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HSCT FOR PEDIATRIC DISEASES

Adriana Seber[17,18,16,27], Alessandra Gomes[25,22], Ana Karine Vieira[7], Ana Luiza Melo Rodrigues[11], Ana Maria Marinho da Silva[2], Antonella Zanette[11], Antonio Vaz de Macedo[6,13], Carla Nolasco Monteiro Breviglieri[17,20,25], Carla Zanchetta[17,19], Cilmara Kuwahara[15], Cinthya Rocha Carvalho[23], Fernanda Lima Lelis[21], Gabriele Zamperlini Netto[12,25], Gustavo Zamperlini[17,19], Julia Lopes Garcia[12,25], Juliana Folloni Fernandes[12,25], Karoline Helena Silva da Silva[24], Laila Rigolin Fortunato[5], Lauro José Gregianin[10], Liane Esteves Daudt[32], Luciana Domingues[17,20], Luiz Guilherme Darrigo Jr[31], Maria Gabriela Matos[17], Maria Lucia Lee[3], Mariana Bohns Michalowski[32], Maura Ikoma[1], Monica Cypriano[24], Natália Maria Tavares Ferreira Borges[21], Neysimelia Costa Villela[8], Paola Soriano[17,20], Patrícia Shimoda Ikeuti[8], Paulo Henrique dos Santos Klinger[24] ,Raul Ribeiro[30], Renata Fittipaldi Guimaraes[24], Rita Barbosa Tavares[26], Roseane Gouveia[17,19], Samantha Nichele[9], Simone de Castro Resende Franco[4], Valeria Cortez Ginani[17,19], Victor Gottardello Zecchin[3], Virginio Fernandes[24], Cláudio Galvão de Castro Junior[28,29,12,29], Carmem Bonfim[15]

1 Hospital Amaral Carvalho – Jaú - SP - 2 Hospital Aristides Maltez – Salvador - BA- 3 Hospital Beneficência Portuguesa – São Paulo - SP - 4 Hospital da Criança de Brasília – Brasília – DF - 5 Hospital da Criança e Maternidade - São José do Rio Preto - SP 6 Hospital da Polícia Militar – Belo Horizonte – MG - 7 Hospital das Clínicas - Universidade Federal de Minas Gerais – Belo Horizonte - MG - 8 Hospital de Amor Infanto Juvenil de Barretos – Barretos - SP - 9 Hospital de Clínicas – Universidade Federal do Paraná – Curitiba - PR - 10 Hospital de Clínicas de Porto Alegre – Porto Alegre - RS - 11 Hospital Erastinho - Complexo Erasto Gaertner – Curitiba - PR - 12 Hospital Israelita Albert Einstein – São Paulo – SP - 13 Hospital Luxemburgo – Instituto Mário Penna – Belo Horizonte - MG - 14 Hospital Martagão Gesteira – Salvador – BA - 15 Hospital Pequeno Príncipe – Curitiba - PR 16 Hospital Sabará – São Paulo - SP - 17 Hospital Samaritano Higienópolis – São Paulo - SP - 18 Hospital São Camilo – São Paulo – SP - 19 Hospital São Camilo Pompéia – São Paulo - SP - 20 Hospital São Camilo Santana – São Paulo - SP 21 Hospital São Rafael – Salvador - BA - 22 Hospital Sírio Libanês - 23 Instituto de Medicina Integral Professor Fernando Figueira (IMIP) – Recife - PE - 24 Instituto de Oncologia Pediátrica – GRAACC – UNIFESP - São Paulo – SP - 25 Instituto do Tratamento do Câncer Infantil ITACI – Hospital das Clínicas – Universidade de São Paulo – São Paulo - SP 26 Instituto Nacional do Cancer – Rio de Janeiro - RJ - 27 Pediatric HCT Committee - Sociedade Brasileira de Oncologia Pediátrica (SOBOPE) and Sociedade Brasileira de Transplante de Medula Óssea (SBTMO) - 28 Santa Casa de Misericórdia de Porto Alegre – Porto Alegre – RS - 29 Sociedade Brasileira de Oncologia Pediátrica – São Paulo – SP - 30 St. Jude Children's Research Hospital – Memphis - TN - 31 Universidade de São Paulo – Ribeirão Preto - SP - 32 Universidade Federal do Rio Grande do Sul – Porto Alegre - RS

The Brazilian Society of Bone Marrow Transplantation (SBTMO) started in 2009[1] its Consensus Meetings to discuss the indications for Hematopoietic Stem Cell Transplantation (HCT), and the resulting consensus guidelines have ever since remained freely available at the SBTMO website (www.sbtmo.org.br/consenso).[2] Now, in its 5th edition, the Consensus material will, for the first time, be published in the Journal of Bone Marrow Transplantation and Cellular Therapy (JBMTCT - www.jbmtct.com.br) recently launched by SBTMO, the first scientific journal in Latin America focused on HCT.[3] The recommendations will remain in Portuguese at the SBTMO website, and in English at the Journal website.

All prior meetings have been presential except for this one, on October 26, 2020, initially planned to be hosted in the city of São Paulo, immediately before the XXIV SBTMO Annual Meeting, and modified to a digital platform (www.congressosbtmo.org.br) due to the SARS-Cov2 pandemic, as has been the case with so many other national and international meetings in the field.

Although a significant impact of COVID-19 on the activity of solid organ transplantation has been witnessed in the country over the past few months, when comparing the first half of 2019 to that of 2020, an overall reduction of only 10% in allogeneic HCT was observed,[4] which highlights the critical relevance of this procedure and the boundless commitment of both donors and healthcare professionals to the treatment of an array of life-threatening diseases that may be effectively treated with a timely transplant. Hence, the annual number of transplants has been growing continuously worldwide,[5] as well as in our country.[4]

The addition of post-transplant cyclophosphamide to haploidentical transplantation for graft-versus-host disease (GVHD) prophylaxis, initially developed within experimental platforms[,6] has been used in clinical trials since 2002[7] with an astounding impact on donor selection and transplantation practices worldwide. As a result, hundreds of publications on haploidentical HCT have shown very similar outcomes to those obtained with unrelated HCT[8,9] To date, the only randomized-controlled trial available comparing double unrelated cord blood with haploidentical marrow transplantation (BMT-CTN 1101) showed a lower transplant-related mortality and better overall survival with the use of haploidentical donors.[10]

Allogeneic HCT, traditionally a therapeutic option restricted to patients with an HLA-compatible donor, is now available to virtually all who need it, since parents and children invariably share a common haplotype, in addition to half of the siblings. The worldwide and Brazilian experience acquired during the past several years with the various types of donors and grafts has enabled us to change our rationale for recommending HCT.

Many current consensuses for HCT indications no longer differentiate between indications for transplants using grafts from HLA-identical related and haploidentical donors, adult unrelated donors, and umbilical cord blood units.[11] Nonetheless, each transplant strategy has its own particularities, risks and benefits. When performing any HCT with HLA incompatibility, it is essential to look for donor-specific antibodies (DSA) and to have strategies to desensitize the patient if antibodies against the donor are found.

Patients with an indication for allogeneic HCT should be transplanted with the best available donor as soon as the procedure is indicated, before disease progression or deterioration of the patient's clinical status. These are the most important prognostic factors for treatment outcome.

Pediatric diseases requiring HCT have a much lower prevalence in the population than diseases affecting adults. The discovery of a myriad of specific genetic abnormalities has changed our understanding of many malignant and non-malignant pediatric diseases. When all these specificities are combined to the various types of donor and transplant strategies now available, we understand that the classical model used to define HCT indications in adults, with meta-analyses and randomized trials, are not applicable in pediatrics. In addition, many pediatric diseases do not have therapeutic alternatives with curative potential that can be compared to HCT results. Thus, in this 2020 Consensus, we chose to follow international guidelines[11] and make recommendations for indications of autologous and allogeneic HCT, regardless of the type of graft or donor.

Members of the Pediatric Working Group participated in several meetings to discuss the specific consensuses on bone marrow failure syndromes, hemoglobinopathies, autoimmune diseases, and sinusoidal obstruction syndrome (Supplementary Table 1). These topics were not included in this document.

Six groups were formed to review the indications for non-malignant diseases and fifteen groups for the review of malignant diseases (Supplementary Table 2). All reviews were discussed during the group's weekly meetings on the www.Cure4Kids.org website, kindly offered by St. Jude Children's Research Hospital.

The main changes in relation to the previous consensus are presented in this article and were orally presented at the SBTMO – Consensus Plenary Session on October 26, 2020 for comments. A supplement of the JBMTCT will follow, discussing all Pediatric HCT indications in depth. The indications are summarized in Tables 1 to 3 and the recommendations of essential medications used to perform allogeneic HCT are listed in Table 4.

For each disease, we have defined whether autologous and/or allogeneic HCT are recommended or not and have added a few important notes on the implications regarding specific indications and the approach to performing the transplants. In the tables, the letter Y means Yes, HCT is indicated", and N means "No, it is not indicated".

Of note, we have only included the most common pediatric indications in this guideline. Diseases that have not been previously discussed as treated with HCT are not included in the tables, which does not mean that HCT may not be performed as an exemption or under compassionate use, as far as it is based on a strong rationale, or on documented previous HCT successes. A rare indication does not imply that a transplant is experimental; it means that that there are not enough patients under that indication to perform a formal clinical trial. Therefore, sound clinical judgment is advised at all times when faced with the challenge of an indication for transplant.

We thank all of those who have dedicated their time and effort toward updating these guidelines and hope that this 2020 Consensus succeeds in providing solid evidence-based guidance to all healthcare workers involved in the continuous care of HCT patients in Brazil and developing countries alike.

TABLE 1- Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Non-Malignant Diseases in Pediatrics

	Observations/indications	Allo	Auto
Inherited inborn errors of metabolism			
Osteopetrosis	Urgent HCT due to the risk of blindness and hearing loss, except in the presence of neurodegeneration (OSTM1 mutation) and with RANKL mutations	Y	N
Mucopolysaccharidosis type I - MPS-IH, Hurler syndrome		Y	N
Mucopolysaccharidosis type II, Hunter syndrome		Y	N
Mucopolysaccharidosis type VI, Maroteaux-Lamy Syndrome	ONLY if unresponsive to enzyme replacement therapy	Y	N
X-linked adrenoleukodystrophy	ONLY progressive cerebral form, early stage	Y	N
Leukodystrophy of globoid cells – Krabbe disease	Warning: family donors should not be used if healthy carriers of the disease	Y	N
Metachromatic leukodystrophy		Y	N
Immunodeficiencies	We strongly suggest following ESID recommendations for conditioning therapies https://esid.org		
Severe combined immunodeficiency		Y	N
Severe combined immunodeficiency due to ADA deficiency	Alternative: enzyme replacement and gene therapy	Y	N
Wiskott Aldrich syndrome		Y	N
Familial hemophagocytic lymphohistiocytosis	HCT with active disease has worse results	Y	N
Chediak-Higashi syndrome		Y	N
Griscelli syndrome - type II		Y	N
X-linked lymphoproliferative disease		Y	N
Chronic granulomatous disease	HCT from mismatched unrelated donors or cord blood have inferior results	Y	N
HyperIgM Syndrome (CD40/CD40L)		Y	N
Leaky- Severe combined immunodeficiency		Y	N
Leukocyte adhesion deficiency		Y	N
Class II MHC deficiency		Y	N
Purine nucleoside phosphorylase (PNP) deficiency		Y	N
Complete gamma-interferon receptor deficiency	Attention to higher graft failure rate	Y	N
Severe congenital neutropenia	Patients refractory to GCSF, with a history of major infections	Y	N
Early-onset inflammatory bowel disease (IL10, IL10-R, XIAP)		Y	N
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome		Y	N
Other immunoregulation defects (CTLA4, LRBA, STAT3 GOF)	Some may have good response to immunobiologicals	Y	N
Langerhans cell histiocytosis	Multisystemic involvement beyond first remission or 1st remission of refractory disease	Y	N

TABLE 2 - Indications for Hematopoietic Stem Cell Transplantation for Malignant Hematological Pediatric Diseases

		Allo	Auto
Acute myeloid leukemia			
1st remission	Only if minimal residual disease > 0.1% after second induction or unfavorable genetics (karyotype or molecular findings)	Y	N
> 2nd remission, persistent disease after 2nd induction/ refractory disease		Y	N
Acute promyelocytic leukemia			
1st remission		N	N
> 2nd remission or persistently positive PML-RARA	If PML-RARA negative, autologous HCT. If PML-RARA positive, allogeneic HCT	Y	Y
Acute lymphoblastic leukemia			
1st remission			
Ph+ Acute Lymphoblastic Leukemia (Bcr/ Abl)	Only if there is not a good response to treatment	Y	N
Hypodiploid	Only if there is not a good response to treatment	Y	N
Age <6 months and KMT2A (MLL) positive	Only if >300,000 leukocytes /mm3 or poor response to corticosteroid	Y	N
Inductive failure (M2/M3 marrow) after 4 weeks of treatment	Except if hyperdiploid and age < 6 years	Y	N
Minimal Residual Disease (MRD) ≥10-3 (0.1%) at the end of consolidation		Y	N
2nd remission			
T-lineage	Any relapse	Y	N
B-lineage			
Isolated or combined medullary relapse	Early: 1st remission < 36 months	Y	N
	Late: 1st remission > 36 months only if positive minimal residual disease	Y	N
Isolated extramedullary relapse	Early: 1st remission < 18 months	Y	N
	Late: 1st remission > 18 months	N	N
3rd remission (B or T lineages)		Y	N
Refractory disease	Absence of morphological remission	N	N
Chronic myeloid leukemia			
1st chronic phase	Only if therapeutic failure (lack of response or intolerance) is the tyrosine kinase inhibitor	Y	N
	Mutation T315I	Y	N
Accelerated phase		Y	N
Blast crisis	In 2nd chronic phase	Y	N
Myelodysplastic syndrome			
Refractory cytopenia	Only if unfavorable karyotype, transfusion dependence or severe neutropenia	Y	N
Advanced stages		Y	N
Any MDS secondary to chemotherapy		Y	N
Juvenile myelomonocytic leukemia	Except Noonan syndrome or germline CBL with spontaneous remission.	Y	N
Lymphomas Burkitt, diffuse large B cell, anaplastic large cell, Hodgkin lymphoma	Only if poor response to treatment or 2nd remission If relapsed after autologous transplantation or failure to mobilize autologous stem cells	Y N	N Y

TABLE 3 - Indications for Autologous Hematopoietic Transplantation for Pediatric Solid Tumors

Disease	Stage of the disease with indication for autologous transplantation	Auto	Allo
Neuroblastoma	All patients with high-risk disease in 1st complete or partial remission	Y	N
	> 2nd remission	Y	Y
Germ cell tumors: gonadal, extra-gonadal and central nervous system	In 1st remission only patients with unfavorable risk factors	Y	N
	> 2nd complete or partial remission	Y	N
Wilms tumor	> 2nd complete or partial remission	Y	N
Clear Cell Sarcoma	> 1st complete or partial remission. Extremely aggressive tumor	Y	N
Ewing's sarcoma	1st remission if unfavorable risk factors	Y	N
	> 2nd complete or partial remission	Y	N
Alveolar soft part sarcoma	> 1st complete or partial remission	Y	N
Retinoblastoma	> 1st remission of extra-ocular disease	Y	N
	> 1st trilateral disease remission	Y	N
Pinealoblastoma	> 1st complete or partial remission	Y	N
Rhabdoid teratoid tumor	> 1st complete or partial remission of central or extracranial nervous system disease	Y	N
Medulloblastoma	1st complete or partial remission in young children as an option for radiotherapy, except for low-risk disease	Y	N
	> 2nd complete or partial remission	Y	N
Choroid Plexus Carcinoma	> 2nd complete or partial remission	Y	N

TABLE 4 - High-cost drugs that are fundamental to transplant and unavailable in the domestic market or for specific indications in bone marrow transplantation

Medicine/ Procedure	Use
Thiotepa	Single chemotherapy that achieves optimal concentration in the cerebrospinal fluid and brain parenchyma
Treosulfan	Similar to busulfan, but significantly less toxic
Defibrotide	Sinusoidal obstruction syndrome
Eculizumab	Single effective treatment for post-HCT thrombotic microangiopathy, extremely serious complication
Graft versus host disease	
Mycophenolate mofetil	Prevention and treatment of graft-versus-host disease, IV presentation is unavailable
Tacrolimus	Prevention and treatment of graft-versus-host disease
Ruxolitinib	Treatment of refractory graft-versus-host disease
Ibrutinib	Treatment of refractory graft-versus-host disease
Extracorporeal photopheresis	Treatment of refractory graft-versus-host disease
Antivirals	
Cidofovir	Single antiviral with activity against poliomavirus and adenovirus
Probenecid	Combination with cidofovir, increase bioavailability and decrease renal toxicity
Foscarnet	Ganciclovir-resistant cytomegalovirus (CMV) infection
Ribavirin (IV and inhaled)	Single antiviral with spectrum against respiratory syncytial virus, unavailable in our country
Palivizumab	Specific immunoglobulin anti- respiratory syncytial respiratory virus
Pentamidine	Prevention and treatment of Pneumocystis jirovecii pneumonia in patients with G6PD deficiency

SUPPLEMENTARY TABLE 1 - Participation of pediatricians in other groups:

Pathology	Participants
Acquired and Hereditary Bone Marrow Failure Syndromes	Carmem Bonfim, Luiz Guilherme Darrigo Jr
Hemoglobinopathies	Luiz Guilherme Darrigo Jr, Julia Lopes Garcia, Ana Karine Vieira, Laila Rigolin
Autoimmune diseases	Luiz Guilherme Darrigo Jr
High-cost medications	Luiz Guilherme Darrigo Jr, Antonio Vaz de Macedo
Acute lymphoblastic leukemia	Liane Daudt, Claudio Galvão
Acute myeloid leukemia	Ana Luiza Melo Rodrigues
Graft-versus-host disease	Rita Barbosa Tavares
SOS/VOD	Gabriele Zamperlini, Natalia Borges

SUPPLEMENTARY TABLE 2 - Participation of the Pediatric Groups:

Non-malignant diseases		
Coordinator	**Diagnosis**	**Participants**
Carmem Bonfim Juliana Folloni	**Immunodeficiencies**	
	Severe combined immunodeficiency	Samantha Nichele
	Other	Samantha Nichele
	Hmephphagocytic lympho	Gabriele Zamperlini, Samantha Nichele
Carmem Bonfim Juliana Folloni	**INBORN ERRORS**	
	Osteopetrosis	Alessandra Gomes
	Mucopolysaccharidoses	Alessandra Gomes
	Adrenoleukodystrophy and other leukodystrophies	Alessandra Gomes
Malignant diseases		
Coordinator	**Diagnosis**	**Participants**
Liane Daudt	ALL	Adriana Seber, Antônio Vaz de Macedo, Claudio Galvão, Cinthya Rocha, Renata Guimaraes, Luciana Domingues, Maria Gabriela Matos, Maura Ikoma, Virginio Fernandes
Ana Luiza Melo	AML	Antonella Zanette, Victor Zecchin, GELMAI - Ana Maria Marinho da Silva, Maria Lucia Lee, Raul Ribeiro
Roseane Gouveia	CML	Antonio Vaz de Macedo, Luciana Domingues, Paola Soriano
Neysimelia Villela	JMML	Patricia Ikeuti Simone Franco
Neysimelia Villela	MDS, JMML, and other MPS	Carla Zanchetta, Gustavo Zamperlini, Roseane Gouveia, Simone Franco, Patricia Ikeuti, Carla Zanchetta, Pediatric SMD Group
Carla Nolasco	Lymphomas	Cilmara Kuwahara, Gabriele Zamperlini, Mariana Michalowsky, Valeria Ginani
Monica Cypriano Victor Zecchin	Histiocytosis	Gustavo Zamperlini, Monica Cypriano
Solid tumors		
Coordinator	**Diagnosis**	**Participants**
Claudio Galvão - SOBOPE	Neuroblastoma, Ewing, Soft tissue sarcoma, Rhabdomyosarcoma, Osteosarcoma, Hepatoblastoma, Extra ocular retinoblastoma, Germ cell tumors, Brain tumors, GCT	Carla Nolasco, Fernanda Lima, Gabriele Zamperlini, Karoline Helena da Silva, Lauro Gregianin (guest), Mariana Michalowski (guest), Natalia Borges, Patricia Ikeuti, Paulo Klinger, Simone Franco
High cost medications	Antonio Vaz de Macedo, Luiz Guilherme Darrigo Jr	

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