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Determination of *Streptococcus* sp. and *Candida albicans* in the oral cavity of patients undergoing bone marrow transplantation.

Determinación de *Streptococcus* sp. y *Candida albicans* en la cavidad oral de pacientes sometidos a trasplante de médula ósea.

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Abstract: Introduction: Chemotherapy can lead to an imbalance in the ecosystem of the oral cavity, allowing the development of mucositis in the immunosuppression phase due to interaction with microbial agents. The objective of this study was to identify bacterial and fungal species that contribute to oral complications in patients undergoing marrow translantation and compare their susceptibility to various antimicrobial agents before and during the immunosuppression period. Material and Methods: This observational-longitudinal study was performed on 18 patients undergoing bone marrow transplantation from the Oncohematology Service of Sanatorio Allende (2018/2019), with buccal mucosa swabs before treatment (I) and mid-stage (M), fourteen days after transplantation. The samples were cultured in selective media for *Streptococcus* and fungal species and a susceptibility study was performed on Müller Hinton agar. Results: At (I), 82.30% of patients were found to be positive for *Streptococcus mutans*, 11.30% for *Streptococcus salivarius*, 5.50% for *Streptococcus sobrinus* and 9.40% grew mixed commensal microorganisms. At (M), 96.60% were positive for *Streptococcus mutans* and 23.10% for *Streptococcus salivarius*, without any growth of *Streptococcus sobrinus* or mixed microorganisms. In (I), a 27.00% incidence of *Candida albicans* was observed, while in (M) the incidence was 73.00%. The antibiotics to which the microorganisms were most sensitive in (I) were vancomycin (88.80%), amikacin (83.30%), amoxicillin + clavulanic acid (78.00%), ciprofloxacin (77.75%) and azithromycin (66.60%). In (M) sensitivity to amikacin was 92.30%, vancomycin, 76.90%; amoxicillin + clavulanic acid, 38.50%; azithromycin, 23.10%; and ciprofloxacin, 15.40%. A statistically significant prevalence of *Streptococcus mutans* was observed in comparison to other species. Conclusion: During the immunosuppression period, there was a significant increase in *Candida albicans*. The antibiotics to which the bacteria were most sensitive were amikacin and, to a lesser extent, vancomycin, showing significant resistance to ciprofloxacin, azithromycin and amoxicillin + clavulanic acid.

Keywords: *Streptococcus; Candida albicans; mouth; bone marrow transplantation; microbial sensitivity tests; drug resistance, microbial.*

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Resumen: **Introducción:** La quimioterapia podría conducir a un desequilibrio en el ecosistema de la cavidad oral, permitiendo el desarrollo de mucositis en la fase de inmunosupresión debido a la interacción con agentes microbianos. El objetivo de este estudio fue identificar especies bacterianas y fúngicas que inciden en las complicaciones orales en pacientes sometidos a trasplante de médula y comparar su susceptibilidad a diversos agentes antimicrobianos antes y durante el período de inmunosupresión. **Material y Métodos:** El estudio observacional-longitudinal se realizó en 18 pacientes sometidos a trasplante de médula ósea del Servicio de Oncohematología del Sanatorio Allende (2018/2019), con hisopado de mucosa bucal antes del tratamiento (I) y en etapa media (M), catorce días después del trasplante. Las muestras se cultivaron en medios selectivos para *Streptococcus* y especies fúngicas y se realizó un estudio de susceptibilidad en agar Müller Hinton. **Resultados:** En (I), se encontró que el 82,30% de los pacientes tenían desarrollo de *Streptococcus mutans*, el 11,30% *Streptococcus salivarius*, el 5,50% *Streptococcus sobrinus* y el 9,40% microbiota saprofita mixta. En (M), se demostró que el 96,60 % tenían desarrollo de *Streptococcus mutans* y el 23,10 % *Streptococcus salivarius*, sin desarrollar *Streptococcus sobrinus* ni microbiota mixta. En (I) se observó una incidencia de *Candida albicans* de 27,00%, mientras que en (M) la incidencia fue de 73,00%. Los antibióticos a los que los microorganismos fueron más sensibles en (I) fueron vancomicina (88,80%), amikacina (83,30%), amoxicilina + ácido clavulánico (78,00%), ciprofloxacina (77,75%) y azitromicina (66,60%). En (M) la sensibilidad a amikacina fue 92,30%, vancomicina, 76,90%; amoxicilina + ácido clavulánico, 38,50%; azitromicina, 23,10%; y ciprofloxacino, 15,40%. Se observó una prevalencia estadísticamente significativa de *Streptococcus mutans* en comparación con otras especies. **Conclusión:** Durante el período de inmunosupresión, hubo un aumento significativo de *Candida albicans*. Los antibióticos a los que las bacterias fueron más sensibles fueron la amikacina y, en menor medida, la vancomicina, mostrando una importante resistencia al ciprofloxacino, azitromicina y amoxicilina + ácido clavulánico.

Palabras Clave: *Streptococcus; Candida albicans; boca; trasplante de médula ósea; pruebas de sensibilidad microbiana; farmacorresistencia microbiana.*

INTRODUCTION.

The properties of the oral cavity are similar to those of other organs and it contains a natural microbiota with a characteristic composition and a dynamically balanced relationship.[1,2] Different factors can promote an imbalance of this ecosystem, and some bacteria, which usually behave like commensals, become pathogens. The absolute immunosuppre-ssion patients experience during bone marrow transplantation (BMT) generates transitory systemic changes.[3-5]

The changes analyzed under immunosuppressive conditions, along with other factors already described, would predispose the oral cavity to a loss of homeostasis. In previous studies, we reported severe changes in the behavior of the antioxidant battery and the salivary oxidative profile against the imbalance generated by oxidative substances during chemotherapy.[6]

Several reports describe modifications or possible alterations in the oral microbiome of patients undergoing high-dose chemotherapy, with contradictory results.[7-9] In the present study, we analyze some components of the oral microbiota in bone marrow transplantation patients, in order to identify possible alterations in some microbial species.

Also, we compare their susceptibility to various antimicrobial agents before and during the immunosuppression period.

MATERIALS AND METHODS.

An observational-longitudinal study was carried out in 18 patients with indications for autologous BMT at the Oncohematology Service of Sanatorio

Allende (Córdoba, Argentina) between March 2018 and March 2019.

The protocol was approved by the Ethics Committee of Sanatorio Allende in the framework of the SeCyT-UNC project entitled "Some factors that affect the pathophysiology of the salivary glands. Its impact on the oral cavity," dated 07/10/14.

Inclusion criteria

Patients who agreed to sign informed consent forms, were over 18 and under 70 years of age, had no prior history of radiotherapy treatment in the craniofacial region, had no head and neck tumors, and were not under psychiatric treatment were included. After signing the informed consent form, the medical history was obtained and the oral cavity was examined. Patients were instructed on the technique for carrying out routine dental hygiene. Before chemo-therapy, they were told to use a toothbrush suited to the characteristics of their dental condition and their periodontal needs.

They were advised to brush their teeth three times per day. In addition, rinsing with chlorhexidine gluconate 0.12% mouthwash was indicated three times per day.

Due to the risk of gingivorrhagia (low platelet concentration) during high-dose chemotherapy, patients were instructed to substitute the toothbrush with careful cleaning with cotton swabs to remove bacterial plaque. Chlorhexidine was also used three times per day.

At both stages, a team of dentists prepared for this purpose checked the adequacy of the patients' dental hygiene. The sample included 18 patients of which 11 were female and 7 were male. The average age was 43 years for men and 49 years for women.

During the conditioning period, the broad spectrum antibiotic ciprofloxacin was used in all patients with the purpose of decontaminating intestinal bacteria during the hospitalization course.

Collection of samples

A buccal mucosa swab specimen was obtained prior to treatment, considered the initial stage (I), and then repeated fourteen days after bone marrow transplantation, considered the middle stage (M).

Subsequently, *Streptococcus* spp and *Candida albicans*, were isolated and identified, culturing the samples in Mitis Salivarius Agar and CHROm agar *Candida* (Laboratorios W. Brizuela S.A.Córdoba, Argentina), selective media for *Streptococcus* (Figure 1A, Figure 1B, and Figure 1C) and yeast species (Figure 2A and Figure 2B). Gram staining was then conducted on bacterial colonies.

When we obtained mixed commensals, we proceeded to culture on trypticase soy agar and brain heart infusion agar. Subsequently, we took the samples from isolated colonies and subjected them to Gram staining. If the isolates were *cocci* or *bacilli*, we proceeded to subculture them on trypticase soy agar and brain heart infusion agar, while if they were yeasts, they were subcultured on Sabouraud agar.

Colonies were subcultured until individual colonies were obtained. Finally, we transferred the bacterial colonies to plates with salivarius mitis agar to identify the species to colony color. (Table 1)

The guideline considered for the analysis of *Streptococcus* was by the CLSI (Clinical and Laboratory Standards Institute).

Microbial sensitivity study

Microbial sensitivity tests were performed on all the bacterial cultures. Susceptibility to antimicrobial agents was studied *in vitro* on Müller Hinton agar (Figure 3).

Basal saliva collection and pH measurement

In these patients, pH of basal saliva was measured at both stages of treatment. Collection and analysis of the conditions for basal salivary samples were: Fasting or during the first or the second hour after breakfast, taking into consideration the circadian rhythm of salivary secretion, with patients at rest, in a sitting position and without speaking. Patients rinsed their mouths with distilled water.

Basal saliva accumulated in the oral cavity was collected for five minutes in a disposable plastic conical centrifuge tube previously weighed on a precision scale. Prior to bone marrow transplantation, patients were considered a control group.[10,11] The saliva was transferred in a hermetically sealed container with refrigerating gel at -5°C.

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Then it was centrifuged, and the pH was determined with a Hanna Instruments digital pH meter, calibrated weekly with Orion™ pH 7 Buffers. The samples were processed and analyzed in the Chair of Physiology's laboratory, School of Dentistry, National University of Córdoba (Argentina).

Statistical analysis

The statistical description of the qualitative data was carried out by comparing the frequency of percentages of individuals who developed changes due to an increase or decrease of bacterial/fungal species and of microbial sensitivity during the middle stage of treatment with the total number of subjects included.

The Fisher test was applied to evaluate the association between the initial and middle stages for each species studied considering all samples. A *p*-value of <0.05 was set for rejection of the null hypothesis. The results of the determination of basal saliva pH were analyzed by using the Student's t-test (*p*-value<0.05 for statistical significance).

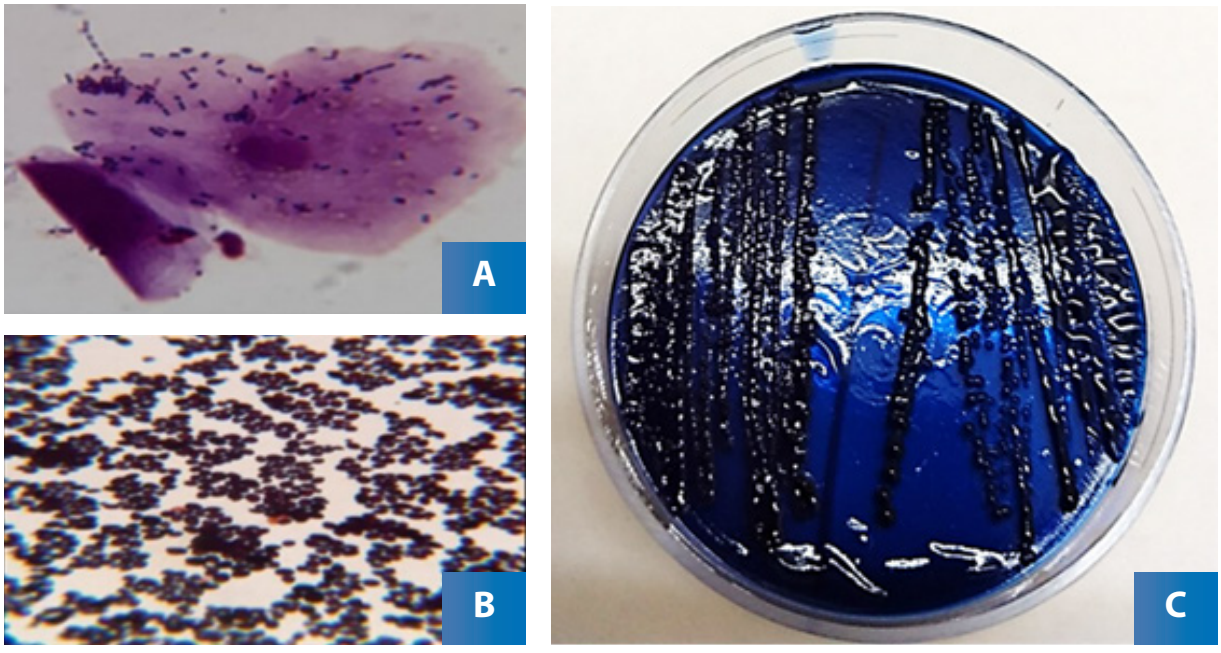
RESULTS.

The study sample consisted of 18 patients with a mean age of 46 years. Most were female (n=11). With regard to the diagnosis, there were eight cases of leukemia, six cases of lymphoma and four cases of multiple myeloma. No statistically significant differences were observed in the composition of the cultured microbiota of the patients according to the underlying pathology. Neither were there clinical lesions in the mucosa of the patients attributable to the microorganisms analyzed in the present study.

During stage I, 82.30% of the swab samples grew *Streptococcus mutans*; 11.30%, *Streptococcus salivarius*; 5.50% *Streptococcus sobrinus*; and 9.40%, mixed saprophytic commensals.

During stage M, 96.60% of the samples showed

Figure 1. Culture of samples of *Streptococcus* spp and *Candida albicans,* in Mitis Salivarius Agar and CHROM *Candida* agar (Laboratorios W. Brizuela S.A.Córdoba, Argentina).



A. Representative buccal mucosa cell obtained from a swab of a patient undergoing bone marrow transplantation (at middle stage). Note the *Streptococcus* infiltrate. Direct Gram staining. 100x magnification.
B. Gram staining of *Streptococcus* cultured on brain heart infusion agar, during both stages of treatment.
C. *Streptococcus* culture on mitis salivarius agar selective medium.

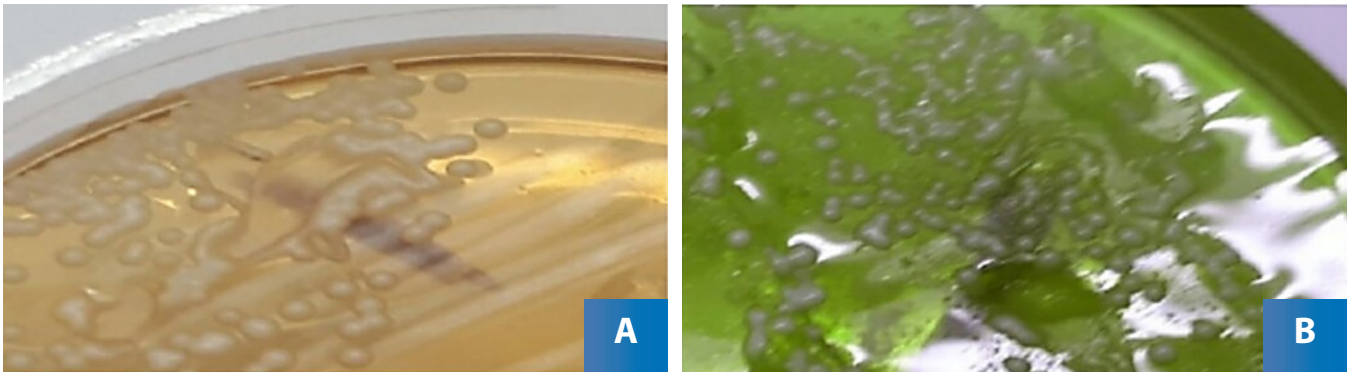
Streptococcus mutans and 23.10% *Streptococcus salivarius*, without developing *Streptococcus sobrinus* or mixed saprophytic commensals (Table 1).

With regard to the analysis of fungal species, at stage I, *Candida albicans* grew from 27.0% of the samples, while in M, the development of these microorganisms was significantly higher, corresponding to 73.00% of the samples (Table 2). With regard to the microbial sensitivity study, the antibiotics to which the bacteria were most sensitive in stage I were vancomycin (88.80%), amikacin (83.30%), amoxicillin + clavulanic acid (78.00%), ciprofloxacin (77.75%) and azithromycin (66.60%).

In stage M, microorganism sensitivity, in decreasing order, was 92.30% to amikacin, 76.90% to vancomycin, 38.50% to amoxicillin + clavulanic acid, 23.10% to azithromycin, and 15.40% to ciprofloxacin (Figure 3).

Salivary pH measurement: During stage I, the mean value of basal saliva pH of the patients undergoing

Figure 2. Gram stain on bacterial colonies.



A. *Candida albicans* on Sabouraud glucose agar. **B.** *Candida albicans* on CHROMagar *Candida*.

Figure 3. Microbial sensitivity at initial and middle stages of treatment in patients undergoing bone marrow transplantation.

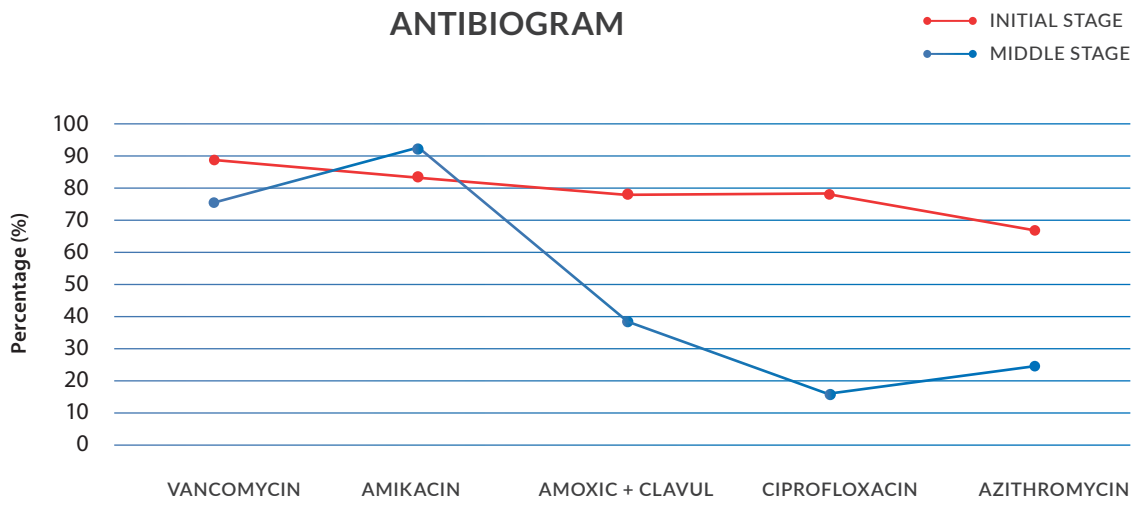


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Figure 4. Determination of the basal pH of saliva of patients undergoing bone marrow transplantation, at the initial and middle stages: $p<0.0001$ initial stage *versus* middle stage.

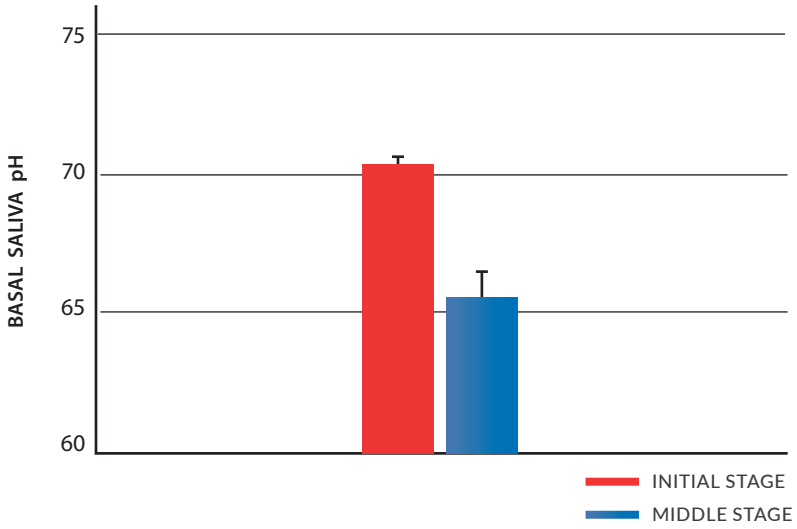

Table 1. Characterization of some initial and middle stage bacterial species of patients undergoing bone marrow transplantation.

Bacterial Species	Initial Stage (%)	Middle Stage (%)
Streptococcus mutans	82.30	96.60
Streptococcus salivarius	11.30	23.10
Streptococcus sobrinus	5.50	0
Mixed saprophytic commensals	9.40	0

Fisher test: *Streptococcus mutans*, *Streptococcussalivarius*, *Streptococcus sobrinus*, mixed saprophytic commensals: *p*-value: 0.0015; 0.0375; 0.0465 and 0.0114 respectively.

Table 2. Characterization of *Candida albicans* in initial and middle stages in patients undergoing bone marrow transplantation.

Fungal Species	Initial Stage (%)	Middle Stage (%)
Candida albicans	27.00	73.00
Mixed saprophytic commensals	9.40	0

Fisher test: *p*-value: 0.0001.

BMT was 7.05± 0.11. In stage M, after conditioning by high-dose chemotherapy and transplantation, there was a significant decrease in pH, with a mean value of 6.60 ± 0.33 (p<0.0001) (Figure 4).

DISCUSSION.

Chemotherapy is a type of systemic treatment that inhibits neoplastic cells and also produces immunosuppression, changes in tissues with a high rate of mitosis, and changes in the function of the oral mucosa and its microbiome.[12-14]

The objective was to analyze the impact of high-dose chemotherapy during the conditioning period prior to BMT on some bacterial and yeast species of the oral cavity.[15] When comparing the experimental design and results with other similar studies, in line with the bibliographical review, we detected a great variety and heterogeneity of criteria in participant selection, population size, cancer diagnoses, therapeutic schemes and sample collection sites, among others, with controversial discrepancies in the results obtained.[16]

A study showed that the regular use of Chlorhexidine during the immunosuppression period in patients diagnosed with lymphoma caused a significant decrease in some bacterial species, including *Streptococcus mutans*.

In this study, according to Meurman et al. criteria for oral hygiene and prophylaxis indications, we found a significant predominance of the same species during stage M.

In agreement with other authors, the increase in *Streptococcus mutans* after BMT could lead to an increased risk of dental caries once oncological treatment has been completed.[18] With regard to the saliva, it is known that the pH of this fluid found in the oral cavity conditions different events, both biochemical and microbiological, and has the capacity to neutralize organic acids from bacterial fermentation, thereby protecting the enamel.

For its part, the increased acidity of the oral environment stimulates the secretion of basal saliva. This facilitates bacterial metabolic processes, which include promoting the acidogenic power of the saliva. From this perspective, it could be inferred that the difference in pH in the oral cavity observed in these patients would predispose both hard and soft tissues to the appearance of various manifestations.[19] Chlorhexidine is a local antiseptic commonly used in the oral cavity of patients undergoing BMT. It is active against both Gram positive and Gram-negative bacteria, reaching its highest activity at a pH of 8.

However, it is inactivated in the presence of blood, and its effect decreases as the pH becomes more acidic, losing its bactericidal activity when the pH is below 5. In this study, we observed that salivary pH decreased during stage M of treatment. Suggestively, the analyzed patients continued to receive chlorhexidine prophylaxis, although the mouth wash would not reach its critical point of therapeutic effectiveness.

The bactericidal effect would be reduced in an oral medium acidified by the action of saliva, whose pH was altered, with an increase in *Streptococcus mutans*, plus other local complications from the treatment. Exacerbated gingival diseases and mucositis (involving the presence of blood in the saliva) were reported in previous studies by our team and also by another group.[6,20,21]

On the other hand, it is known that the microorganisms present in the oral cavity, including *Streptococcus mutans*, lack enzymes that allow them to use xylitol as an energy source and, therefore, to produce acids from it as it usually occurs with saccharose. For this reason, rather than decreasing, the pH of the dental biofilm increases, which is also associated with the stimulation of the salivary flow caused by xylitol.

Thus, demineralization of the dental surface is inhibited and remineralization is stimulated. All of this leads to a decreased risk of dental caries.[22] From this perspective, we hypothesize that, given the reduction in the bactericidal effectiveness of chlorhexidine during the immunosuppression period for the causes mentioned above, the administration of xylitol could help reduce the increase in *Streptococcus mutans* in stage M of

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treatment and these patients' consequent susceptibility to an increased risk of dental caries.

As such, during the period of immunosuppression, it would be advisable to replace the use of saccharose with xylitol and if this is not possible due to its high cost, the intake of natural sugars from the diet should be reduced. Another interesting finding was the unusual increase in *Streptococcus salivarius*.

This bacterial species also corresponds to the group of Gram-positive microorganisms with the capacity to colonize the oral cavity and the upper respiratory tract. Dysbiosis is also considered in neutropenic patients which, together with other local and systemic factors, would predispose them to be more susceptible to aggravated oral mucositis.

This situation was correlated with the immunosuppression period after conditioning with high-dose chemotherapy and BMT. Coinciding with other reports that analyzed samples from patients with hematologic malignancies, the observed population showed concurrent symptoms predisposing them to infections by Gram-positive bacterial species. In the present work, the increase in *Streptococcus salivarius* could be considered an oral indicator of neutropenia during the period of deep and prolonged immunosuppression.

Also, and in agreement with other authors, the salivary pH acidification observed would be related to systemic neutropenia conditions in patients undergoing cancer treatment, with a higher incidence of *Candida albicans*. This situation would favor the adherence of yeasts to the surface of the oral mucosa.[23]

Consequently, the alteration of oral cavity homeostasis due to a decrease in its defensive capacity leads to a significant increase in *Candida albicans* in stage M of treatment.[24]

Regarding the microbial sensitivity study, unlike other investigations that considered vancomycin as a firstline antibiotic during the isolation and immunosuppression period, our results showed that, in this type of patient, the bacteria were most sensitive to amikacin, followed by vancomycin.

Finally, the studied population showed significant resistance to Amoxicillin + Clavulanic Acid, Ciprofloxacin and Azithromycin.[25]

However, due to these preliminary results, it is advisable to continue developing new studies to allow a greater understanding of these highly complex and diverse processes.

It would be convenient to carry out new studies with a larger number of patients who underwent bone marrow transplantation in order to evaluate the behavior of each group according to the diagnosis and therapeutic scheme used.

CONCLUSION.

The antibiotics to which the bacteria were most sensitive before immunosuppression of the patients subjected to bone marrow transplant were vancomycin and amikacin.

Susceptibility to azithromycin and ciprofloxacin was greatly reduced during immunosuppression. *Streptococcus mutans* was the most common isolated species of *Streptococcus* both before and during immunosuppression. During the immunosuppression period, there was a significant increase in the incidence of *Candida albicans*.

Conflict of interests: All authors declare that there are no potential conflicts of interest regarding the authorship and/or publication of this article.

Ethics approval: Not necessary

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Authors' contributions: Bachmeier E: investigation, supervision and writing-review and editing. Migueles Goitea MM: resources. Linares JA: methodology and resources. Wietz FM: investigation. Jarchum S: investigation. Jarchum G: investigation and supervision. Brunotto M: formal analysis. Marcelo Adrián Mazzeo: methodology, funding acquisition, investigation, writing-original draft and review and editing.

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