

DOI: 10.46765/2675-374X.2022V3N2P175

HEMATOPOIETIC STEM CELL TRANSPLANTATION AND GUT MICROBIOTA: OUTCOMES AND USE OF PROBIOTICS, A NARRATIVE REVIEW

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Received: 25 Oct 2022 • Revised: 07 Nov 2022 • Accepted: 13 Nov 2022.

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a complex procedure used to treat several onco-hematological neoplasms, benign hematological diseases, and some types of solid tumors. In recent years, the role of the gut microbiota in HSCT has been studied, revealing that the microbiota has a direct interaction with the immune system and the microbial balance within the body (eubiosis), providing beneficial health effects, and changes in such state result in dysbiosis, which has been associated with several pathological states. The process in which the patient undergoes HSCT can cause microbiota imbalance with reduced diversity, which would be related to negative post-HSCT outcomes, including increased mortality and development of graft-versus-host disease (GVHD). The modulation of the gut microbiota through methods such as the use of probiotics has been explored as an alternative for the recovery and/or maintenance of the gut microbiota.

Keywords: Hematopoietic stem cell transplantation. Microbiota. Gut microbiota. Probiotics.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a complex procedure used to treat several onco-hematological neoplasms, benign hematological diseases, and some types of solid tumors. The conditioning step for HSCT consists of chemotherapy, with or without radiotherapy, with the objective of immunosuppression and eradication or reduction of the disease. Subsequently, an intravenous infusion of hematopoietic progenitor cells is performed, to restore the patient's bone marrow function^{1,2}.

The cells used for HSCT can be from the patient (autologous HSCT) or from a donor, who can be related or unrelated (allogeneic HSCT). In this last type of transplant, graft-versus-host disease (GVHD) can occur, which results from an alloreactivity reaction

of the graft's lymphocytes against the histocompatibility antigens of the host, which is one of the main causes of post-transplant morbidity and mortality³.

In recent years, the role of the gut microbiota in HSCT and its outcomes has been studied. The relationship between the microbiota and the pathogenesis of GVHD was suggested many years ago after a study with germ-free mice⁴. It should be noted that GVHD occurs very frequently in the gastrointestinal tract (GIT), one of the main sites of bacterial colonization.

The gut microbiota can be considered as a virtual and metabolic organ⁵, comprising an ecosystem formed by microorganisms synergistically adjusted to human physiology. It performs essential functions

for the organism as a physical, functional, and immunological barrier of the GIT^{6,7}.

The microbiota interacts directly with the immune system, and the intestinal defense barrier is composed of the microbiota, the mucosal barrier, and the gut-associated lymphoid tissue (GALT), the latter being responsible for communication of T and B lymphocytes with cells from other tissues and production of immunoglobulin A⁸.

The balance state of the microbiota (eubiosis) promotes beneficial health effects, and changes in such state result in dysbiosis⁹. The process to which the patient undergoes HSCT can cause an imbalance of the microbiota¹⁰, since, in addition to chemotherapy and radiotherapy, which cause gastrointestinal toxicity effects, there may be a breakdown of the epithelial barrier with consequent bacterial translocation, in many cases influenced by the prophylactic or therapeutic use of broad-spectrum antibiotics¹¹.

Holler *et al.* demonstrated that, at the time of admission for transplantation, patients have a predominance of commensal bacteria while, after transplantation, there is a tendency for an increase in *Enterococcus*, whose prominence is facilitated by the use of prophylactic antibiotics or in the treatment of febrile neutropenia and, in particular, among patients who develop GIT GVHD¹².

The decrease in gut microbiota diversity at the time of grafting appears to have a strong relationship with mortality¹⁰. Thus, the assessment of microbiota diversity through methods such as next generation 16S rRNA gene sequencing¹³, with the purpose of taxonomic and phylogenetic assessment and, later, interventions with the aim of preserving the microbiota, such as the use of probiotics, could help reduce morbidity and mortality in HSCT patients.

According to the National Consensus on Oncology Nutrition in Brazil, the use of probiotics for neutropenic patients is not indicated¹⁴. However, studies using some types of probiotics have shown that their use can be safe in HSCT^{15,16}.

According to the World Health Organization (WHO), probiotics can be defined as "live microorganisms capable of improving the intestinal microbial balance, producing beneficial effects on the health of the individual." Some of the main benefits are increased immune defense with activation of T lymphocytes, NK cell activity, and acting on inflammatory mediators with a decrease in pro-inflammatory cytokines (interleukins 12, 6, and 4) and an increase in interleu-

kin 10, which has anti-inflammatory action¹⁷.

Evidence shows that, in healthy individuals, the use of probiotics can, in addition to improving the immune response, help with bowel movements and stool consistency. Thus, they act against the colonization and translocation of pathogenic microorganisms and could also help to reduce the risk of antibiotic resistance. And, although colonization by probiotics may not occur upon their use, the passage of the probiotic through the intestine seems to be sufficient to reduce colonies of pathogenic bacteria due to reduced adhesion and competitive nature¹⁷.

The bacteria most used as probiotics and with the most widely known effects are *Lactobacilli* and *Bifidobacteria*, and they are also the most tested in the context of HSCT, as seen in an experimental study with animals, in which the consumption of *Lactobacillus rhamnosus GG*, before and after transplantation, was evaluated. The use of such probiotic improved the survival of the animals and reduced the incidence of acute GVHD¹⁹. This same *Lactobacillus* was used in a sample of allogeneic HSCT patients at the time of grafting and showed no effect on the severity or incidence of GVHD¹⁶. However, more studies are needed regarding the use of probiotics in such patients, with different moments of use, dose, and strains.

NORMAL GUT MICROBIOTA AND CHANGES IN HSCT

The human gut microbiota contains several microorganisms that colonize the surfaces of the GIT with diverse composition throughout the digestive tract¹⁹. In healthy individuals, the composition of the microbiota is relatively stable, with six phyla of bacteria dominating the microbiota: Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria, Actinobacteria, and Verrucomicrobia. Among them, there is a predominance of Gram-positive Firmicutes followed by Gram-negative Bacteroidetes^{20,21}.

There are already known factors related to changes in the gut microbiota, considering its malleability and/or fragility in the face of environmental and diet changes, which are the use of antibiotics, geographic location, pathologies, lifestyle, fiber supply, aging, type of delivery, among others^{6,19,21,22}.

The microbiota performs essential functions for the human organism such as nutrients digestion, protection against pathogens, and interaction with the immune system, as well as production of metabolites^{23,24,25}. For some time, it has been considered a

virtual and metabolic organ⁵ that, in general, will act as a physical, functional, and immunological barrier of the gastrointestinal tract²⁶. Therefore, understanding that the alteration of the microbiota balance state, in which eubiosis can become dysbiosis, a state of unbalance that can result in the loss of beneficial health effects and the initiation of a potentially pathological state, is essential⁹.

Several studies show that there is a decrease in microbiota diversity in HSCT^{12,27-31} with losses of beneficial bacteria such as *Faecalibacterium* and *Ruminococcus*²⁸. In the study by Montassier *et al.* with Non-Hodgkin Lymphoma patients admitted for HSCT, it was seen that there was a significant decrease in Firmicutes and Actinobacteria and an increase in Proteobacteria after conditioning³².

One of the causes for the loss of diversity may be the chemotherapy used in conditioning, which has several effects on the patient, including GIT mucositis, which leads to alteration of intestinal villi and loss of enterocytes. The inflammatory process could partly explain changes in the taxonomic composition and metabolic capacity of the gut microbiota³².

In addition to chemotherapy, the use of antibiotics required during the transplantation process also affects the gut microbiota^{27,29,33,34} although different types of antibiotics have different impacts on the diversity of the microbiota³⁵.

A study with a large cohort of patients showed that early antibiotic treatment in transplant patients is associated with significant changes in the microbiota³⁴. Such study found a lower overall survival and a higher transplant-related mortality in patients who started using antibiotics earlier than in those who started after transplantation, and the lowest transplant-related mortality was found in the group that did not receive additional antibiotics³⁴. Such data are in line with the idea that changes in the microbiota are related to worse outcomes for these patients.

Other studies have also shown that changes and loss of diversity may be related to negative outcomes after HSCT, such as increased mortality¹⁰, decrease in survival³⁶, pulmonary complications³⁷, and bacteremia related to the predominance of certain types of bacteria in this context^{27,38}. In addition, there is a relationship to decrease in overall survival¹⁰, which may be influenced by the colonization of the gut microbiota by antibiotic-resistant bacteria^{39,40}.

There also seems to be a relationship between gut microbiota composition and post-transplant re-

lapse/progression, as seen in a study that found a lower cumulative incidence of progression/relapse in patients with an abundance of a group of bacteria composed mostly of *Eubacterium limosum*, when compared to a group that did not have such bacteria⁴¹.

On the other hand, a study published in 2017 analyzed the composition of the preconditioning gut microbiota and found no differences in outcomes such as mortality and post-transplant survival among groups with low, moderate, or high diversity. However, it did find differences in the composition of the microbiota of those who had GVHD, when compared to those who did not⁴². Similarly, another study that analyzed pre-transplant stool samples found that there seems to be less diversity in the microbiota of those patients who developed bacteremia when compared to those who did not⁴³, which suggests the importance of eubiosis pre-transplant.

Another important aspect regarding the gut microbiota is the production of short-chain fatty acids (SCFA), which can also be compromised in HSCT^{28,44}. SCFA can be produced from bacterial fermentation of carbohydrates in the intestine and serve as a source of energy, have anti-inflammatory action, and stimulate the production of some hormones, among other important functions for the host's health.

In the study by Biagi *et al.*, it was found from stool samples from post-HSCT patients, who developed acute GVHD, that there is a decrease of about 76% in the production of SCFA post-transplantation²⁸. Moreover, it appears to take about two months post HSCT to recover the microbiota ecosystem and its metabolic capacity²⁸. In some cases, dysbiosis remains up to one year post-transplantation⁴⁵.

There are already ways to assess the "health" of the gut microbiota, through biomarkers such as urinary 3-*indoxyl sulfate* (3-IS). 3-IS is a product of tryptophan degradation by commensal bacteria that inhabit the intestine and appears to be a predictor of intestinal GVHD^{10,46}. Furthermore, low levels of 3-IS up to 10 days post-HSCT are associated with higher HSCT-related mortality and worse overall survival, with high levels of 3-IS being correlated with Clostridiales while low levels are associated with the Bacilli class⁴⁷.

As for the strategies that could help in the maintenance or recovery of the microbiota during transplantation, studies suggest the rational use of antibiotics, as well as the possibility of fecal transplantation and use of probiotics^{29,35,44,48-50}.

MICROBIOTA AND GVHD

There seem to be differences in the composition and diversity of the microbiota of patients who develop GVHD when compared to those who do not^{28,51,52}, and GVHD may be related to the loss of the protective effect of commensal bacteria^{10,12}.

One of the possible mechanisms for the alteration of the microbiota in GVHD is via Paneth cells. These cells, located in the intestine, which have a regulatory function through the expression of alpha-defensins, which result in the death of non-commensal bacteria and preservation of commensal bacteria, seem to be the target of GVHD⁵³. The damage caused to Paneth cells would lead to the reduction of alpha-defensins, altering the normal intestinal environment^{53,54}, making such cells another focus for approaches to preserve or recover the microbiota⁵⁵. It is known that the intestinal expression of several antimicrobial peptides is reduced in the presence of acute GIT GVHD and is associated with dysbiosis⁵⁶.

With the microbiota in dysbiosis, there is a growth in pathogenic bacteria such as the *Enterococcus* spp. And, consequently, a higher risk of bacteremia^{10,12}. In the presence of GIT GVHD, there appears to be an even greater risk of bacteremia caused by enteric bacteria⁵⁷. In addition, a study showed a higher incidence of transplant-related mortality in patients with acute GI GVHD who developed blood infection by enteric bacteria⁵⁸. Relatively recent studies have indicated that the diversity of the gut microbiota during the grafting period is associated with acute GVHD^{59,60}.

A study with pediatric patients found in the pre-transplant analysis that patients who did not develop GVHD had a greater abundance of propionate-producing Bacteroidetes (a SCFA), that were persistent after HSCT-induced microbiota changes²⁸. In a study with adult patients, the pre-transplantation analysis of those who had GVHD had significantly greater abundance of the Firmicutes phylum and a lower tendency for Bacteroidetes when compared to those who did not have GVHD⁴². Studies also suggest the influence of the donor's microbiota on the development of GVHD^{59,61}.

An animal model study showed that, in the acute phase of intestinal GVHD, there is a shift in favor of bacteria from the most pro-inflammatory species, the Enterobacteriaceae family, while there is a decrease in *Lactobacilli*, *Clostridia*, *Bifidobacteria*, and *Bacillus* spp., indicating that, in acute intestinal in-

flammation, there is an alteration in the intestinal flora, as well as a decrease in its diversity⁶².

In humans, an association of bacterial microbiota diversity with the development of GVHD in pediatric patients has already been found⁶³, with GVHD-related mortality in adult patients⁶⁴. Also, the genus *Blautia* would be associated with the development of GVHD when in small quantity⁶³, with lower GVHD-related lethality and better overall survival when in abundance⁶⁴.

Regarding genetic aspects, the *fucosyltransferase-2* (FUT2) gene, which regulates the expression of the H antigen, was evaluated in HSCT patients for its relationship with the gut microbiota, since the ABH antigens in the mucosa serve as a source of energy for the bacteria and adhesion receptors for many microbes. FUT2 genotype seems to influence the risk for bacteremia and GVHD in such patients. However, the authors emphasize that there are several other factors that influence the diversity of the microbiota and can interfere with post-HSCT outcomes, such as the use of antibiotics⁶⁵ previously mentioned.

The use of antibiotics that target intestinal bacteria as prophylaxis in HSCT has already been associated with the severity of acute GVHD of GIT organs and liver, as well as impacted on overall survival in a retrospective study with 500 patients⁶⁶. In this same study, the incidence of GIT GVHD was twice as high in the group that received antibiotics compared to those that did not⁶⁶.

Differences in the activity spectrum of antibiotics could influence the frequency and severity of GVHD, and the use of antibiotics that preserve anaerobic commensal bacteria could reduce the risk and incidence of GVHD^{67,68}. However, there may be differences in antibiotic use and between populations in terms of microbiota, since, in a study with Japanese patients undergoing allogeneic HSCT, the use of fourth generation cephalosporins was associated with the development of GVHD, while piperacillin tazobactam was not⁶⁹, a result that is different from the one found in a sample of American patients⁶⁷. In addition, use of carbapenem for more than seven days has also been associated with risk of intestinal GVHD⁷⁰.

Routy *et al.* point out that, in addition to the epithelial damage caused by conditioning, the use of prophylactic antibiotics or in episodes of febrile neutropenia, fasting and the use of parenteral nutrition also influence the change in the composition and di-

versity of the microbiota⁶⁶. The stimulus for oral and enteral ingestion, as well as the use of less intense conditioning, when possible, could help in the preservation of bacteria that seem to be favorable, such as those of the genus *Blautia*, as discussed by Jenq *et al.* in their paper published in 2015⁶⁴.

PROBIOTICS AND HSCT

The use of probiotics has already been shown to be beneficial in several clinical situations, such as in the prevention and treatment of diarrhea associated with the use of antibiotics, inflammatory bowel diseases, and *Clostridium difficile* infection. Its use seems to favor the intestinal-related immune response. But the safe use of probiotics in immunosuppressed patients is still uncertain.

Cases of negative events in post-HSCT patients related to microorganisms that are used as probiotics are described in the literature. There is a case report of meningitis in a pediatric patient with acute lymphoblastic leukemia after allogeneic transplantation whose microorganism was identified as *Lactobacillus rhamnosus*. In such case, there was no known probiotic consumption. However, the authors are aware that the use of some antibiotics and the presence of such microorganisms as part of the normal microbiota may be related to the development of infections in these patients, even if there is no consumption of the probiotic itself⁷¹.

On the other hand, there are cases of sepsis in HSCT patients directly associated with the consumption of probiotic yogurts with *Lactobacillus acidophilus*⁷² and *Lactobacillus rhamnosus*⁷³. However, in both cases the patients consumed the probiotic post-transplantation, in large amounts in the first case (6-8 units of yogurt daily) and at times of severe neutropenia, in addition to being two isolated case reports.

However, infections by microorganisms that are used as probiotics seem to be less frequent in HSCT patients⁷⁴. A retrospective study with a cohort of 3796 patients evaluated episodes of bacteremia/sepsis caused by *Lactobacillus*, *Bifidobacterium*, *Streptococcus thermophiles*, and *Saccharomyces* in up to one year post-transplantation, without evaluating whether there was consumption of probiotics, and found only 0.5% of cases, most of them in allogeneic

HSCT patients (71%) caused by *Lactobacillus* and within the first 100 days post-transplant.

The safety of using probiotics in such patients, as can be seen, is still controversial. In this sense, Ladas *et al.* carried out a pilot study to verify the safety and viability of the probiotic *Lactobacillus plantarum* in children and teenagers undergoing allogeneic HSCT from D-7 or D-8 to D+14, and found that there were no adverse effects related to the use of the probiotic, suggesting that this probiotic would be safe to use for these patients¹⁵.

But an observational study published in 2012 evaluated nutritional habits of patients before transplantation and found a negative correlation between yogurt intake and episodes of febrile neutropenia⁷⁵.

Regarding the relationship between the use of probiotics and GVHD, this review found a randomized clinical trial that used *Lactobacillus rhamnosus* GG in capsules at the time of grafting and followed the development of GVHD in such patients. This study showed that the use of the probiotic was safe, but there was no difference in the incidence or degree of GVHD, nor evidence of significant changes in microbiota diversity⁷⁶.

Therefore, we can conclude that there is a need for further studies to understand how changes in the microbiota can interfere with the host's health and alter the development of GVHD⁷⁷, in addition to the importance of testing other probiotics in different moments of transplantation, since there are still no validated methods or approaches for the effective preservation of the microbiota⁷⁸.

However, there is a lot of evidence, including genomic ones, that demonstrate the predictive role of the gut microbiota as a biomarker for GVHD, in addition to the significant relationship with other negative outcomes in the presence of dysbiosis. Thus, the modulation of the gut microbiota through methods such as the use of prebiotics, adequate use of antibiotics, fecal microbiota transplantation when applicable, and the use of probiotics are still controversial approaches, whose possible positive results deserve to be explored due to the potential for improvement in post-HSCT results and due to their relationship with the development of GVHD^{46,79-83}.

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