Safety and Benefit of Using Probiotics in Patients Undergoing HSCT: Integrative Review

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Segurança e Benefício do Uso de Probióticos em Pacientes Submetidos ao TCTH: Revisão Integrativa

Seguridad y Beneficio del Uso de Probióticos en Pacientes Sometidos al TCTH: Revisión Integradora

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Abstract

Introduction: Hematopoietic stem cell transplantation (HSCT) is one of the potential curative treatments used for patients with hematological and other immune diseases. During transplantation, the patient undergoes conditioning and other treatments, such as radiotherapy and chemotherapy, which may cause loss of the intestinal microbiota diversity. The manipulation of the intestinal microbiota with probiotics has been pointed out as a strategy to prevent complications in patients undergoing HSCT. **Objective**: To identify if there is scientific evidence related to the safety and benefits of the use of probiotics in patients submitted to HSCT. **Method**: Integrative review based on studies addressing the use of probiotics for the specific case of patients undergoing HSCT published between 2000 and 2018. **Results**: Five studies that met the inclusion and exclusion criteria were eligible, with a total of 52 patients. The use of probiotics in the prevention and/or treatment of diarrhea has shown positive results in patients with antibiotic-induced diarrhea or bacterial infections, but the studies do not yet emphasize the benefits of using probiotics in the specific case of patients submitted to HSCT. Few studies show the use of probiotics to help the improvement of the symptoms associated to infections or bacteremia in immunosuppressed patients. **Conclusion:** The use of probiotics in the population submitted to HSCT and immunosuppressed is still controversial, and further studies are necessary to demonstrate the benefits of using probiotics for this public.

Key words: Probiotics; Hematopoietic Stem Cell Transplantation; Immunocompromised Host; Gastrointestinal Microbiome; Immunity.

Resumo

Introdução: O transplante de células-tronco hematopoiéticas (TCTH) é um dos potenciais tratamentos curativos utilizados para pacientes com doenças hematológicas e outras doenças imunes. Durante o transplante, o paciente é submetido ao condicionamento e a outros tratamentos, como radioterapia e quimioterapia, o que pode causar a perda da diversidade da microbiota intestinal. A manipulação da microbiota intestinal com probióticos vem sendo apontada como uma estratégia de prevenção de complicações nos pacientes submetidos ao TCTH. **Objetivo:** Identificar se há evidências científicas relacionadas à segurança e aos benefícios da utilização de probióticos em pacientes submetidos ao TCTH. **Método:** Revisão integrativa com base em estudos que abordassem o uso de probióticos para o caso específico de pacientes submetidos ao TCTH publicados entre 2000 a 2018. **Resultados:** Foram selecionados cinco estudos que atenderam aos critérios de inclusão e exclusão, com um total de 52 pacientes. A utilização de probióticos na prevenção e/ou tratamento da diarreia tem mostrado resultados positivos em pacientes com diarreia induzida por antibióticos ou por infecções bacterianas, porém os estudos ainda não destacam benefícios no uso de probióticos no caso específico de pacientes submetidos ao TCTH. Poucos estudos mostram o uso de probióticos para auxílio na melhora dos sintomas associados a infecções ou bacteremias em pacientes imunossuprimidos. **Conclusão:** O uso de probióticos na população submetida ao TCTH e em imunossuprimidos ainda é controverso, sendo necessários mais estudos que demonstrem os benefícios no uso dessa estratégia para esse público.

Palavras-chave: Probióticos; Transplante de Células-Tronco Hematopoéticas; Hospedeiro Imunocomprometido; Microbioma Gastrointestinal; Imunidade.

Resumen

Introducción: El trasplante de células madre de las hematopoyéticas (TCTH) es uno de los posibles tratamientos curativos utilizados para pacientes con enfermedades hematológicas y otras enfermedades inmunes. Durante el transplante, el paciente es sometido al condicionamiento ya otros tratamientos, como radioterapia y quimioterapia, lo que puede causar la pérdida de la diversidad de la microbiota intestinal. La manipulación de la microbiota intestinal con probióticos viene siendo apuntada como una estrategia de prevención de complicaciones en los pacientes sometidos al TCTH. **Objetivo**: Identificar si hay evidencias científicas relacionadas con la seguridad y beneficios de la utilización de probióticos en pacientes sometidos al TCTH. **Método**: Revisión integradora basada em estúdios que abordan el uso de probióticos para el caso específico de pacientes sometidos a TCMH publicados entre 2000 y 2018. **Resultados**: Fueron elegibles 4 estudios que atendieron a los criterios de inclusión y exclusión, con un total de 52 pacientes. La utilización de probióticos en la prevención y/o tratamiento de la diarrea ha mostrado resultados positivos en pacientes con diarrea inducida por antibióticos o por infecciones bacterianas, pero los estudios aún no aportan beneficios en el uso de probióticos en pacientes sometidos al TCTH. Pocos estudios muestran infecciones o bacterias en pacientes inmunosuprimidos que utilizaron probióticos para ayudar en la mejora de los síntomas asociados al tratamiento. **Conclusión**: El uso de probióticos en la población sometida al TCTH e inmunosuprimidos aún es controvertido, siendo necesarios más estudios que comprueben los beneficios en el uso de probióticos para este público.

Palabras clave: Probióticos; Trasplante de Células Madre Hematopoyéticas; Huésped Inmunocomprometido; Microbioma Gastrointestinal; Inmunidad.

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INTRODUCTION

Hematopoietic stem-cells transplantation (HSCT) is one of the potential curative treatments utilized for patients with malignant hematologic diseases and other diseases[1]. In the pre-HSCT period, the patient is submitted to the regimen of conditioning and other treatments such as chemotherapy and radiotherapy that has the finality of eradicating the residual disease[2], depleting the malignant or defective cells as well as healthy cells[1]. In this period, loss of diversity of the intestinal microbiota occurs, which is being indicated as an important factor of increasing the morbidity and mortality post-HSCT[3]. Studies suggest that, during the period of neutropenia, the species present in the intestinal microbiota decrease approximately 30% as compared to the pre-HSCT period[4].

Current studies have indicated that the manipulation of the intestinal microbiota with probiotics could be beneficial in patients submitted to HSCT to reduce the morbidity caused by the loss of the microbial diversity[4]. However, the manipulation of the intestinal microbiota with probiotics can be risky for these patients considering the intense immunosuppression they are submitted to[5]. Taking into consideration the above, the present review had the objective of identifying the current scientific evidences related to the safety and benefit of using probiotics in patients submitted to HSCT.

METHOD

This study was elaborated as an integrative literature review and was developed according to the following stages: elaboration of a guiding question, definition of the descriptors for the literature search, search in the databases, exclusion of repeated articles, definition of the inclusion and exclusion criteria, analysis and interpretation of the results. The guiding question was: "Is the use of probiotics safe for immunosuppressed patients submitted to HSCT?".

The descriptors utilized in the search were defined after consultation to the Descriptors of Sciences of Health (DeCS): Probióticos/*Probiotics*, Transplante de Células-Tronco Hematopoéticas/*Hematopoietic Stem Cell Transplantation*, Hospedeiro Imunocomprometido/*Immunocompromised Host*, Microbioma Gastrointestinal/*Gastrointestinal Microbiome* and Imunidade/*Immunity*. After the definition of the descriptors, the search was conducted in the databases of Latin American and Caribbean Health Sciences Literature (LILACS) and MEDLINE/PubMed, in English in PubMed and in Portuguese in LILACS. The descriptor probiotics was associated to the descriptors hematopoietic stem-cells transplantation, immunocompromised host, gastrointestinal microbiome and immunity.

The inclusion criteria were articles published between 2000 and 2018, patients submitted to HSCT and intervention with probiotic strains. The exclusion criteria for the selection of the articles were: patients submitted to other types of transplantation, studies with animals and review articles.

Although this literature review could not be characterized as a systematic review, the flowchart of eligibility (Figure 1) was elaborated according to the method PRISMA (main items to report systematic reviews and meta-analyses) to facilitate the understanding of how the selection of articles was organized. This method consists in a flowchart developed in four stages to determine the eligibility of the articles[6].

RESULTS

The selection of the articles available, according to the inclusion and exclusion criteria resulted in 118 articles.

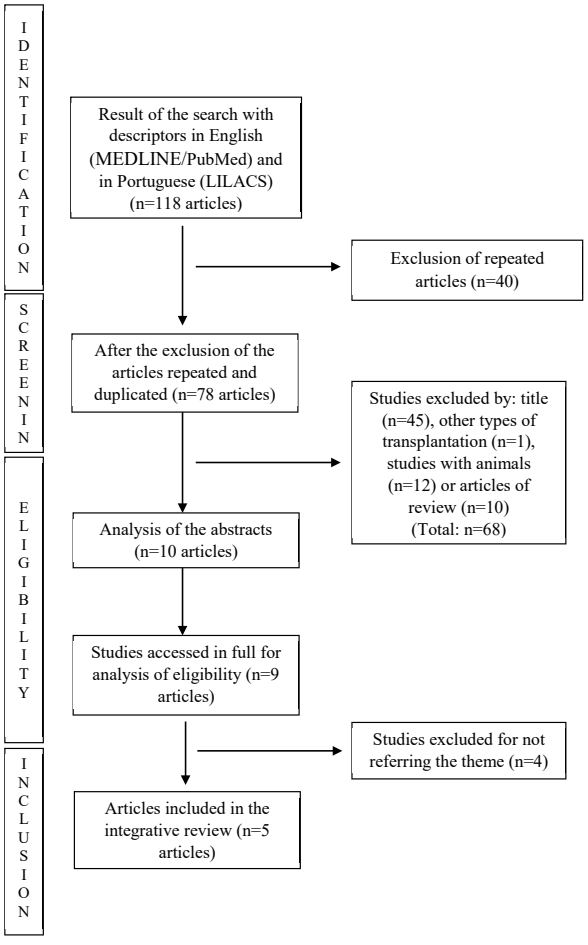

Figure 1. Flowchart of selection of the studies adapted by the method PRISMA

Of these 118 articles, resulting from the search including all the keywords, 40 articles were repeated and then, excluded. This first stage resulted in 78 articles. Of these, those articles where the title was not related to the theme (n=45), that referred to other types of transplantation (n=1), studies with animals (n=12) or review articles (n=10) were excluded, remaining ten articles. The abstracts of these ten articles were read and five articles were excluded because they failed to reference the theme (4) or were unavailable in full (1), remaining five articles for reading. The year of publication of each study analyzed, authors, participants, study design and results are listed in Table 1[7-9,3,10].

Of the articles eligible for analysis, 52 patients were evaluated within the age range of eight months and 69 years old. The origin country of the 52 patients were the United States of America and Italy. Two patients were submitted to autologous HSCT and the others, to allogeneic.

Three studies were case report, one, retrospective cohort and one, clinical trial.

In the case report of Cesaro et al.[7], about an eight years old child with diagnosis of acute myeloid leukemia (AML), the patient was neutropenic in chemotherapy treatment and receiving probiotic tablets with *S. boulardii* strain for prevention of diarrhea associated to antibiotics. After the termination of the second cycle of the chemotherapy, the patient was neutropenic and febrile. The *S. boulardii* strain was isolated from the central venous catheter (CVC) and the administration of the probiotic was suspended. After the removal of the CVC, although the patient was still neutropenic, there was no more report of fever. The patient continued with chemotherapy and was submitted to HSCT. The utilization of *Saccharomyces boulardii* strains may not be safe because studies demonstrated that some probiotic strains present strong adherence to the intestinal mucosa, which leads to the increase of the risk of bacterial translocation, among them the *S. boulardii* strains. It is important to mention that this is not among the species approved by the Brazilian Health Regulatory Agency (ANVISA) for utilization[11]. A study conducted by Wada et al.[12] evaluated 42 patients submitted to chemotherapy with malignant diseases who were neutropenic or not. The patients were divided in two groups, one received the probiotic strain *Bifidobacterium breve* and, the other, placebo. The administration of the probiotic and of the placebo initiated two weeks before the protocol of chemotherapy and continued along six weeks. The utilization of parenteral antibiotic and the frequency and duration of the fever were lower in patients who used probiotic. There was no difference between the groups in relation to the use of oral antibiotic, counting of bacteria and frequency of diarrhea. The authors justified there was no difference in the frequency of diarrhea because the dose utilized of the probiotic (10^4-10^6 colony forming units (CFU)/g) was not sufficient to compensate the changes in bacterial flora induced by chemotherapy.

In the case report of Mehta et al.[8], t the case of a 69 years old patient with diagnosis of mantle lymphoma, stage III, who developed sepsis associated to the excessive consumption of yogurt enrichened with probiotics of the specie *Lactobacillus acidophilus* was described. The patient was submitted to autologous HSCT and developed severe mucositis, vomiting, diarrhea, enterorrhagia acute and chronic inflammation and there was growth of *Lactobacillus acidophilus* in the blood culture. The patient's report evidenced the consumption of six to eight yogurt cups daily enriched with strains of *L. Acidophilus*. The infection was resolved after the interruption of the intake of yogurt, without changing the antibiotics. The *Lactobaccilus* can be present in food as yogurts, cheeses, sauerkraut and other fermented food. Cases of infection and complications are quite rare when using *Lactobacillus*, but the immunosuppressed patients are more vulnerable to infections[13].

Cohen et al.[9] evaluated the occurrence of blood flow infections caused by probiotics in patients submitted to HSCT in a Seattle, Washington center. The database of this center was reviewed from 2002 and 2011. The patients were advised to eat food that potentially contained probiotics as yogurts. It was considered infection of the blood flow when the patient had at least one positive blood culture for species of *Lactobacillus*, *Bifidobacterium*, *Streptococcus thermophiles* and *Saccharomyces* in the period of one year after HSCT. The deaths were considered attributable to the probiotic in case they would have occurred 14 days from the isolation of one probiotic strain in culture and if the patients had compatible previous signs or symptoms. A total of 3,796 patients were eligible for evaluation. Of these, 19 patients (0.5%) developed infection of blood flow within one year after HSCT. Of the 19 patients, 18 had bacteremia related to *Lactobacillus*, which occurred in average 84 days after HSCT. In addition, 17 had only one positive culture, but one patient presented prolonged bacteremia for *Lactobacillus* (25 consecutive positive cultures) and other, prolonged fungemia by *Saccharomyces* (5 consecutive positive cultures). Eight patients (44%) were diagnosed with intestinal graft versus host disease (GVHD) before the development of bacteremia. Of the 17 patients with only one positive culture, four presented symptoms and fever was the most common symptom. Serious infectious complication were not reported and no mortality was attributed to these infections. The authors emphasized

Chart 1. Description of the studies utilized in this review

Author/ Year	Public	Neutropenia	Type	Strains/Mode of administration / Dose	Time of follow up	Period of administration	Medium of identification of strains	Benefits	Symptoms associated	Results/Resolution
Casaro et al.[7], 2000	Infant, 8 months	Yes	Case report	*Saccharomyces boulardii* Administration through oral tablets. Without information of dose	Without information	Pre-HSCT	CVC	Without information	Fever	After the patient presented fever, strain of *S. boulardii* was isolated in CVC and the administration of the probiotic was suspended. After removing the CVC, the patient, although neutropenic, had no more report of fever. Concluded the chemotherapy cycle and underwent HSCT with his brother
Mehta et al.[8], 2013	69 years old man	Yes	Case report	*Lactobacillus acidophilus* Oral administration 6 to 8 cups of yogurt daily. Without information of dose	Without information	From D+10	Blood culture	Without information	Mucositis, vomiting and diarrhea	Patient developed sepsis associated to the excessive intake of yogurt enrichened with probiotics. Infection resolved after interrupting the intake of yogurt without changing the antibiotics. No serious adverse events
Cohen et al.[9], 2016	3,796 patients submitted to HSCT from 2002 to 2011, being included 19 patients who had positive blood cultures	Without information	Retrospective cohort	*Lactobacillus* and *Saccharomyces* Without information about mode of administration. Without information of dose	1 year after HSCT	Without information	Blood culture	Without information	Fever	Of the 19 patients, 18 had *Lactobacillus* related infection. Of these, 17 had only one positive culture and 1 had prolonged bacteremia by *Lactobacillus* (25 positive cultures). The other participant presented fungemia by *Saccharomyces* (5 consecutive positive cultures). No serious complication was reported, and no mortality was attributed to any infection
Ladas et al.[3], 2016	30 infants and adolescents between 2 and 17 years old	Yes	Clinical trial	*Lactobacillus plantarum* Oral or enteral administration 10^8 CFU	4 years post-HSCT	D- 7 or -8 until D+14	Blood culture	None of the patients developed acute GVHD of skin or liver grade 4 or acute GVDH of intestine grade 4	Without information	Results showed feasibility and safety using *L. plantarum*, no report of bacteremia or death related to the use of L. plantarum or serious adverse events
Koyama et al.[10], 2018	54 years old man	Yes	Case report	*Lactobacillus rhamnosus* Oral administration through yogurt enrichened with the strain Without information of dose	Without information	D0 until D+6	Blood culture	Without information	Persistent fever and diarrhea Further, the patient had confusion and dysfunction of multiple organs, indicating shock	Patient presented bacteremia after intake of enrichened yogurt with probiotic strains. After persistent fever and dysfunction of multiple organs associated to mental confusion, he was diagnosed with shock. After changing the antibiotics, in D+17, fever and diarrhea were resolved, the patient improved his condition gradually and was discharged

Captions: CVC: Central Venous Catheter; GVHD: Graft *versus* host disease; HSCT: Hematopoietic Stem-Cells Transplantation; CFU: Colony Forming Units.

that the development of bacteremia in the patients studied was less frequent and that, for those who develop it, no death was directly attributed to this. Most of these events occurred before D+100, period when the immunosuppression peak occurs. The authors concluded that the probiotic incorporated to food products appear to be a rare cause of blood flow infection and are associated to low mortality.

In the study conducted by Ladas et al.[3], strains of *L. plantarum* were applied with probiotic purpose in 30 children and adolescents from 2 to 17 years old evaluated during four years. These patients received 1 x 10^8 CFU, orally from D -8 or -7 until D+14. There were no reports of bacteremia or serious adverse events related to the use of this *Lactobacillus* in this intervention. Three patients included in the study died before D+100, however, none of the deaths was related to the use of probiotics. Still in this study, it was verified that 70% of the patients did not develop acute intestinal GVHD until D+100, which could be a benefit of the administration of probiotics Although the results were safe and viable, the authors reinforced the recommendation of not using probiotics routinely based in the results of their study.

The study of Koyama et al.[10] describes the case of a male patient, 54 years old, with promyelocytic leukemia. The patient had complete remission of the disease followed by high dose chemotherapy and later autologous HSCT. Severe diarrhea occurred since D0, further to the utilization of cefepime, and the patient, voluntarily, utilized yogurt enrichened with *L. rhamnosus* until D+6. Each yogurt cup contained more than 14 billion of CFU. In D+8, the patient had high fever, in addition to persistent severe diarrhea with negative identification of *C. difficile* in the stools. In D+10, in addition to fever and diarrhea, the patient presented mental confusion and multiple dysfunction of organs, indicating shock. After administration of high doses of ampicillin, in D+17, fever and diarrhea were resolved, the general condition of the patient improved, and he was discharged.

DISCUSSION

The available studies that evaluated the use of probiotics in patients submitted to HSCT are scarce and, so far, do not allow the elaboration of a systematic review. Therefore, given the relevance of the theme, we conducted an integrative review with a more comprehensive analysis of the theme in order to offer input for future controlled clinical trials.

To be considered a probiotic, a microorganism needs to meet some conditions: 1) to come from human source, to be recognized by the intestinal immune system also known as gut-associated lymphoid tissue (GALT) as natural component of the human microbiota; 2) do not present pathogenicity (must be beneficial to the intestine and not stimulating diseases); 3) to be resilient to the process of production of food; 4) to be viable after contact with the gastric juice and bile; 5) to present adherence to the intestinal epithelial cell; 6) to be able to persist in the gastrointestinal tract; and 7) to influence the local metabolic activity[5]. In addition to this characterization, the use of probiotics must be approved by the regulatory sanitary agencies whose established assessment criteria may vary among countries.

After updating the norms previously approved, ANVISA[11] currently approves the following species proven beneficial to the human being: *Bacillus coagulans* GBI-30, *Bifidobacterium lactis* HN019 and *Lactobacillus reuteri* DSM 17938. It can be noticed that, from the studies analyzed in this review, none strain would be suitable to the Brazilian population, due to the lack of national scientific data that justify its use. Considering that yogurts and other products with probiotics are widely available to consumers, the article brings a perspective of risk by the unguided use of these products.

Bacteremia associated to the use of probiotics, especially in patients immunosuppressed is a risk and as shown in the study of Koyama et al.[10], septicemia caused by voluntary intake of yogurts available commercially led to a shock condition. Therefore, not only the benefits, but the risks from the use of probiotics are relevant factors to be pondered in relation to the administration of probiotics for patients submitted to HSCT. Overall, probiotics are considered safe, having in mind its wide utilization by the food industry. Nonetheless, some serious effects are reported as infections or even sepsis[13].

Another risk associated to the use of probiotics was referenced in the case report of Cesaro et al.[7] in what crossed contamination in the CVC was presented. In a review that identified cases of bacteremia by *Saccharomyces boulardii*[14] until 2007 it was observed that the patients affected were those in use of CVC. In addition, although some patients did not utilize compounds based in *S. boulardii*, they had contact with patients who did, therefore, the contamination may have occurred through the hands of the caretakers or through the air while opening sachets or capsules.

The results encountered in the literature are still controversial in relation to the use of probiotics in immunocompromised patients. In a study conducted by Esaiassen et al.[15] bacteremia was observed in immunocompromised pediatric patients who utilized strains of *Bifidobacterium*. In a study performed by Wolf et al.[16] with HIV-positive immunocompromised patients

the use of *Lactobacillus reuteri* was safe and well tolerated, no medical complication occurred during the use of probiotics, however, there was not significant reduction of the number of diarrheic evacuations in these patients. It is important to emphasize that the neutropenia that occurs in patients submitted to HSCT should be taken into account when considering the use of probiotics.

In a systematic review conducted by Wei et al.[17], 12 studies with 1,554 participants were analyzed and the authors concluded that there are limited evidences to support the use of probiotics for the prevention or treatment of radiotherapy-related diarrhea (with or without chemotherapy). The studies included presented low impact and high heterogeneity, even considering that serious adverse event were not observed. It is worth mentioning that this systematic review addressed studies with patients in use of radiotherapy for cancer treatment and that the clinical condition of the patients submitted to HSCT, object of the present review, is singular, since the patients are submitted to an intense regimen of conditioning, which leads to a more aggressive immunosuppression in relation to the treatment of cancer in general .

The only clinical trial conducted with neutropenic patients submitted to HSCT based in the criteria of this integrative review was the study of Ladas et al.[3], when probiotics were utilized either orally or enterally and the use has shown to be safe. Although no patient has developed GVHD of the skin or liver grade 4 or acute GVHD grade 4, it was not clear whether in this study, the use of probiotic strains would be beneficial. In addition, the study presented some limitations as the lack of a control group, blinding and reduced number of participants. In April 2014, the inclusion of patients who were using levofloxacin and other probiotics was approved, and these criteria may have compromised the quality of the study and its results.

Lactobacillus plantarum, utilized in the work of Ladas et al.[3], has been utilized in large scale in intestinal infections and in reducing the risk of diarrhea associated to the use of antibiotics[7]. A review performed by Hemaiswarya et al.[18] showed that the use of *L. plantarum* is related to the modulation of the intestinal microbiota and the integrity of the epithelium. In addition, it is involved in the exclusion of pathogens and secretion of antimicrobial peptides.

In other studies, including the prospective study of Cohen et al.[9], the symptoms related to the use of probiotics were reported as: fever, vomiting and diarrhea, although they may have not been associated to the use of this product. In the work of Cohen et al.[9], a greater number of individuals was evaluated, however, the lack of some important information to understand the intervention limits its critical analysis. For instance, it was not possible to identify whether the patients were neutropenic, the period of utilization of probiotics or products containing probiotics as well as the dose and route of administration.

Another key aspect to emphasize is that it was not possible to identify in the literature a homogeneity of the methodologies adopted for the scientific design and the specificity for patients submitted to HSCT. More often, the studies available are studies with patients in chemotherapy or immunosuppressed unrelated to the conditioning for transplantation and, in these cases several species of bacteria or mixtures of species in diverse quantities were administered in diverse frequencies and with no clear limit of daily ingestion. In addition, the clinical characteristics of the patients can be quite heterogeneous, making it even more difficult to establish a protocol to be utilized in clinical trials and to achieve the goal of defining the safe use of probiotics.

Overall, the quantity proposed for the administration of probiotics in order to be beneficial to health is five billion ($5x10^9$) of CFU per day, at least for five days, although some studies that evaluate the benefic effects of the use of probiotics recommend doses between 10^6 to 10^9 CFU[17].

The studies of Ladas et al.[3], Mehta et al.[8] and Cesaro, et al.[7], that informed the periods when the probiotics were administered (D -8 or -7; D+10 and pre-HSCT, respectively), are compatible with the period proposed to benefit the patient. In Brazil, the minimum daily number of probiotics is determined as 10^8 to 10^9 CFU per day[14] for healthy population. Nonetheless, as mentioned, because of the paucity of studies with immunosuppressed patients that underwent HSCT, it is uncertain to affirm the safe dose to use for this public.

Two aspects can be highlighted: the beneficial clinical effect of the use of probiotics and the safety of its use in patients immunosuppressed. In the articles evaluated in this review, the benefits of the utilization of probiotics in patients submitted to HSCT were not clear. Regardless of the formulation to be used, a key point in the administration of the strains is the safe handling of probiotics. It is recommended the use of gloves for handling, preparation, and administration of probiotic strains. The gloves must be discarded after using and hands washing. This practice aims to minimize the exposure of other patients to the probiotic strains. In addition, healthcare professionals should be aware of the risk of contamination through the CVC and peripheral accesses while probiotics are being manipulated. The opening of sachets containing the strains should be done far from the patients in a contained space to avoid formation of aerosol

of spores and contamination of sterile places. Therefore, it is recommended that capsules instead of sachets are used because of lower risk of contamination[19].

Even with the elaboration of an integrative review, the available articles were not sufficient to guide the understanding about the use of probiotics for patients submitted to HSCT; however, it is worth mentioning that it is a field for future studies to evaluate the effects and safety of probiotics in this case. Despite not being possible to indicate a position about the findings of the studies evaluated in this review, an important limitation of this methodology is the lack of risk analysis of bias of the studies encountered.

CONCLUSION

Although the use of probiotics in patients submitted to HSCT is a theme of current interest, the evidences are still scarce and it is not possible to identify risks and benefits, doses and mode of administration of probiotics

Serious adverse events or deaths resulting from the use of probiotics have not been found in the studies evaluated, however, it is worth to mention that there was a report of bacteremia in patients who used strains with probiotic finality. The benefits that, perhaps, have been observed in other populations of immunosuppressed individuals were not verified in the studies included in this review, therefore, more studies are necessary to verify the effects of the utilization of probiotics in patients submitted to HSCT.

CONTRIBUTIONS

Paola Dantas Pinheiro de Oliveira contributed for the conception, wording and final approval of the version for publication. Denise Johnsson Campos and Vaneuza Araújo Moreira Funke contributed for the conception, critical review with intellectual contribution and final approval of the version for publication. Sarah Mehl Coradi contributed for the wording and its final approval for publication. Regina Maria Vilela contributed for the study design, critical review with intellectual contribution and final approval of the version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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