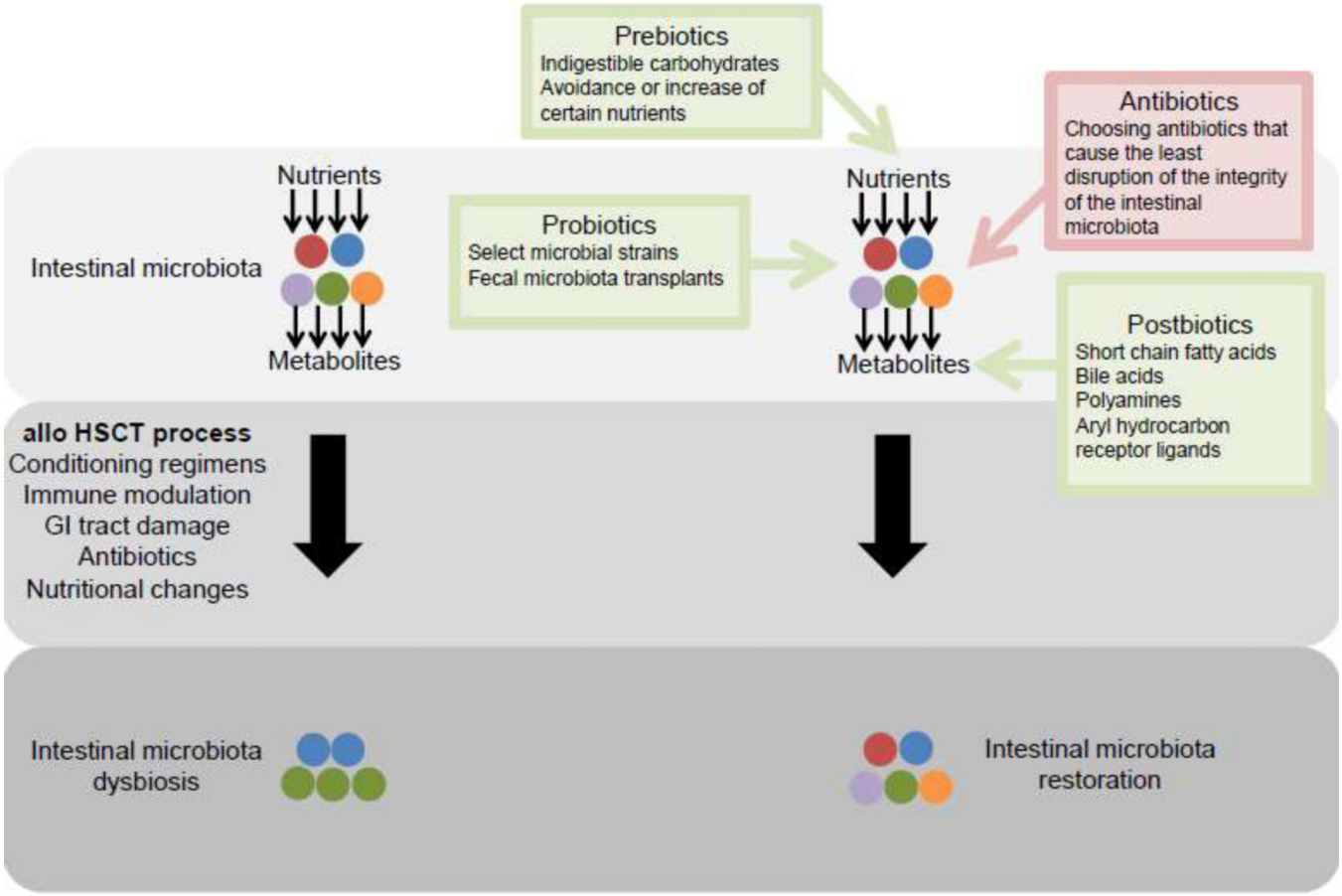

Figure 1.

Points for clinical intervention to alter the intestinal microbiota

The process of allogeneic hematopoietic stem cell transplantation (allo HSCT) results in dysbiosis of the intestinal microbiota. This figure depicts different strategies to restore the architecture of the intestinal microbiota in patients undergoing allo HSCT.

Table 1.

Known roles of microbial metabolites in acute graft versus host disease (GVHD)

Microbial metabolites	**Short chain fatty acids (SCFAs)**	**Aryl hydrocarbon receptor (AhR) ligands**	**Bile Acid metabolite taurine**
Known roles in acute GVHD	Direct effect of the SCFAs butyrate and propionate on intestinal epithelial cells (IECs) - > reduced severity of experimental acute GVHD	lower levels of urine 3- indoxyl sulfate -> increased clinical acute GVHD	contributes to the mechanism of NLRP6-mediated GVHD toxicity in mice post allo HSCT