



























# Hematopoietic stem cell transplantation for pediatric acute myeloid leukemia

Ana Luiza de Melo Rodrigues<sup>1,2\*</sup> , Adriana Seber<sup>3,4</sup> , Luciana Domingues<sup>5</sup> , Victor Gottardello Zecchin<sup>6</sup> , Maria Lúcia de Martino Lee<sup>6</sup> , Liane Daudt<sup>7</sup> , Luiza de Souza<sup>8</sup> , Adriana Martins de Sousa<sup>9</sup> , Antonella Adriana Zanette<sup>1</sup> , Carla Nolasco<sup>3</sup> , Virgínio Climaco<sup>8</sup> , Ana Carolina Ribeiro<sup>4</sup> , Thábata Cristina Paradas Moreira da Silva<sup>10</sup> , Paulo Klinger<sup>11</sup> , Cinthya Rocha<sup>12</sup> , Isis Magalhães<sup>13</sup> , Raul Corrêa Ribeiro<sup>14</sup> 

1. Hospital Erastinho – Department of Pediatric Oncology and Bone Marrow Transplant – Curitiba (PR), Brazil.
2. Universidade Federal do Paraná  – Department of Internal Medicine/Hematology – Curitiba (PR), Brazil.
3. Hospital Samaritano de São Paulo  – Department of Pediatric Oncology and Bone Marrow Transplant – São Paulo (SP), Brazil.
4. Universidade Federal de São Paulo  – Department of Pediatric Oncology and Bone Marrow Transplant – Pediatric Oncology Institute – São Paulo (SP), Brazil.
5. Grupo de Pesquisa e Assistência ao Câncer Infantil – São Paulo (SP), Brazil.
6. Beneficência Portuguesa de São Paulo  – Department of Pediatric Oncology and Bone Marrow Transplant – São Paulo (SP), Brazil.
7. Universidade Federal do Rio Grande do Sul  – Department of Pediatric Oncology and Bone Marrow Transplant – Clinical Hospital – Porto Alegre (RS), Brazil.
8. Grupo de Pesquisa e Assistência ao Câncer Infantil – Department of Pediatric Oncology and Bone Marrow Transplant – Sorocaba (SP), Brazil.
9. Universidade Federal do Rio de Janeiro  – Department of Pediatric Hematology of the Martagão Gesteira – Institute of Childcare and Pediatrics – Rio de Janeiro (RJ), Brazil.
10. Complexo Hospitalar de Niterói – Department of Pediatric Oncology and Bone Marrow Transplant – Niterói (RJ), Brazil.
11. Hospital AC Camargo  – Department of Pediatric Oncology and Bone Marrow Transplant – São Paulo (SP), Brazil.
12. Real Hospital Português  – Department of Pediatric Oncology and Bone Marrow Transplant – Recife (PE), Brazil.
13. Hospital da Criança de Brasília José Alencar – Department of Pediatric Oncology – Brasília (DF), Brazil.
14. St. Jude Children's Research Hospital  – Department of Oncology and Global Pediatric Medicine – Memphis (TN), United States.

\*Corresponding author: [anamelorodrigues@yahoo.com.br](mailto:anamelorodrigues@yahoo.com.br)

Section editor: Fernando Barroso Duarte 

Received: Sept. 14, 2025 • Accepted: Nov. 3, 2025

## ABSTRACT

Acute myeloid leukemia (AML) accounts for 15% to 20% of pediatric acute leukemia cases. Treatment failure is influenced by both genetic risk and response to therapy<sup>1,2,3,4</sup>. Although the initial remission rate exceeds 90%, more than 30-40% of children with AML die of refractory/relapsed disease or treatment-related toxicity<sup>5</sup>. Improved survival outcomes are associated with comprehensive strategies that combine intensive chemotherapy, effective supportive care, and hematopoietic stem cell transplantation (HCT), adjusted to the relapse risk profile of each patient<sup>6-10</sup>. In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and

Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to provide general guidance on HSCT for childhood AML, to provide evidence-based guidance for the appropriate management of this disease. This is the 2025 update of the previously guideline<sup>11</sup>.

**Keywords:** Stem Cell Transplantation. Leukemia. Myeloid. Acute. Child. Guideline.

## INTRODUCTION

Acute myeloid leukemia (AML) accounts for 15 to 20% of pediatric acute leukemia cases. Treatment failure is influenced by both genetic risk and response to therapy<sup>1-4</sup>. Although the initial remission rate exceeds 90%, more than 30–40% of children with AML die of refractory/relapsed disease or treatment-related toxicity<sup>5</sup>. Improved survival outcomes are associated with comprehensive strategies that combine intensive chemotherapy, effective supportive care, and hematopoietic stem cell transplantation (HCT), adjusted to the relapse risk profile of each patient<sup>6-10</sup>.

In 2020, the Brazilian Group for Pediatric Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation and Cellular Therapy (SBTMO) and the Brazilian Society for Pediatric Oncology (SOBOPE) convened a task force to provide general guidance on HCT for childhood AML, and to establish evidence-based recommendations for the optimal management of this disease. This is the 2025 update of the previously guideline<sup>11</sup>.

## HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FIRST REMISSION

Patients classified as high risk, either for genetic/molecular factors or for persistent disease after induction therapies, should be referred for HCT in first clinical remission (CR1)<sup>6</sup>. Currently, HCT is not recommended for patients CR1 when they are classified as low or intermediate risk.

In AML, relapses occur predominantly during the early post-diagnosis period, with the majority emerging within the first six months. When allogeneic HCT (allo-HCT) is not performed during this critical timeframe, the relapse risk increases substantially. This temporal pattern may potentially negate the benefit of proceeding with transplantation CR1 when significantly delayed. For cases in which allo-HCT cannot be performed within this optimal window, we recommend comprehensive case review and multidisciplinary discussion to reassess transplant indications.

## MOLECULAR AND GENETIC EVALUATION

With the evolution of methods for detecting genetic/molecular alterations, novel genetic alterations have been correlated with different clinical and prognostic characteristics<sup>6,12</sup>. Table 1 shows the abnormalities with a more consolidated prognostic impact.

**Table 1.** Molecular genetic abnormalities with prognostic impact in pediatric acute myeloid leukemia.

Favorable
t(15;17)/PML-RARA
t(8;21)/RUNX1-RUNX1T1
inv(16)(p13.1;q22)/CBFβ-MYH11
t(16;16)(p13.1;q22)/CBFβ-MYH11
t(1;11)(q21;23)/MLL AF1Q
NPM1 mutated without FLT3/ITD
Biallelic mutation CEBPA
M6 or M7 with GATA-1 in Down syndrome or mosaic for Down syndrome*
Unfavorable

Continued...

Continuation.

-7
-5/del5q
t(6;11)(q27;q23)/MLLT4-KMT2A
t(10;11)(p12;q23)/MLLT10-KMT2A
t(10;11)(p11.2;q23)/ABI1-KMT2A
t(6;9)/DEK-CAN (NUP214)
t(8;16)(p11;p13)/MYST3-CREBBP
t(16;21)(q24;q22)/RUNX1-CBFA2T3
t(5;11)(q35;p15.5)/NUP98-NSD1
t(9;22)(q34;q11)/BCR/ABL
inv(16)(p13.3q24.3)/CBFA2T3-GLIS2 in megakaryoblastic LMA**
t(11;15)(p15;q35)/NUP98-KDM5A
Complex karyotype (≥ three changes)
FLT3/ITD
FAB M0, M6 e M7 without t(1;22) or without GATA-1
Secondary AML (Myelodysplastic Syndrome or previous treatment)

\*Mast KJ, Taub JW, Alonzo TA, Gamis AS, Mosse CA, Mathew P, Berman JN, Wang YC, Jones HM, Campana D, Coustan-Smith E, Raimondi SC, Hirsch B, Hitzler JK, Head DR. Pathologic features of Down syndrome myelodysplastic syndrome and acute myeloid leukemia: a report from the Children's Oncology Group Protocol AAML0431. Arch Pathol Lab Med. 2020;144(4):466–72. <https://doi.org/10.5858/arpa.2018-0526-OA>; \*\*Gruber TA, Larson Gedman A, Zhang J, Koss CS, Marada S, Ta HQ, Chen SC, Su X, Ogden SK, Dang J, Wu G, Gupta V, Andersson AK, Pounds S, Shi L, Easton J, Barbato MI, Mulder HL, Manne J, Wang J, Rusch M, Ranade S, Ganti R, Parker M, Ma J, Radtke I, Ding L, Cazzaniga G, Biondi A, Kornblau SM, Ravandi F, Kantarjian H, Nimer SD, Döhner K, Döhner H, Ley TJ, Ballerini P, Shurtleff S, Tomizawa D, Adachi S, Hayashi Y, Tawa A, Shih LY, Liang DC, Rubnitz JE, Pui CH, Mardis ER, Wilson RK, Downing JR. An Inv(16)(p13.3q24.3)-encoded CBFA2T3-GLIS2 fusion protein defines an aggressive subtype of pediatric acute megakaryoblastic leukemia. Cancer Cell. 2012;22(5):683–97. <https://doi.org/10.1016/j.ccr.2012.10.007>. Source: Elaborated by the authors.

## MINIMAL RESIDUAL DISEASE

In recent years, the assessment of minimal residual disease (MRD) has been incorporated as an additional risk stratifier in the treatment of pediatric AML, usually after the first induction cycles. Due to the different methodologies to assess residual disease, the clinical value of MRD is still evolving and should be interpreted in the context of specific therapeutic protocols.

There is great difficulty in reproducibility and standardization of the methodology used in flow cytometry to quantify low levels of residual disease in AML, which makes interpreting these results and determining their impact on clinical decisions very complex.

Given the challenge, patients previously categorized as low or intermediate risk—referred for HCT exclusively due to detectable levels of residual disease after the induction phase—have the flow archive reviewed by the MRD group of the SBTMO, for further definition of the HCT indication by its Pediatric Group<sup>5</sup>.

The risk classification is outlined in Table 2.

**Table 2.** Risk classification based on diagnostic characteristics associated with measurable residual disease (MRD).

Classification	Diagnostic characteristics + MRD
Low risk	Favorable genetic alterations and MRD < 0.1% after second induction
Intermediate risk	Patients who do not have criteria for low or high risk
High risk	Unfavorable genetic alterations or MRD ≥ 0.1% after second induction

Source: Elaborated by the authors.

## RELAPSED ACUTE MYELOID LEUKEMIA

In relapses, the second remission is achieved in about two-thirds of patients with AML, but, with only chemotherapy regimens, lasting remissions in these cases are rare. Thus, in relapsed disease, allogeneic transplantation constitutes an absolute indication and ought to be performed without delay upon confirmation of renewed remission<sup>10,13</sup>.

## ACUTE PROMYELOCYTIC LEUKEMIA

For patients with acute promyelocytic leukemia in second complete remission (CR2) following first relapse who achieve complete molecular remission (undetectable PML-RARA in bone marrow), autologous transplantation represents the preferred approach, demonstrating lower morbidity and mortality compared to allogeneic transplantation. Conversely, for cases with persistent molecular or flow cytometry-detectable disease, as well as those in third or subsequent remissions (CR3+), allogeneic transplantation is indicated due to its superior cure rates in these high-risk scenarios<sup>14,15</sup>.

## DOWN SYNDROME

In pediatric patients with AML and Down syndrome, HCT should be considered in specific scenarios, such as high-risk genetic abnormalities, or relapsed/refractory disease. These individuals exhibit heightened sensitivity to chemotherapy, but also an increased risk of treatment-related toxicity, necessitating a careful risk-benefit assessment, tailored to their unique biological and clinical characteristics<sup>16</sup>.

## GRANULOCYTIC SARCOMA

In children and adolescents with granulocytic sarcoma, also referred as myeloid sarcoma, HCT should be considered in cases of relapse following initial treatment, refractory disease, or when granulocytic sarcoma presents as a manifestation of AML with high-risk features, such as poor-risk cytogenetics or persistent MRD<sup>17,18</sup>.

## AUTOLOGOUS TRANSPLANT

To date, the benefit of autologous transplantation has not been proven when compared to isolated intensive chemotherapy and/or to allogeneic transplantation for non-promyelocytic AML in CR1<sup>19,20</sup>. Thus, autologous transplantation as remission consolidation should only be performed in research protocols.

## BRIDGING THE GAP: HEMATOPOIETIC STEM CELL TRANSPLANTATION OUTCOMES FOR ACUTE MYELOID LEUKEMIA IN BRAZIL *VERSUS* INTERNATIONAL BENCHMARKS

A study reviewing the outcomes of 1,940 pediatric AML patients treated with the BFM protocol from 1987 to 2012 demonstrated that although event-free survival has remained similar since the 1990s, improvements in supportive care and HCT have made patients who become in CR2 potentially redeemable, and this resulted in an increase of approximately 20% in overall survival in the last 30 years<sup>9</sup>.

In a study with Brazilian HCT centers for children, adolescents, and young adults, overall and event-free survival in four years were 47 and 40%, respectively<sup>10</sup>. Brazilian outcomes of HCT in children with AML are inferior to those reported in the United States of America and Europe<sup>7,8,20-22</sup>. *ACUTE MYELOID LEUKEMIA* SCT-BFM study aimed at standardizing pediatric HCT for AML across centers in Germany and Austria reported four-year event-free survival and overall survival of 61 and 70%, respectively<sup>23</sup>. When assessing the survival advantage of HCT, the increased transplant-related mortality rate in our setting should be taken into account.

The main prognostic factor for the success of HCT in patients with AML remains the stage of the disease. Center for International Blood and Marrow Transplant Research data show three-year overall survival of 70, 65, and 31%, respectively, for patients under 18 years old undergoing related HCT in early (CR1), intermediate (CR2), and advanced stages (active disease or  $\geq$  CR3) of Acute Myeloid Leukemia<sup>20</sup>. Patients with treatment-refractory AML or with more than one relapse still have a dismal prognosis<sup>24</sup>.

The current indications for transplantation are summarized in Table 3.

**Table 3.** Hematopoietic stem cell transplantation indications for pediatric patients: Brazilian Bone Marrow Transplantation Society Consensus recommendations for acute myeloid leukemia.

Disease	Allogeneic				Autologous
	Familiar		Unrelated		
	MSD	HAPLO	MUD	MMUD	
AML 1 CR high risk	Yes	Yes	Yes	Yes	No
2 CR	Yes	Yes	Yes	Yes	No
3 CR	Yes	Yes	Yes	Yes	No
Refractory	Yes	Yes	Yes	Yes	No
APL CR2 CMR	No	No	No	No	Yes
APL CR2 non CMR	Yes	Yes	Yes	Yes	No

AML: acute myeloid leukemia; CR: complete remission; APL: acute promyelocytic leukemia; CMR: complete molecular remission; MSD: matched sibling donor; HAPLO: familiar haploidentical donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor. Source: Elaborated by the authors.

## DONOR AND STEM CELL SOURCE

The results of transplants using related, unrelated (matched or partially matched, with a greater than 8/10 HLA-match), and haploidentical donors are very similar in AML, with no significant difference between type of donor, whether in overall survival and incidence of acute or chronic graft-versus-host disease (GVHD)<sup>10,25</sup>.

In children, bone marrow is preferable in comparison to peripheral blood as stem-cell source, given the higher extensive chronic GVHD and transplant-related mortality with the use of peripheral blood stem cells<sup>26,27</sup>. The use of umbilical cord blood is associated with higher transplant-related mortality in Brazil and should only be used by centers experienced with this stem cell source<sup>28</sup>.

In haploidentical hematopoietic cell transplantation, maternal donors are associated with an elevated risk of chronic GVHD, reduced overall survival, and inferior graft-versus-host relapse-free survival. Consequently, maternal donors should be avoided when alternative options exist. If maternal donation is utilized, preferential use of bone marrow over peripheral blood as the stem cell source is recommended, to mitigate additional chronic GVHD risk<sup>29</sup>.

An important consideration is that haploidentical transplantation is widely performed in Brazil. In such cases, meticulous attention must be paid to the presence of anti-HLA antibodies against the donor, along with their clinical implications and management strategies. This complex discussion should be guided by HLA specialists.

## CONDITIONING REGIMENS

For patients scheduled for autologous HCT, the standard conditioning regimen comprises busulfan and melphalan<sup>14,15,19</sup>.

As for conditioning in allogeneic transplants, there are better results (toxicity *versus* relapse) with the use of myeloablative protocols based on busulfan AUC 4,000–5,000  $\mu\text{Mol}\cdot\text{min}$  or based on total body irradiation (TBI)<sup>23,30–36</sup>.

Although transplantation for active disease ( $\geq 5\%$  blasts in the bone marrow) is controversial, in cases with adequate performance benefit from the adapted FLAMSA conditioning scheme has been reported, curing at least 20% of these children with refractory disease<sup>37,38</sup>.

A contemporary Brazilian single-center study, initially encompassing eight patients and subsequently expanded to 13 pediatric cases of refractory AML treated with a modified FLAMSA regimen, reported 46% overall survival. Mortality analysis revealed relapse as the predominant cause of death (43%), followed by infectious complications (29%)<sup>39</sup>.

Due to important differences in the transplant-related mortality rate (TRM) regarding age and conditioning regimen, according to the risk/benefit and rates of event-free survival and overall survival for patients in

pre-HCT remission, we propose different conditioning for children over or under 6 years old undergoing either matched sibling donor (MSD) or unrelated donor (MUD)<sup>40-42</sup>. The preparatory regimen will consist of busulfan, cyclophosphamide, and melphalan in those patients who are 6 years old or younger (TRM was considerably higher in older children, especially those aged 12 and over). The rationale for implementing a triple-alkylating agent conditioning regimen derived from multiple lines of clinical evidence, associated with a better event-free survival and a lower incidence of relapse<sup>40-42</sup>. For patients aged above 6, the conditioning regimen will comprise busulfan, fludarabine, and melphalan.

The recent advent of haploidentical transplantation has made the search for a more agile donor and, consequently, has allowed transplants to be carried out for a larger number of patients. According to the exciting results presented by Jaiswal et al.<sup>43</sup>, for transplants with haploidentical donors, the suggested scheme is an adaptation of the therapeutic strategy of those studies.

Young children (under 10 years old) may develop GVHD up to eight times more frequently than adults when receiving post-transplant cyclophosphamide. For these patients, the use of donor lymphocyte infusion post-transplantation requires careful consideration to avoid potential harm<sup>44</sup>.

Depending on the experience of each transplant unit, there is the possibility of adopting other conditioning protocols.

An overview of the proposed conditioning schemes is provided in Table 4. The weight-adjusted Busulfan doses are detailed in Table 5.

**Table 4.** Suggested conditioning regimen.

HCT	Conditioning
Autologous (BuMel)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-7 to D-4 + MEL (140 $\text{mg}/\text{m}^2$ ) D-2
Haploidentical (Jaiswal adapted BuFluMel regimen)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-6 to D-4 + FLU (150 $\text{mg}/\text{m}^2$ ) D-7 to D-3 + MEL (140 $\text{mg}/\text{m}^2$ ) D-2 + PTCY (100 $\text{mg}/\text{kg}$ ) D+3 and D+4 + Mesna (1.4 $\times$ dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + DLI: D+21 ( $1 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells), D+35 ( $5 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells), D+60 ( $5 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells)
For children with active disease (FLAMSA adapted regimen)	Intrathecal chemotherapy D-14 + VP16 (600 $\text{mg}/\text{kg}$ ) D-13 to D-10 + FLU (120 $\text{mg}/\text{m}^2$ ) D-13 to D-10 + ARA-C (8,000 $\text{mg}/\text{m}^2$ ) D-13 to D-10 (4 h after FLU) + CY (120 $\text{mg}/\text{kg}$ ) D-3 and D-2 + Mesna (1.4 $\times$ dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + BU (9.6 $\text{mg}/\text{kg}$ ) D-6 and D-5 + DLI: D+21 ( $1 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells), D+35 ( $5 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells), D+60 ( $5 \times 10^6/\text{kg}$ of $\text{CD}3^+$ cells) + AZA (160 $\text{mg}/\text{m}^2$ ), divided in five consecutive days, with one, two, three, four, and five months after transplantation (total of five cycles).
For children < 6 years old MSD (BuCyMel)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-8 to D-5 + CY (120 $\text{mg}/\text{kg}$ ) D-4 and D-3 (start 24 h after BU) + Mesna (1.4 $\times$ dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + MEL (140 $\text{mg}/\text{m}^2$ ) D-2
For children < 6 years old MUD (BuCyMel)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-8 to D-5 + CY (120 $\text{mg}/\text{kg}$ ) D-4 and D-3 (start 24 h after BU) + Mesna (1.4 $\times$ dose of CY, divided into five doses: 0, 3, 6, 9, and 12 hours of CY) + MEL (140 $\text{mg}/\text{m}^2$ ) D-2 + ATG (0.5 $\text{mg}/\text{kg}/\text{day}$ ) D-8, ATG (2.5 $\text{mg}/\text{kg}/\text{day}$ ) D-5 to D-6
For children > 6 years old MSD (BuFluMel)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-7 to D-4 + FLU (150 $\text{mg}/\text{m}^2$ ) D-7 to D-3 + MEL (140 $\text{mg}/\text{m}^2$ ) D-2
For children > 6 years old MUD (BuFluMel)	BU (AUC 4,000–5,000 $\mu\text{Mol}\cdot\text{min}$ ) D-7 to D-4 + FLU (150 $\text{mg}/\text{m}^2$ ) D-7 to D-3 + MEL (140 $\text{mg}/\text{m}^2$ ) D-2 + ATG (0.5 $\text{mg}/\text{kg}/\text{day}$ ) D-8, ATG (2.5 $\text{mg}/\text{kg}/\text{day}$ ) D-5 to D-6

MSD: matched sibling donor; MUD: matched unrelated donor; Cy: cyclophosphamide; FLU: fludarabine; BU: busulfan; ATG: thymoglobulin; VP16: etoposide; MEL: melphalan; ARA-C: cytarabine; DLI: donor lymphocyte infusion; total doses (shown in parentheses) should be appropriately fractionated for each chemotherapy administration. Start DLI regardless of hematological engraftment, and suspend it in case of graft-versus-host disease. Depending on patient tolerance, the dose of AZA may be escalated incrementally with each cycle, up to a maximum of 75  $\text{mg}/\text{m}^2/\text{day}$ . If available AUC for busulfan, start busulfan one day earlier, then leave a day without the drug, to wait for the result and make necessary adjustments the day after the break. In patients with relevant central nervous system involvement, total body irradiation (TBI) + CY may be considered as a conditioning regimen option. In patients scheduled for FLAMSA who fail to achieve remission after the first chemotherapy phase (etoposide, fludarabine, and cytarabine), but remain in good clinical condition, substituting busulfan with 1,200 centigray TBI (maintain cyclophosphamide) may improve therapeutic efficacy. Source: Elaborated by the authors.

**Table 5.** Busulfan dosage.

Weight in kg	Busulfan dose (mg/kg/day)	Cumulative dose of busulfan (mg/kg)
≤9	4	16
>9–≤16	4.8	19.2
>16–≤23	4.4	17.6
>23–≤34	3.8	14.2
>34	3.2	12.8

Source: European Society for Blood and Marrow Transplantation (EBMT) guidelines for hematopoietic stem cell transplantation.

## GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS REGIMEN

Immunosuppressive protocol selection in pediatric HCT is intrinsically linked to donor type and compatibility.

For MSD transplants, calcineurin inhibitors—either cyclosporine (CSP) or tacrolimus—are administered as monotherapy<sup>45–47</sup>. In contrast, MUD HCT typically employs a combined prophylactic approach, incorporating short-course methotrexate (MTX) alongside a calcineurin inhibitor<sup>45–47</sup>.

Post-transplant cyclophosphamide has gained recognition as a promising therapeutic approach for both MUD and haploidentical HCT, although further studies are awaited to define the optimal regimen regarding long-term outcomes for these patients<sup>48–50</sup>.

The therapeutic utility of anti-thymocyte globulin in MUD transplantation remains a subject of ongoing debate, primarily owing to heterogeneity in both preparation methods and dosage regimens<sup>51</sup>.

For umbilical cord blood transplantation, the immunosuppressive regimen usually comprises the combination of a calcineurin inhibitor with mycophenolate mofetil. Studies on the association of CSP with low-dose MTX or with corticosteroids have yielded worse results, as well as a greater graft failure rate<sup>47</sup>.

A comprehensive breakdown of regimen-specific protocols is delineated in Table 6.

**Table 6.** Graft-versus-host disease (GVHD) prophylaxis regimen in childhood acute myeloid leukemia.

Matched sibling donor	CSP 2 mg/kg or TAC 0.05 mg/kg in two divided IV doses—started on D-1 (SL CSP: 100–200 mcg/L or TAC: 5–15 ng/mL)
Matched unrelated donor	Short-term MTX (D+1, D+3, D+6)* + CSP or TAC
Haploidentical	PTCy 50 mg/kg (D+3 and D+4)** + CSP or TAC + MMF 15 mg/kg/dose q8h; maximum 2 g/day—started on D+5
Umbilical cord blood	Combination of CSP or TAC + MMF 15 mg/kg/dose q8h; maximum 2 g/day

CSP: cyclosporin; TAC: tacrolimus; SL: serum levels; MTX: methotrexate; PTCy: post-transplant cyclophosphamide; MMF: mycophenolate mofetil; UCB: umbilical cord blood; \*MTX is used at doses of 10 mg/m<sup>2</sup>; \*\*coupled with mesna (140% of the Cy dose). Source: Elaborated by the authors.

## BEST-TIME POINTS FOR MINIMAL RESIDUAL DISEASE ASSESSMENT

- Pre-HCT: MRD assessments should be made immediately before allo-HCT;
- Post-HCT: MRD assessments by multiparameter flow cytometry and/or reverse transcription quantitative polymerase chain reaction (RT-qPCR) are accurate in predicting relapse at days +30, +60, +90, +180, +270, and +365 post-HCT.

Any detectable MRD level post-HCT is highly predictive of relapse and poor survival<sup>52</sup>. When decisions that may change patient management are based on low levels of MRD, we would recommend that the SBTMO MRD Working Group review the flow cytometric data to increase accuracy of the results.

## MANAGEMENT OF RELAPSE AND STRATEGIES TO MINIMIZE POST-TRANSPLANT RELAPSE

The persistently poor overall survival observed post-HCT, especially in high-risk and MRD-positive individuals, represents an unmet clinical need demanding novel relapse prevention strategies<sup>53</sup>.

This consensus document features a comprehensive chapter dedicated to the management of leukemic relapse, incorporating: an extensive literature review, recommended therapeutic regimens for remission induction, and specialized strategies to minimize post-transplant relapse risk in AML, particularly for high-risk disease. Specific interventions discussed include early post-transplant intrathecal chemotherapy, incorporation of novel agents (venetoclax, azacitidine), and targeted therapies for actionable genetic markers (e.g., FLT3-ITD mutations)<sup>13,54,55</sup>. The chapter additionally provides detailed protocols for disease monitoring, including recommended methods and frequency of reassessment.

## FINAL CONSIDERATIONS

Despite the immunological effect of the grafted cells against leukemia, the toxicity and mortality related to the procedure remain an obstacle to be overcome. The heterogeneity of data related to patient selection and type of conditioning for HCT and donors makes data interpretation difficult in the pediatric population, particularly in developing countries, but procedure-related mortality is estimated to be between 10–25% in our country<sup>10,22</sup>.

Another key point for better results is carrying out the transplant without delay, which is hampered by the scarcity of beds for patients dependent on the public health system. Patients in CR1 and CR2 are potentially redeemable with HCT, but from the second relapse and/or when the patient has a disease in progress, there is a drastic reduction in the chances of cure. Delay in HCT is harmful both due to the risk of losing remission and suffering a relapse, as well as exposure to the toxicity of a new cycle of chemotherapy, which can worsen the child's performance for transplantation, or even be fatal<sup>10</sup>.

In the management of AML, it is advisable to consider HLA typing of the patient, parents, and siblings at diagnosis. If no related donor is identified, collect the patient's anti-HLA antibody test and start searching for a donor at the Brazilian Registry of Voluntary Bone Marrow Donors.

In the current context, many advances have been achieved, in particular through the connection between the SBTMO, the SOBOPE, and the Brazilian Association of Hematology, Hemotherapy and Cell Therapy (ABHH), in the challenged goal of better treatment conditions for children and adolescents with AML, and greater knowledge of Brazilian data.

## CONFLICT OF INTEREST

Nothing to declare.

## DATA AVAILABILITY STATEMENT

The data will be available upon request.

## AUTHORS' CONTRIBUTIONS

**Substantive scientific and intellectual contributions to the study:** Rodrigues ALM, Seber A, Ribeiro RC, Zecchin VG, Lee MLM, Daudt L, Souza L, Sousa AM, Zanette AA, Nolasco C, Climaco V, Ribeiro AC, Domingues L, Silva TCPM, Klinger P, Rocha C, Magalhães I. **Conception and design:** Rodrigues ALM, Seber A, Ribeiro RC. **Analysis and interpretation of data:** Rodrigues ALM, Seber A, Ribeiro RC. **Technical procedures:** Rodrigues ALM, Seber A, Ribeiro RC. **Statistics analysis:** Rodrigues ALM, Seber A, Ribeiro RC. **Manuscript writing:** Rodrigues ALM, Seber A, Ribeiro RC. **Final approval:** Rodrigues ALM.

## FUNDING

Not applicable.

## ACKNOWLEDGEMENTS

The authors express their gratitude to the Brazilian Society of Cellular Therapy and Bone Marrow Transplantation, the Brazilian Society of Pediatric Oncology, and the Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy for their support and efforts in gathering, analyzing, and disseminating data on the treatment of acute myeloid leukemia in Brazilian children and adolescents. This collaboration facilitates initiatives aimed at improving survival and cure rates in Brazil.

## REFERENCES

1. Estey E, Döhner H. Acute myeloid leukaemia. *Lancet*. 2006 Nov 25;368(9550):1894–907. [https://doi.org/10.1016/S0140-6736\(06\)69780-8](https://doi.org/10.1016/S0140-6736(06)69780-8)
2. Lagunas-Rangel FA, Chávez-Valencia V, Gómez-Guijosa MÁ, Cortes-Penagos C. Acute myeloid leukemia-genetic alterations and their clinical prognosis. *Int J Hematol Oncol Stem Cell Res*. 2017;11(4):328–39.
3. Rubnitz JE. Current management of childhood acute myeloid leukemia. *Paediatr Drugs*. 2017;19(1):1–10. <https://doi.org/10.1007/s40272-016-0200-6>
4. Sadeghian MH, Rezaei Dezaki Z. Prognostic value of EVI1 expression in pediatric acute myeloid leukemia: a systematic review. *Iran J Pathol*. 2018;13(3):294–300.
5. Burke MJ, Wagner JE, Cao Q, Ustun C, Verneris MR. Allogeneic hematopoietic cell transplantation in first remission abrogates poor outcomes associated with high-risk pediatric acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2013;19(7):1021–5. <https://doi.org/10.1016/j.bbmt.2013.04.001>
6. Rubnitz JE, Kaspers GJL. How I treat pediatric acute myeloid leukemia. *Blood*. 2021;138(12):1009–18. <https://doi.org/10.1182/blood.2021011694>
7. Gibson BE, Webb DK, Howman AJ, De Graaf SS, Harrison CJ, Wheatley K. Results of a randomized trial in children with acute myeloid leukaemia: medical research council AML12 trial. *Br J Haematol*. 2011;155(3):366–76. <https://doi.org/10.1111/j.1365-2141.2011.08851.x>
8. Abrahamsson J, Forestier E, Heldrup J, Jahnukainen K, Jónsson OG, Lausen B, Palle J, Zeller B, Hasle H. Response-guided induction therapy in pediatric acute myeloid leukemia with excellent remission rate. *J Clin Oncol*. 2011;29(3):310–5. <https://doi.org/10.1200/jco.2010.30.6829>
9. Rasche M, Zimmermann M, Borschel L, Bourquin JP, Dworzak M, Klingebiel T, Lehrnbecher T, Creutzig U, Klusmann JH, Reinhardt D. Successes and challenges in the treatment of pediatric acute myeloid leukemia: a retrospective analysis of the AML-BFM trials from 1987 to 2012. *Leukemia*. 2018;32(10):2167–77. <https://doi.org/10.1038/s41375-018-0071-7>
10. de Melo Rodrigues AL, Bonfim C, Seber A, Colturato VAR, Zecchin VG, Nichele S, Daudt LE, Fernandes JF, Vieira AK, Darrigo Junior LG, Gomes AA, Arcuri L, Lenzi L, Picharski GL, Ribeiro RC, de Figueiredo BC. Allogeneic hematopoietic stem cell transplantation for children and adolescents with acute myeloid leukemia in Brazil: a multicentric retrospective study. *Cell Transplant*. 2020;29:963689720949175. <https://doi.org/10.1177/0963689720949175>
11. de Melo Rodrigues AL, Zecchin VG, Lee MLM, Zanette AA, Seber A, Ribeiro RC. Hematopoietic Stem Cell Transplantation for Pediatric Acute Myeloid Leukemia - SBTMO/SOPOBE 2020 Consensus Guidelines. *J Bone Transplant Cell Ther*. 2021;2(4):139. <https://doi.org/10.46765/2675-374X.2021v2n4p139>

12. Shiba N, Yoshida K, Hara Y, Yamato G, Shiraishi Y, Matsuo H, Okuno Y, Chiba K, Tanaka H, Kaburagi T, Takeuchi M, Ohki K, Sanada M, Okubo J, Tomizawa D, Taki T, Shimada A, Sotomatsu M, Horibe K, Taga T, Adachi S, Tawa A, Miyano S, Ogawa S, Hayashi Y. Transcriptome analysis offers a comprehensive illustration of the genetic background of pediatric acute myeloid leukemia. *Blood Adv.* 2019;3(20):3157–69. <https://doi.org/10.1182/bloodadvances.2019000404>
13. Graff Z, Wachter F, Eapen M, Lehmann L, Cooper T. Navigating treatment options and communication in relapsed pediatric AML. *Am Soc Clin Oncol Educ Book.* 2024;44(3):e438690. [https://doi.org/10.1200/EDBK\\_438690](https://doi.org/10.1200/EDBK_438690)
14. Dvorak CC, Agarwal R, Dahl GV, Gregory JJ, Feusner JH. Hematopoietic stem cell transplant for pediatric acute promyelocytic leukemia. *Biol Blood Marrow Transplant.* 2008;14(7):824–30. <https://doi.org/10.1016/j.bbmt.2008.04.015>
15. Yamamoto S, Tomizawa D, Kudo K, Hasegawa D, Taga T, Yanada M, Kondo T, Nakazawa Y, Eto T, Inoue M, Kato K, Atsuta Y, Ishida H. Hematopoietic stem cell transplantation for pediatric acute promyelocytic leukemia in Japan. *Pediatr Blood Cancer.* 2020;67(5):e28181. <https://doi.org/10.1002/pbc.28181>
16. Miladinovic M, Reinhardt D, Hasle H, Goemans BF, Tomizawa D, Hitzler J, Klusmann JH. Guideline for treating relapsed or refractory myeloid leukemia in children with Down syndrome. *Pediatr Blood Cancer.* 2024;71(9):e31141. <https://doi.org/10.1002/pbc.31141>
17. Bakst RL, Tallman MS, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. *Blood.* 2011;118(14):3785–93. <https://doi.org/10.1182/blood-2011-04-347229>
18. Shallis RM, Gale RP, Lazarus HM, Roberts KB, Xu ML, Seropian SE, Gore SD, Podoltsev NA. Myeloid sarcoma, chloroma, or extramedullary acute myeloid leukemia tumor: A tale of misnomers, controversy and the unresolved. *Blood Rev.* 2021;47:100773. <https://doi.org/10.1016/j.blre.2020.100773>
19. Woods WG, Neudorf S, Gold S, Sanders J, Buckley JD, Barnard DR, Dusenbery K, DeSwarte J, Arthur DC, Lange BJ, Koblinsky NL; Children's Cancer Group. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. *Blood.* 2001;97(1):56–62. <https://doi.org/10.1182/blood.v97.1.56>
20. Locatelli F, Masetti R, Rondelli R, Zecca M, Fagioli F, Rovelli A, Messina C, Lanino E, Bertaina A, Favre C, Giorgiani G, Ripaldi M, Ziino O, Palumbo G, Pillon M, Pession A, Rutella S, Prete A. Outcome of children with high-risk acute myeloid leukemia given autologous or allogeneic hematopoietic cell transplantation in the aieop AML-2002/01 study. *Bone Marrow Transplant.* 2015;50(2):181–8. <https://doi.org/10.1038/bmt.2014.246>
21. Bitan M, He W, Zhang MJ, Abdel-Azim H, Ayas MF, Bielezai B, Carpenter PA, Cairo MS, Diaz MA, Horan JT, Jodele S, Kitko CL, Schultz KR, Kletzel M, Kasow KA, Lehmann LE, Mehta PA, Shah N, Pulsipher MA, Prestidge T, Seber A, Shenoy S, Woolfrey AE, Yu LC, Davies SM. Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. *Blood.* 2014;123(10):1615–20. <https://doi.org/10.1182/blood-2013-10-535716>
22. Simione A, Silva C, Silva Sabaini P, Macedo A, Neves H, Geraldo B, et al. Current use and outcomes of hematopoietic stem cell transplantation: Brazilian Summary Slides–2024. *J Bone Marrow Transplant Cell Ther.* 2024;5(1):228. <https://doi.org/10.46765/2675-374X.2024v5n1p228>
23. Sauer MG, Lang PJ, Albert MH, Bader P, Creutzig U, Eylich M, Greil J, Gruhn B, Holter W, Klingebiel T, Kremens B, von der Leyen H, Mauz-Körholz C, Meisel R, Mischke K, Müller I, Niemeyer CM, Peters C, Pohler C, Reinhardt D, Burkhardt B, Schlegel PG, Schulz AS, Schrum J, Sedlacek P, Strahm B, Woessmann W, Handgretinger R, Zimmermann M, Borkhardt A. Hematopoietic stem cell transplantation for children with acute myeloid leukemia—results of the AML SCT-BFM 2007 trial. *Leukemia.* 2020;34(2):613–24. <https://doi.org/10.1038/s41375-019-0584-8>

24. Golub TR, Arceci RJ. Acute myelogenous leukemia. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. Philadelphia: Lippincot; 2002. p. 545–89.
25. Leung W, Campana D, Yang J, Pei D, Coustan-Smith E, Gan K, Rubnitz JE, Sandlund JT, Ribeiro RC, Srinivasan A, Hartford C, Triplett BM, Dallas M, Pillai A, Handgretinger R, Laver JH, Pui CH. High success rate of hematopoietic cell transplantation regardless of donor source in children with very high-risk leukemia. *Blood*. 2011;118(2):223–30. <https://doi.org/10.1182/blood-2011-01-333070>
26. Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, Lang P, Sykora KW, Schrum J, Kremens B, Ehlert K, Albert MH, Meisel R, Matthes-Martin S, Gungor T, Holter W, Strahm B, Gruhn B, Schulz A, Woessmann W, Poetschger U, Zimmermann M, Klingebiel T. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. *J Clin Oncol*. 2015;33(11):1265–74. <https://doi.org/10.1200/JCO.2014.58.9747>
27. Burke MJ, Verneris MR, Le Rademacher J, He W, Abdel-Azim H, Abraham AA, Auletta JJ, Ayas M, Brown VI, Cairo MS, Chan KW, Diaz Perez MA, Dvorak CC, Egeler RM, Eldjerou L, Frangoul H, Guilcher GMT, Hayashi RJ, Ibrahim A, Kasow KA, Leung WH, Olsson RF, Pulsipher MA, Shah N, Shah NN, Thiel E, Talano JA, Kitko CL. Transplant outcomes for children with t cell acute lymphoblastic leukemia in second remission: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2015;21(12):2154–9. <https://doi.org/10.1016/j.bbmt.2015.08.023>
28. Tavares RCB, Bonfim CS, Seber A, Pereira Lermontov S, Coulturato V, Zecchin VG, Ribeiro L, Fernandes JF, Daudt LE, Grecco CS, Darrigo-Jr LG, Villela N, Nichele S, Gouveia R, Bouzas LF, Hamerschlak N, Vigorito AC, da Silva PM, da Silva PO, da Silva CC, de Souza Fernandez C, Flowers ME, Arcuri LJ. Hematopoietic cell transplantation in pediatric patients with acute leukemias or myelodysplastic syndrome using unrelated adult or umbilical cord blood donors in Brazil. *Pediatr Transplant*. 2020;24(7):e13789. <https://doi.org/10.1111/petr.13789>
29. Rocha V, Arcuri LJ, Seber A, Colturato V, Zecchin VG, Kuwahara C, Nichele S, Gouveia R, Fernandes JF, Macedo AV, Tavares R, Daudt L, De Souza MP, Darrigo-Jr LG, Villela NC, Mariano LCB, Ginani VC, Zanette A, Loth G, Gomes AA, Hamerschlak N, Flowers ME, Bonfim C; Paediatric Working Group and the Brazil-Seattle Consortium Study Group (GEDECO) of the Brazilian Bone Marrow Transplantation Society (SBTMO). Impact of mother donor, peripheral blood stem cells and measurable residual disease on outcomes after haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide in children with acute leukaemia. *Bone Marrow Transplant*. 2021;56(12):3042–8. <https://doi.org/10.1038/s41409-021-01453-0>
30. Michel G, Gluckman E, Esperou-Bourdeau H, Reiffers J, Pico JL, Bordignon P, Thuret I, Blaise D, Bernaudin F, Jouet JP. Allogeneic bone marrow transplantation for children with acute myeloblastic leukemia in first complete remission: impact of conditioning regimen without total-body irradiation--a report from the Société Française de Greffe de Moelle. *J Clin Oncol*. 1994;12(6):1217–22. <https://doi.org/10.1200/JCO.1994.12.6.1217>
31. Small TN, Young JW, Castro-Malaspina H, Prockop S, Wilton A, Heller G, Boulad F, Chiu M, Hsu K, Jakubowski A, Kernan NA, Perales MA, O'Reilly RJ, Papadopoulos EB. Intravenous busulfan and melphalan, tacrolimus, and short-course methotrexate followed by unmodified HLA-matched related or unrelated hematopoietic stem cell transplantation for the treatment of advanced hematologic malignancies. *Biol Blood Marrow Transplant*. 2007;13(2):235–44. <https://doi.org/10.1016/j.bbmt.2006.10.005>
32. Kobos R, Steinherz PG, Kernan NA, Prockop SE, Scaradavou A, Small TN, Shukla N, Khalaf R, O'Reilly RJ, Boulad F. Allogeneic hematopoietic stem cell transplantation for pediatric patients with treatment-related myelodysplastic syndrome or acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2012;18(3):473–80. <https://doi.org/10.1016/j.bbmt.2011.11.009>

33. Pession A, Masetti R, Rizzari C, Putti MC, Casale F, Fagioli F, Luciani M, Lo Nigro L, Menna G, Micalizzi C, Santoro N, Testi AM, Zecca M, Biondi A, Pigazzi M, Rutella S, Rondelli R, Basso G, Locatelli F; AIEOP AML Study Group. Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. *Blood*. 2013;122(2):170–8. <https://doi.org/10.1182/blood-2013-03-491621>
34. Beier R, Albert MH, Bader P, Borkhardt A, Creutzig U, Eyrich M, Ehlert K, Gruhn B, Greil J, Handgretinger R, Holter W, Klingebiel T, Kremens B, Lang P, Mauz-Körholz C, Meisel R, Müller I, Peters C, Reinhardt D, Sedlacek P, Schulz A, Schuster FR, Schrauder A, Strahm B, Sykora KW, Wössmann W, Zimmermann M, Sauer MG. Allo-SCT using BU, CY and melphalan for children with AML in second CR. *Bone Marrow Transplant*. 2013;48(5):651–6. <https://doi.org/10.1038/bmt.2012.204>
35. de Berranger E, Cousien A, Petit A, Peffault de Latour R, Galambrun C, Bertrand Y, Salmon A, Rialland F, Rohrlisch PS, Vannier JP, Lutz P, Yakouben K, Duhamel A, Bruno B, Michel G, Dalle JH. Impact on long-term OS of conditioning regimen in allogeneic BMT for children with AML in first CR: TBI+CY versus BU+CY: a report from the Société Française de Greffe de Moelle et de Thérapie Cellulaire. *Bone Marrow Transplant*. 2014;49(3):382–8. <https://doi.org/10.1038/bmt.2013.185>
36. Solomon SR, Sizemore CA, Sanacore M, Zhang X, Brown S, Holland HK, Morris LE, Bashey A. Total body irradiation-based myeloablative haploidentical stem cell transplantation is a safe and effective alternative to unrelated donor transplantation in patients without matched sibling donors. *Biol Blood Marrow Transplant*. 2015;21(7):1299–307. <https://doi.org/10.1016/j.bbmt.2015.03.003>
37. Owattanapanich W, Ungprasert P, Wais V, Kungwankiattichai S, Bunjes D, Kuchenbauer F. FLAMSA-RIC for stem cell transplantation in patients with acute myeloid leukemia and myelodysplastic syndromes: a systematic review and meta-analysis. *J Clin Med*. 2019;8(9):1437. <https://doi.org/10.3390/jcm8091437>
38. Holtick U, Shimabukuro-Vornhagen A, Chakupurakal G, Theurich S, Leitzke S, Burst A, Hallek M, von Bergwelt-Baildon M, Scheid C, Chemnitz JM. FLAMSA reduced-intensity conditioning is equally effective in AML patients with primary induction failure as well as in first or second complete remission. *Eur J Haematol*. 2016;96(5):475–82. <https://doi.org/10.1111/ejh.12615>
39. Correa A, Martins A, Donatelli A, Santos C, Cardos M, Quintino L, Zamperlini G, Domingues LDS, Sousa AVL, Seber A. Allogeneic hematopoietic stem cell transplants (HSCT) with adapted FLAMSA can cure half of the pediatric patients with refractory acute myelogenous leukemia (AML). *Hematol Transfus Cell Ther*. 2023;45(Suppl. 4):S544. <https://doi.org/10.1016/j.htct.2023.09.1000>
40. Locatelli F, Pession A, Comoli P, Bonetti F, Giorgiani G, Zecca M, Taibi RM, Mongini ME, Ambroselli F, de Stefano P, Severi F, Paolucci G. Role of allogeneic bone marrow transplantation from an HLA-identical sibling or a matched unrelated donor in the treatment of children with juvenile chronic myeloid leukaemia. *Br J Haematol*. 1996;92(1):49–54. <https://doi.org/10.1046/j.1365-2141.1996.00276.x>
41. Locatelli F, Niemeyer C, Angelucci E, Bender-Götze C, Burdach S, Ebell W, Friedrich W, Hasle H, Hermann J, Jacobsen N, Klingebiel T, Kremens B, Mann G, Pession A, Peters C, Schmid HJ, Stary J, Suttorp M, Uderzo C, van't Veer-Korthof ET, Vossen J, Zecca M, Zimmermann M. Allogeneic bone marrow transplantation for chronic myelomonocytic leukemia in childhood: a report from the European Working Group on Myelodysplastic Syndrome in Childhood. *J Clin Oncol*. 1997;15(2):566–73. <https://doi.org/10.1200/JCO.1997.15.2.566>
42. Strahm B, Nöllke P, Zecca M, Korthof ET, Bierings M, Furlan I, Sedlacek P, Chybicka A, Schmutz M, Bordon V, Peters C, O'Marcaigh A, de Heredia CD, Bergstraesser E, Moerloose BD, van den Heuvel-Eibrink MM, Stary J, Trebo M, Wojcik D, Niemeyer CM, Locatelli F; EWOG-MDS study group. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome in children: results of the EWOG-MDS 98 study. *Leukemia*. 2011;25(3):455–62. <https://doi.org/10.1038/leu.2010.297>

43. Jaiswal SR, Zaman S, Chakrabarti A, Sen S, Mukherjee S, Bhargava S, Ray K, O'Donnell PV, Chakrabarti S. Improved outcome of refractory/relapsed acute myeloid leukemia after post-transplantation cyclophosphamide-based haploidentical transplantation with myeloablative conditioning and early prophylactic granulocyte colony-stimulating factor-mobilized donor lymphocyte infusions. *Biol Blood Marrow Transplant.* 2016;22(10):1867–73. <https://doi.org/10.1016/j.bbmt.2016.07.016>
44. Jaiswal SR, Chakrabarti A, Chatterjee S, Ray K, Chakrabarti S. Haploidentical transplantation in children with unmanipulated peripheral blood stem cell graft: The need to look beyond post-transplantation cyclophosphamide in younger children. *Pediatr Transplant.* 2016;20(5):675–82. <https://doi.org/10.1111/ptr.12724>
45. Lv X, Qi J, Zhou M, Shi B, Cai C, Tang Y, Pan T, Han Y. Comparative efficacy of 20 graft-versus-host disease prophylaxis therapies for patients after hematopoietic stem-cell transplantation: A multiple-treatments network meta-analysis. *Crit Rev Oncol Hematol.* 2020;150:102944. <https://doi.org/10.1016/j.critrevonc.2020.102944>
46. Elgarten CW, Arnold DE, Bunin NJ, Seif AE. Outcomes of matched sibling donor bone marrow transplantation in children using single-agent calcineurin inhibitors as prophylaxis for graft versus host disease. *Pediatr Blood Cancer.* 2018;65(1):e26726. <https://doi.org/10.1002/psc.26726>
47. Lawitschka A, Lucchini G, Strahm B, Dalle JH, Balduzzi A, Gibson B, Diaz De Heredia C, Wachowiak J, Dalissier A, Vetterranta K, Yaniv I, Bordon V, Bauer D, Bader P, Meisel R, Peters C, Corbacioglu S; European Society for Blood, Marrow Transplantation (EBMT) Pediatric Diseases Working Party. Pediatric acute graft-versus-host disease prophylaxis and treatment: surveyed real-life approach reveals dissimilarities compared to published recommendations. *Transpl Int.* 2020;33(7):762–72. <https://doi.org/10.1111/tri.13601>
48. Jacoby E, Chen A, Loeb DM, Gamper CJ, Zambidis E, Llosa NJ, Huo J, Cooke KR, Jones R, Fuchs E, Luznik L, Symons HJ. Single-agent post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis after human leukocyte antigen-matched related bone marrow transplantation for pediatric and young adult patients with hematologic malignancies. *Biol Blood Marrow Transplant.* 2016;22(1):112–8. <https://doi.org/10.1016/j.bbmt.2015.08.034>
49. Kwon M, Bailèn R, Pascual-Cascón MJ, Gallardo-Morillo AI, García Sola A, Balsalobre P, Solán L, Dorado N, Muñoz C, Serrano D, Martínez-Laperche C, Buno I, Anguita J, Díez-Martin JL. Posttransplant cyclophosphamide vs cyclosporin A and methotrexate as GVHD prophylaxis in matched sibling transplantation. *Blood Adv.* 2019;3(21):3351–9. <https://doi.org/10.1182/bloodadvances.2019000236>
50. Yerushalmi R, Shem-Tov N, Danylesko I, Shouval R, Nagler A, Shimoni A. The combination of cyclosporine and mycophenolate mofetil is less effective than cyclosporine and methotrexate in the prevention of acute graft-versus host disease after stem-cell transplantation from unrelated donors. *Am J Hematol.* 2017;92(3):259–68. <https://doi.org/10.1002/ajh.24631>
51. Locatelli F, Bernardo ME, Bertaina A, Rognoni C, Comoli P, Rovelli A, Pession A, Fagioli F, Favre C, Lanino E, Giorgiani G, Merli P, Pagliara D, Prete A, Zecca M. Efficacy of two different doses of rabbit anti-T-lymphocyte globulin to prevent graft-versus-host disease in children with haematological malignancies transplanted from an unrelated donor: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(8):1126–36. [https://doi.org/10.1016/S1470-2045\(17\)30417-5](https://doi.org/10.1016/S1470-2045(17)30417-5)
52. Nagler A, Baron F, Labopin M, Polge E, Esteve J, Bazarbachi A, Brissot E, Bug G, Ciceri F, Giebel S, Gillece MH, Gorin NC, Lanza F, Peric Z, Ruggeri A, Sanz J, Savani BN, Schmid C, Shouval R, Spyridonidis A, Versluis J, Mohty M. Measurable residual disease (MRD) testing for acute leukemia in EBMT transplant centers: a survey on behalf of the ALWP of the EBMT. *Bone Marrow Transplant.* 2021;56(1):218–24. <https://doi.org/10.1038/s41409-020-01005-y>

53. Short NJ, Zhou S, Fu C, Berry DA, Walter RB, Freeman SD, Hourigan CS, Huang X, Noguera Gonzalez G, Hwang H, Qi X, Kantarjian H, Ravandi F. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol.* 2020;6(12):1890–9. <https://doi.org/10.1001/jamaoncol.2020.4600>
54. Egan G, Tasian SK. Relapsed pediatric acute myeloid leukaemia: state-of-the-art in 2023. *Haematologica.* 2023;108(9):2275–88. <https://doi.org/10.3324/haematol.2022.281106>
55. Breviglieri CNM, Gouveia RV, Ginani VC, Santos CN, de Oliveira MRS, Batalha ABW, de Alencar GS, Goto EH, Marques JF, Pupim MPV, Seber A. Post-stem cell transplant maintenance for pediatric acute leukemias: insights from a Brazilian institution with a Latin American perspective. *Front Oncol.* 2025;15:1540158. <https://doi.org/10.3389/fonc.2025.1540158>