

# IMPLICATIONS OF COVID-19 IN A HEMATOPOIETIC STEM CELL TRANSPLANTATION SERVICE REFERENCE IN LATIN AMERICA

## IMPLICAÇÕES DA COVID-19 NUM SERVIÇO DE TRANSPLANTE DE CÉLULAS-TRONCO HEMATOPOÉTICAS REFERÊNCIA NA AMERICA LATINA

## IMPLICACIONES DEL COVID-19 EN UN SERVICIO DE TRASPLANTE DE CÉLULAS MADRE HEMATOPOYÉTICAS DE REFERENCIA EN AMÉRICA LATINA

Natália Naome Oshiro<sup>1</sup>  
Luciana de Alcantara Nogueira<sup>2</sup>  
Luana Aparecida Alves da Silva<sup>3</sup>  
Teresinha Keiko Kojo<sup>4</sup>  
Celina Angélica Mattos Machado<sup>5</sup>  
Fernanda Rackes da Silva Fagundes<sup>6</sup>  
Luciana Puchalski Kalinke<sup>7</sup>

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Objective: to describe the implications caused by the COVID-19 pandemic in a reference service for Hematopoietic Stem Cell Transplantation in Latin America. Method: observational, cross-sectional study conducted between March and October 2020. The changes instituted in the transplant service were descriptively analyzed and compared with the care protocols developed by international and national institutions, and the reflection of these actions in outpatient care, hospitalizations, transplants and multiprofessional staff. Results: of the 137 hospitalizations, 25 (18%) patients had respiratory symptoms or fever, of which 2 were positive for SARS-CoV-2. Of the 72 professionals, 8 (11%) were infected, with 5 asymptomatic. New care flows were adopted in order to minimize risks and exposure, such as rescheduling appointments and postponing transplants. Conclusion: the interventions performed were efficient and are in accordance with the recommendations of national and international bodies, however, constant surveillance is a necessity.

Descriptors: Hematopoietic Stem Cell Transplantation. Bone Marrow Transplant. Coronavirus Infections. SARS Virus. Nursing Care.

<sup>1</sup> Nurse. MSc in Collective Health. Nurse at the Unidade de Transplante, Oncologia e Hematologia of the Complexo Hospitalar de Clínicas. Curitiba, Paraná, Brazil. [natoshirokahlo@gmail.com](mailto:natoshirokahlo@gmail.com). <http://orcid.org/0000-0002-8290-4796>.

<sup>2</sup> Nurse. PhD in Nursing. Professor at the Departamento da Universidade Federal do Paraná. Curitiba, Paraná, Brazil. <http://orcid.org.0000-0002-5985-7418>.

<sup>3</sup> Nurse. MSc in Nursing. Nurse at the Unidade de Transplante, Oncologia e Hematologia of the Complexo Hospitalar de Clínicas. Curitiba, Paraná, Brazil. <http://orcid.org/0000-0003-0210-2791>.

<sup>4</sup> Nurse. Nursing Chief at the Unidade de Transplante, Oncologia e Hematologia of the Complexo Hospitalar de Clínicas. Curitiba, Paraná, Brazil. <http://orcid.org/0000-0002-1939-0630>.

<sup>5</sup> Nurse. MSc in Nursing. Nurse at the Unidade de Transplante, Oncologia e Hematologia of the Complexo Hospitalar de Clínicas. Curitiba, Paraná, Brazil. <http://orcid.org/0000-0002-7241-7169>.

<sup>6</sup> Nurse. Nurse at the Unidade de Transplante, Oncologia e Hematologia of the Complexo Hospitalar de Clínicas. Curitiba, Paraná, Brazil. <http://orcid.org/0000-0002-7194-6501>.

<sup>7</sup> Nurse. PhD in Health Sciences. Professor at the Nursing Department of the Universidade Federal do Paraná. Curitiba, Paraná, Brazil. <http://orcid.org/0000-0003-4868-8193>.

*Objetivo: descrever as implicações ocasionadas pela pandemia COVID-19 num serviço de referência para Transplante de Células-Tronco Hematopoéticas na América Latina. Método: estudo observacional, transversal, realizado entre março e outubro de 2020. Foram analisadas descritivamente as mudanças instituídas no serviço de transplante e comparadas com os protocolos de cuidado desenvolvidos por instituições internacionais e nacionais, e o reflexo dessas ações nos atendimentos ambulatoriais, nas internações, nos transplantes e na equipe multiprofissional. Resultados: das 137 internações, 25 (18%) pacientes apresentaram sintomas respiratórios ou febre, dos quais 2 estavam positivos para SARS-CoV-2. Dos 72 profissionais, 8 (11%) foram contaminados, sendo 5 assintomáticos. Foram adotados novos fluxos de atendimento com o intuito de minimizar os riscos e a exposição, como o reagendamento de consultas e o adiamento de transplantes. Conclusão: as intervenções realizadas mostraram-se eficientes e estão de acordo com as recomendações de órgãos nacionais e internacionais, no entanto, a constante vigilância é uma necessidade.*

*Descritores: Transplante de Células-Tronco Hematopoéticas. Transplante de Medula Óssea. Infecções por Coronavírus. Vírus da SARS. Cuidados de Enfermagem.*

*Objetivo: describir las implicaciones causadas por la pandemia de COVID-19 en un servicio de referencia para el Trasplante de Células Madre Hematopoyéticas en América Latina. Método: estudio observacional transversal realizado entre marzo y octubre de 2020. Los cambios instituidos en el servicio de trasplante fueron analizados descriptivamente y comparados con los protocolos de atención desarrollados por instituciones internacionales y nacionales, y el reflejo de estas acciones en atención ambulatoria, hospitalizaciones, trasplantes y personal multiprofesional. Resultados: de las 137 internaciones, 25 (18%) pacientes tenían síntomas respiratorios o fiebre, cuyo 2 eran positivos para SARS-CoV-2. De los 72 profesionales, 8 (11%) estaban infectados, con 5 asintomáticos. Se adoptaron nuevos flujos de atención para minimizar los riesgos y la exposición, como la reprogramación de citas y el aplazamiento de trasplantes. Conclusión: las intervenciones realizadas fueron eficientes y están de acuerdo con las recomendaciones de los organismos nacionales e internacionales, sin embargo, la vigilancia constante es una necesidad.*

*Descriptores: Trasplante de Células Madre Hematopoyéticas. Trasplante de Médula Ósea. Infecciones por Coronavirus. Virus del SARS. Cuidados de Enfermería.*

## Introduction

Since the emergence and beginning of notifications of the first cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019, in Wuhan city, China, several epidemiological and clinical evidences are presented to aid in the construction of the natural history of this disease. The rapid evolution to a pandemic brought a series of threats to the global order, causing coping strategies to be developed on an emergency basis<sup>(1)</sup>.

The organization of health services and management for coping with and controlling infection needed to be performed with the development of effective measures adopted globally and locally<sup>(1)</sup>. In this scenario of tension, reorganization of health services and change of habits, fear of contamination and the consequences of Coronavirus disease 2019 (COVID-19), possibly caused suffering to patients affected by some pathology<sup>(2)</sup>.

Patients requiring hematopoietic stem cell transplantation (HSCT) make up a vulnerable

population due to underlying disease and immunosuppression caused by previous treatments, for which SARS-CoV-2 infection seems to cause tragic and even fatal consequences<sup>(3)</sup>. When considering the specificity of HSCT, national and international scientific societies dedicated to the area have published guidelines and protocols of care based on documents issued by the World Health Organization (WHO)<sup>(4)</sup> and research developed by scholars in the area of HSCT<sup>(5-7)</sup>. These publications support health professionals with updates that support the establishment of new routines and training, staff, patients and family members, with a view to preventing or delaying the spread of the disease, promoting greater safety to the patient, who faces, in addition to a life-threatening diagnosis, the fear of an unknown disease.

For the general population, the containment measures globally used are: hand hygiene, mask use, social isolation, detection of suspected cases and treatment of confirmed cases<sup>(8)</sup>. However, in

the context of the transplanted population, which presents a higher risk of unfavorable outcome, in addition to this care, there is a need for the adoption of norms, routines and protocols with a view to the specificity of the area, such as reorganizing the flow of hospitalizations to HSCT and prioritizing patients without clinical waiting conditions.

This management is fundamental to identify and prevent contamination by SARS-CoV-2, and the measures may undergo adaptations according to the institutional characteristics, availability of resources and specificities of patients. Thus, the fundamental question of the present study arose: What are the implications of the COVID-19 pandemic in the Hematopoietic Stem Cell Transplantation Service? To answer this, this research aimed to describe the main changes that the COVID-19 pandemic caused in the routine of a reference service in Latin America for Hematopoietic Stem Cell Transplantation.

## Method

This is an observational, cross-sectional study conducted in a Bone Marrow Transplantation Service (STMO, in Portuguese) of a university hospital in southern Brazil, a reference in Latin America<sup>(9)</sup>. The service has the outpatient sector where pre-transplant and continued care is performed to transplant patients (follow-up); and the hospitalization and Hospital Day sectors where transplantation takes place, immediate post-HSCT care to the medullary handle and the care of possible complications.

Data collection occurred from March to October 2020 in the outpatient sector and hospitalization of the STMO, during the COVID-19 pandemic, with the aid of a data collection instrument constructed by the main author. Data regarding the care actions adopted by the STMO to control SARS-CoV-2 infection were collected by documentary consultation, in routines described in standard operating procedure manuals, protocols and service flows, such as: inflow and isolation of suspected and confirmed cases and training records performed during the period.

Information related to patient care was collected by consultation in physical and electronic medical records. The variables collected were: number of transplants, modality, quantity of postponed transplants due to the pandemic and number of tests performed for respiratory virus research in symptomatic patients. The information related to the health team was collected by documentary consultation at the STMO. The variables collected were: index of professionals contaminated and absent by COVID-19.

The care actions that were carried out by the STMO were compared with the protocols of care developed by international institutions – European Society for Blood and Transplantation (EBMT, in Portuguese)<sup>(10-11)</sup>, American Society of Clinical Oncology (ASCO)<sup>(12)</sup> and American Society for Transplantation and Cellular Therapy (ASTCT)<sup>(13)</sup> – and with recommendations from the National Health Surveillance Agency (ANVISA in Portuguese)<sup>(8)</sup>, and the guidelines of the institutions in the area – Brazilian Society of Bone Marrow Transplantation (SBTMO)<sup>(14)</sup> and the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH in Portuguese)<sup>(15)</sup>.

For the comparative analysis of care actions to control SARS-CoV-2 infection developed in the STMO and those recommended by the institutions specialized in the theme, readings of protocols, guidelines and recommendations for care and care were performed.

The variables obtained were tabulated in a Microsoft Excel 2010® spreadsheet. Subsequently, descriptive analysis was performed, with the results expressed in simple, absolute and relative frequencies.

This study is an part of the thematic project “Analysis of The Care Actions of Hematopoietic Stem Cell Transplant recipients and Their Relatives in the COVID-19 Pandemic” with approval by the Research Ethics Committee (REC), Opinion n. 4.290.200.

## Results

Regarding the case series referring to the patient data, Table 1 shows that 60 HSCT,

53 (88%) allogeneic HSCT and the other autologous HSCT were performed. The related allogeneic HSCT had as the most prevalent source of stem cells fresh bone marrow (BM) (without previous freezing). Regarding the

number of transplants postponed due to the pandemic, 22 (36.67%) procedures were suspended. Of these, 16 (26.67%) had not yet been performed until the final date of data collection, October 2020.

**Table 1**– Characterization of allogeneic hematopoietic stem cell transplantation, source of hematopoietic stem cells and transplant infusion modality. Curitiba, Paraná, Brazil, Mar.-Oct. 2020

HSCT (1)		HSC (2)		Infusion of transplants	
Type	n (%)	Source	n (%)	Modality	n (%)
Allogenic not related	17 (28%)	Bone marrow	12 (20%)	Fresh	4 (7%)
				Cryopreserved/defrosted	8 (13%)
		Peripheral blood	5 (8%)	Fresh	2 (3%)
				Cryopreserved/defrosted	3 (8%)
Akin Allogenic	36 (60%)	Bone marrow	29 (48%)	Fresh	27 (45%)
				Cryopreserved/defrosted	2 (3%)
		Peripheral blood	7 (12%)	Fresh	6 (10%)
				Cryopreserved/defrosted	1 (2%)

Source: Created by the authors.

(1) HSCT - Hematopoietic stem cell transplantation.

(2) HSC- hematopoietic stem cells.

Regarding the symptoms presented by the patients, of the 137 hospitalizations, 25 (41.67%) individuals in post-transplant presented fever or respiratory symptoms and had tests collected for Multiple Respiratory Viruses (VRMULT, in Portuguese) and SARS CoV-2, totaling 55 tests. Of these, 53 (96%) were negative for COVID-19. Both (4%) patients who were positive were treated at the Hospital Day. The first presented mild respiratory symptoms and was kept in outpatient care. The second required readmission for respiratory symptoms and neutropenia, but presented progressive worsening with the need for transfer to the Intensive Care Unit (ICU). The patient presented negative tests for COVID-19 at ICU admission and was positive ten days after transfer.

In the pre-HSCT stage, a phase performed at the BMT outpatient clinic during the pandemic, all patients were tested with RT-PCR for SARS-CoV-2 before hospitalization and/or before starting conditioning. Post-HSCT patients underwent more rigorous prevention and control actions and were conducted for evaluations on a case-by-case basis.

In the post-HSCT phase, patients who are discharged from the hospital remain in outpatient

follow-up or in care at the Hospital Day with a care routine up to approximately three months after transplantation. During the pandemic, in order to reduce the displacement of patients and their stay in the STMO and reduce exposure and risk of contamination, among other approaches, the reduction of the frequency of collection of laboratory tests, adaptations regarding the use of intravenous medications replaced for oral and early outpatient discharges were adopted.

Specific care was also adopted in relation to donors, who, in addition to being also tested for SARS-CoV-2, for greater safety of the recipient, evaluations of the clinical and epidemiological history were performed, with risk classification. All results of the 60 pre-transplant patients and the 36 donors received at the unit were negative.

Concerning health professionals, tests were collected to detect the presence of COVID-19 infection in two situations: in the entire team, in the second half of April, with the objective of screening asymptomatic cases; in cases where professionals had symptoms such as runny nose, cough and fever. During the data collection stage, of the 72 professionals, 8 tested positive (4 nurses, 3 physicians and 1 nursing technician), which represents 11% of the service's workforce.

In this sense, it was necessary to restructure the scale of professionals to meet suspected cases or patients waiting for results, to avoid unnecessary exposure during care in respiratory isolation rooms.

In addition, the Hospital Infection Control Service (SCIH) provided training with videos with guidance on paramentation and disparamentation, as well as updates and courses in the distance modality. For those who required absence from their activities during the pandemic period, virtual care was

provided with the Worker Health and Safety Unit (SOST).

For the comparative analysis of the care actions recommended by national and international institutions and those adopted in the STMO for the prevention of the disease caused by SARS-CoV2, Chart 1 separately presents the actions implemented/recommended to the HSCT center to donors, patients during pre-transplantation, hospitalization and post-transplantation, health professionals and also those not implemented.

**Chart 1** – Main actions implemented/not implemented in HSCT service to combat Covid-19

<b>Recipients</b>	<b>Implemented Recommendations</b>	<b>Non-implemented Recommendations</b>
Transplant Centers	Reorganization of the input stream of patients in the transplant service. Instructions regarding detachment between patients. Reagending non-urgent medical consultations. Insulation of patients waiting for examination result for SARS-COV-2. Separation of teams to care for patients with Covid-19. Provision of personal protective equipment (PPEs) for lower exposure to Covid-19. Restriction of visits as much as possible. Guidance on the collections, whenever possible, with the use of peripheral blood as a source of ST and cryopreserved graft.	Availability of telemedicine consultations.
Receptors	Risk Assessment x Benefit to suspend transplants where the clinical conditions of the receiver allowed. Guidance on the need for home insulation, hand hygiene, for at least 14 days before the start of conditioning. Testing by RT-PCR for SARS-COV-2 in pre-admission.	
Transplanted patients	Intensification of monitoring adverse reactions, including classic and respiratory signs and symptoms of SARS-COV-2 infection. Preparation of the patient for hospital discharge throughout the hospitalization. Precocious discharge when the clinical conditions of the patient allowed.	Symptom monitoring through telephone contact.
Donors	Evaluation of epidemiological history for contact with suspected or confirmed cases of SARS-COV-2. Testing by RT-PCR for SARS-COV-2, respecting the periodicity of the exams according to the risk classification.	
Health Professionals	Professional testing with respiratory symptom or who had contact with a suspicious or confirmed case for Covid-19. Departure from the professional for 14 days in the positive case for Covid-19, and new testing after this period. Use of uniform, aiming to exchange external clothing for the hospital's internal. Specific training for paramentation and sparkness. Update of routines and institutional information.	RT-PCR test to all professionals, when a suspicious or confirmed case occurs within the SCT unit, to screen asymptomatic or pre-symptomatic cases.

Source: Created by the authors.

## Discussion

HSCT is a therapeutic modality that brings hope of cure and survival, but carries side effects and numerous risks to patients. The presence of the COVID-19 pandemic overwhelmed the multidisciplinary team and patients with concerns related to the continuity of the treatment of post-transplant recipients, the possibility of potentiating the expected complications, as well as the uncertainty to receive the transplant.

There was no significant reduction in procedures regarding the quantity of transplants performed during the data collection period, considering that, in the same period of the previous year, 64 transplants were performed. This result reveals that, although the service was reorganized due to the pandemic, the patients being followed had their transplants performed. In 2019, there was no use of cryopreserved grafts for patients submitted to allogeneic HSCT, however, in 2020, there were 14 (23%). This data converges with the recommendations of the EBMT<sup>(10-11)</sup> regarding cryopreservation procedures, representing an increase in relation to this practice.

It was not possible to observe, at this first moment, the consequences of cryopreservation. Some studies suggest loss of cell viability after defrosting, compromising graft quality<sup>(16)</sup> or, for example, increased reactions to dimethyl sulfoxide (DMSO), the main substance used in freezing to ensure cell viability<sup>(16)</sup>. This follow-up should be presented in future studies.

Regarding the contamination and lethality of COVID-19 in HSCT receptors, there was divergence with the results of the research conducted in Spain<sup>(17)</sup>, which indicated higher lethality among autologous (24%) than in allogeneic transplants (20%). In most cases, autologous evolved more complicatedly in relation to the frequency of hospitalizations, ICU admission, mechanical ventilation, severe acute respiratory syndrome (SARS) and septic shock; the probable cause of these differences would be due to a higher median age in autologous patients. In the present study, the two patients

who tested positive for COVID-19 underwent allogeneic transplantation, one with mild symptoms and the other, with progression of symptoms and presence of other complicators related to HSCT.

The same Spanish study<sup>(17)</sup> shows that, in cases of post-transplant patients with ongoing immunosuppression, mucositis, malnutrition and/or graft-versus-host disease (GVHD), the risk of complications may increase if associated with COVID-19 infection. In the sector, there was more rigorous monitoring of adverse reactions in transplant patients with continuous guidance since hospital discharge. It is important to guide the patient, in all phases of transplantation, for the strengthening of prevention measures, and the correct use of PPE, by health professionals, to control cross-infection. Without detailing, despite the vulnerability of these patients to the spread and contamination by SARS-CoV-2, added to the contamination of professionals in asymptomatic condition, there were few negative outcomes, considering that 3.34% of patients were infected.

Health professionals, in compliance with Technical Note n. 4/2020<sup>(8)</sup>, reinforced the use of PPE and training on their use, in addition to hand hygiene. It is noteworthy that this is a daily practice in the sector that was efficient<sup>(18)</sup>, because, even with positive professionals asymptomatic for COVID-19, there was no cross-infection. However, this is a worrying situation, as there is no recommendation for periodic testing for asymptomatic employees, with international studies showing that, in every three infected, one is asymptomatic<sup>(17,19-20)</sup>. The increased distance among professionals causes work overload in the team, generating psychological impact, such as fatigue and increased stress, further exposing workers from the "front line" and evidencing the historical demands of the health sector<sup>(21-22)</sup>.

In this scenario, it is necessary to highlight the importance that health professionals had in coping with the pandemic, being essential in the maintenance of all care provided. The measures implemented minimized the impacts of COVID-19 and impacted on the prevention of



the spread of the virus<sup>(23)</sup>, mainly by considering the complexity and vulnerability of the patient in the context of HSCT and asymptomatic cases<sup>(24)</sup>.

According to Technical Note n. 36/2020<sup>(19)</sup>, of the Ministry of Health, the STMO followed the main recommendations for donation and clinical screening, with assessment of the risks and benefits for performing the transplant, elaboration of inflow, isolation for suspected and confirmed cases. The educational guidelines and actions for donors, HSCT recipients and family members were implemented according to epidemiological information and scientific evidence provided by national and international health authorities.

In order to reduce the volume of care, transplants were postponed without risk to the patient, a relevant measure highlighted by studies(14-15,19). According to Technical Note n. 36/2020<sup>(19)</sup>, of the Ministry of Health, all patients in the pre-transplant period were tested for COVID-19 and stayed in specific wards while waiting for the results. However, telemedicine was not used in the service, and consultations were rescheduled according to the clinical condition of each patient.

This publication presents a set of evidence stemming from an overview of the impact of the pandemic on the STMO, presenting the elaboration of strategic plans for the preparation, planning and implementation of best practices recommended for combating and disseminating the infection. The limitations of the study focus on the evaluation of a single transplant center and the execution of a cross-sectional study, which hinders comparing and generalizing the results, as well as the analyses that do not bring the number of rescheduled medical consultations, hospitalization time and expansion of the indications of treatments with oral regimens. This information would contribute to a detailed assessment of the consequences of COVID-19 in the sector under study.

## Conclusion

Several actions have been implemented, including interventions in transplant centers,

care for recipients, transplant patients, donors and conducts with health professionals, in order to reduce the possibilities of contamination of patients and the health team. The interventions carried out were efficient and are in accordance with the recommendations of national and international bodies, however, constant surveillance is a necessity.

The number of transplants performed was similar to the same period of the previous year, revealing that, although the service was reorganized, the number of procedures was not influenced by the pandemic. It is also evident the reference of the service in the care of critically ill patients in need of urgent treatment.

Although vaccination against COVID-19 is ongoing, the main strategy to prevent dissemination remains to avoid exposure to SARS-CoV-2. This study is expected to contribute to the organization of services through actions to mitigate and assist in care processes in emergency situations.

## Collaborations:

1 – conception, design, analysis and interpretation of data: Natália Naome Oshiro;

2 – writing of the article and relevant critical review of the intellectual content: Natália Naome Oshiro, Luciana de Alcantara Nogueira, Luana Aparecida Alves da Silva and Teresinha Keiko Kojo;

3 – final approval of the version to be published: Celina Angélica Mattos Machado and Luciana Puchalski Kalinke.

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