Beyond HLA matching: a practical framework for selecting among HLA-identical donors in hematopoietic stem cell transplantation

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ABSTRACT

Background: Donor selection in allogeneic hematopoietic stem cell transplantation (HSCT) has evolved beyond human leukocyte antigen (HLA) compatibility. Advances in transplant platforms and immunogenetics have highlighted the importance of integrating additional donor-related clinical and biological factors. **Methods:** This Brazilian Society of Bone Marrow Transplantation (SBTMO) consensus was developed through a critical review of the current literature and expert discussion. It addresses the main variables influencing donor selection beyond HLA matching and provides evidence-based recommendations. **Results:** Donor age is the most relevant non-HLA factor and should be prioritized whenever possible. Other variables—including cytomegalovirus serostatus, ABO compatibility, donor sex and parity, germline predisposition variants, donor eligibility, and ethical considerations—should be incorporated into an individualized decision-making process. A practical algorithm summarizes the proposed recommendations. **Conclusion:** Donor selection should integrate HLA compatibility with clinical, biological, and ethical factors to optimize transplant outcomes. This consensus provides a practical framework to support evidence-based donor selection in contemporary allogeneic HSCT.

Keywords: Hematopoietic stem cell transplantation. Donor selection. Donor age.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) remains a potentially curative therapy for a range of malignant and non-malignant hematologic diseases. Historically, matched sibling donors (MSDs) have been considered the preferred option, owing to their broad availability, lower logistical complexity, lower incidence of immunologic complications, particularly graft-*versus*-host disease (GVHD), and association with superior clinical outcomes in classical cohorts[1,2].

However, this paradigm has been progressively redefined. Advances in immunogenetics, the routine incorporation of post-transplant cyclophosphamide (PTCy)–based prophylaxis, and the expansion of alternative donor sources have substantially changed the HSCT landscape[3]. Recent evidence shows that alternative platforms, including haploidentical transplants performed with PTCy and young unrelated donors, may achieve overall survival and disease-free survival comparable to those observed with MSDs in specific

settings, challenging the historical concept of universal superiority of the MSD[4–6]. In parallel, the definition of human leukocyte antigen (HLA) compatibility has evolved significantly, incorporating high-resolution typing and multiple loci, making the concept of complete match more complex and biologically relevant, with direct implications for risk stratification and selection of the optimal donor[4,7].

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show a progressive change in the pattern of donor utilization, characterized by a proportional decline in the use of MSDs with a parallel increase in unrelated and haploidentical donors over the past decade[5]. This trend reflects not only therapeutic advances but also relevant demographic changes, including the aging of the transplant candidate population—frequently associated with equally older siblings carrying a greater burden of comorbidities—, as well as the reduction in family size. Consequently, the availability of MSDs remains limited, estimated at between 13 and 51% of patients[4,8]. Even when available, it does not always represent the best biological or clinical option in the current context. These aspects reinforce the need for a more dynamic and individualized approach to donor selection.

Thus, although the MSD remains an important option, it should no longer be considered universally superior. The selection of the optimal donor should integrate multiple clinical and biological variables, aiming to optimize recipient outcomes without compromising donor safety.

These clinical and biological variables may influence transplant outcomes and should therefore be considered when choosing the best donor; they do not, however, carry the same weight and require an individualized, hierarchical approach. To assist hematologists and transplant physicians, the Brazilian Society of Bone Marrow Transplantation (SBTMO) developed this consensus, which addresses the criteria that guide donor selection beyond HLA compatibility. These criteria apply to HLA-identical donors, whether related or unrelated. Donor eligibility, safety, and ethical aspects are discussed in the context of the related donor. HLA matching itself, registry search strategies, and the selection of umbilical cord blood units are not addressed.

In the following sections, the main variables are discussed individually, together with the SBTMO recommendations, and are ultimately summarized in an algorithm that organizes the hierarchy of priorities and supports decision-making in clinical practice.

METHODS

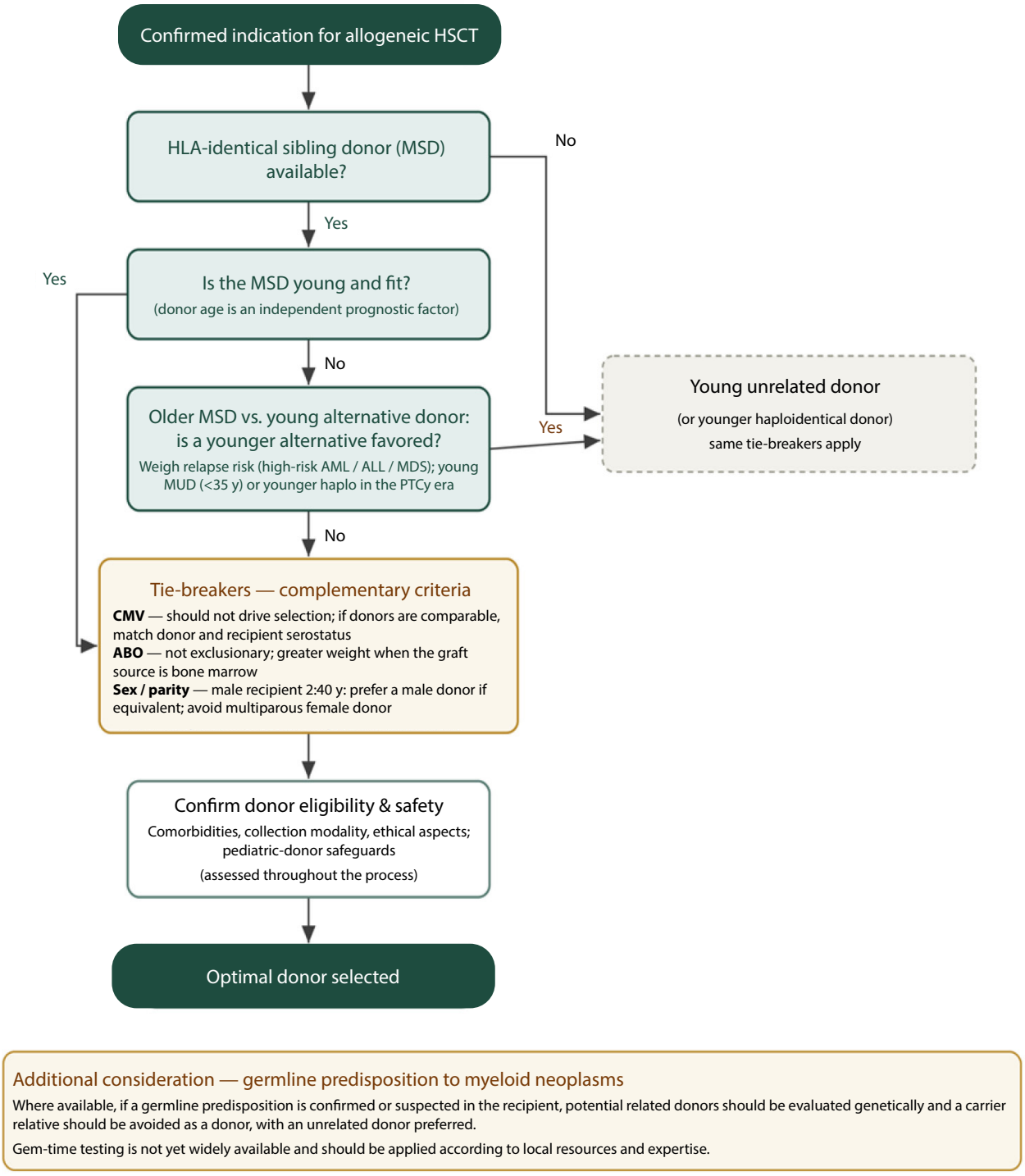
This consensus was developed by the Brazilian Society of Bone Marrow Transplantation (SBTMO) based on a critical review of the available literature and expert discussion among the authors. Current evidence from international guidelines, clinical studies, and registry analyses was considered to identify the main clinical and biological factors influencing donor selection beyond HLA compatibility. Based on the available evidence and expert consensus, practical recommendations were formulated and integrated into a decision-making algorithm (Fig. 1).

RESULTS

Donor age and impact on outcomes

Donor age has emerged as one of the main independent prognostic determinants, with a direct impact on survival and on the incidence of chronic GVHD. In this context, recent data suggest that younger unrelated donors may be preferable to older MSDs, particularly in the PTCy era, reinforcing the need for individualization in donor selection[9–12].

A CIBMTR study that analyzed more than 10,000 patients undergoing unrelated transplantation between 2016 and 2019, with GVHD prophylaxis predominantly based on a calcineurin inhibitor, showed that donors between 18 and 30 years of age have equivalent overall survival outcomes, whereas donors aged 31 or older are associated with a progressive decline in three-year survival, ranging from 1% to slightly more than 3% as donor age increases[13].



Donor age carries the greatest weight; CMV, ABO, and sex/parity are same-level, complementary tie-breakers (no rank among them). Donor eligibility and safety are assessed throughout. The same tie-breakers apply once an alternative donor is chosen. HLA matching, registry search, and cord blood selection are outside the scope. HSCT: hematopoietic stem cell transplantation; MSD: matched sibling donor; MUD: matched unrelated donor; PTCy: post-transplant cyclophosphamide; CMV: cytomegalovirus; HLA: human leukocyte antigen; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia. Source: Elaborated by the authors.

Figure 1. Algorithm for selecting among HLA-identical donors, based on criteria other than HLA compatibility. Donor age carries the greatest weight; CMV, ABO, and sex/parity are same-level, complementary tiebreakers. The same tiebreakers apply once an alternative donor is chosen. Germline predisposition is presented as an additional consideration, as testing is not widely available yet.

However, unlike the unrelated donor setting, there are no rigidly established age limits for MSDs. Therefore, the decision must be individualized, considering the donor's clinical condition and the absence of more suitable alternatives[2,12]. This aspect is particularly relevant in current practice, in which many patients who are candidates for HSCT are older than 55 and have equally older siblings. Comparative studies between young unrelated donors (generally younger than 35–40) and older related donors in the context of acute myeloid leukemia (AML)[5,6,14], acute lymphoid leukemia (ALL)[15], and myelodysplastic syndrome (MDS)[16] point to a lower risk of relapse with the choice of young unrelated donors, which may be particularly beneficial in high-risk patients. Evidence in haploidentical transplantation is less robust, but recent studies suggest a lower risk of complications and a preference for the youngest available haploidentical donor[17–19].

OTHER VARIABLES

Cytomegalovirus

Although serologic compatibility for cytomegalovirus (CMV) has historically been considered a relevant factor in donor selection, study results are heterogeneous and appear to vary according to the transplant platform, conditioning intensity, GVHD prophylaxis, and graft source[11,20,21]. Large CIBMTR analyses have not demonstrated a consistent association between donor CMV serostatus and overall survival[9,13]. However, these studies have important limitations, including the absence of a detailed assessment of viral reactivation and post-transplant CMV disease.

In the unrelated donor transplant setting, CMV serology may influence clinical outcomes. Seronegative recipients have worse survival when they receive grafts from seropositive donors, reinforcing the preference for CMV-negative donors in this group. Among seropositive recipients, some studies suggest a survival benefit with seropositive donors in myeloablative regimens, an effect not observed in reduced-intensity conditioning. These associations have not been well established in transplants with MSDs. A large registry analysis found no impact of donor CMV serostatus on survival in MSD transplants[20]. In contrast, a recent registry analysis of related donors, including MSDs and haploidentical donors, restricted to CMV-seronegative recipients, showed that CMV-seropositive donors are associated with inferior overall survival and higher non-relapse mortality[22].

Regardless, the previously observed negative impact of CMV infection has been significantly reduced with the incorporation of letermovir prophylaxis[23,24]. In a prospective multicenter study conducted in the letermovir era, donor and recipient serology no longer correlated with early clinically significant CMV infection in patients receiving prophylaxis, nor with survival at 12 months[25]. However, letermovir is not universally available, and donor CMV serostatus may retain greater relevance when effective prophylaxis is not accessible. In summary, although donor CMV serostatus should not drive donor selection, when choosing between otherwise comparable HLA-identical donors, we recommend a seronegative donor for a seronegative recipient and in seropositive recipients undergoing myeloablative conditioning, a seropositive donor.

ABO

In a large CIBMTR cohort[26], ABO incompatibility was not associated with a significant impact on overall survival or relapse, reinforcing that it should not be considered an exclusion criterion in donor selection. However, major and bidirectional incompatibilities may be associated with a higher risk of hematologic complications, including delayed erythroid recovery and increased transfusion dependence[11,26,27]. ABO incompatibility–related morbidity may take on clinical relevance in certain settings, particularly when the graft source is bone marrow, a situation in which red-cell depletion strategies may be required. In these cases, the persistence of recipient isohemagglutinins may contribute to prolonged anemia and impact the erythroid engraftment, in addition to potential cell loss associated with graft manipulation[28].

Patients undergoing reduced-intensity conditioning have a higher risk of delayed erythroid chimerism and may benefit from avoiding major ABO incompatibility between donor and recipient[29,30]. Thus, although ABO incompatibility does not contraindicate transplantation, it should be considered a complementary factor in donor selection—carrying greater weight when the graft source is bone marrow or when multiple equivalent donors are available.

Sex and parity

Donor sex and pregnancy history may influence the outcomes of allogeneic transplantation, particularly in the context of male recipients and multiparous female donors. Landmark studies show that female donors, especially multiparous ones, are associated with a higher incidence of GVHD, particularly in male recipients. This phenomenon is attributed to maternal alloimmunization against minor histocompatibility antigens, including H-Y antigens[31,32]. On the other hand, the greater alloreactivity associated with these combinations may contribute to a potential graft-*versus*-leukemia effect, with a possible reduction in relapse risk in certain settings[32,33].

In a recent study involving MSD transplants in a homogeneous population undergoing myeloablative conditioning and CsA + MTX prophylaxis, parity was an independent factor for a higher incidence of severe acute GVHD (hazard ratio [HR] = 3.90) and extensive chronic GVHD (HR = 4.62), with a significant reduction in relapse incidence and no impact on overall survival in multivariate analysis[34]. In male recipients aged ≥ 40, male donors should be preferred when available and equivalent with respect to other selection criteria, since the female-donor → male-recipient combination is associated with higher non-relapse mortality and worse overall survival[35]. Contemporary data suggest that this effect represents a dynamic immunologic balance, in which greater alloreactivity may contribute to a lower relapse risk at the cost of greater immunologic toxicity. However, the clinical impact of these variables appears to vary according to the transplant platform, GVHD prophylaxis, and specific immunogenic characteristics[11]. Thus, donor sex and parity should be considered complementary factors in donor selection, particularly in settings with multiple equivalent donors, always integrated with variables of greater clinical impact, such as donor age and HLA compatibility.

Germline predisposition variants

The routine use of next-generation sequencing for risk stratification in hematologic malignancies has made it possible to identify patients with germline variants associated with myeloid neoplasm predisposition syndromes. The main genes involved include DDX41, CEBPA, GATA2, RUNX1, ANKRD26, ETV6, TERT, and CHEK2[36–39]. The identification of these variants has direct implications for donor selection, since germline mutations may be present in clinically healthy donors.

The use of donors carrying these variants is associated with adverse outcomes, including poor hematopoietic stem cell mobilization, delayed engraftment and graft failure, and the development of donor-derived neoplasms resulting from the transfer of genetically predisposed hematopoietic clones[37,39,40].

In patients with confirmed or strongly suspected germline predisposition, potential related donors should undergo appropriate genetic evaluation before the transplant strategy is defined, when available.

The use of donors carrying pathogenic or likely pathogenic variants associated with hereditary myeloid predisposition syndromes should be avoided. Particularly, germline variants in RUNX1, CEBPA, and DDX41 should be avoided. In these situations, whenever available, an eligible unrelated donor should be considered the preferred alternative[12,39,41,42].

The investigation and confirmation of germline predisposition are summarized in Table 1.

Table 1. Investigation and confirmation of germline predisposition in hematopoietic stem cell transplantation candidates.

Aspect	Recommendation
When to investigate (clinical)	Unexplained long-standing cytopenias or thrombocytopenia; previous malignancy; personal or family history of hematologic neoplasm, bone marrow failure, or cytopenias in first- or second-degree relatives; physical stigmata or pulmonary/hepatic fibrosis—particularly in young patients[38,41,43].
When to investigate (molecular)	DDX41 variant, biallelic CEBPA mutation, or another deleterious variant at near-heterozygous variant allele frequency (VAF) on tumor next-generation sequencing; persistently high VAF in complete remission[38,44].
Caution in interpretation	A high VAF alone does not confirm germline origin—RUNX1 and TP53 are frequently somatic[38,42].
Tissue for confirmation	DNA from non-hematopoietic tissue, preferably cultured skin fibroblasts (hair follicles or another suitable tissue as an alternative)[38].

Source: Elaborated by the authors.

CLINICAL EVALUATION AND DONOR ELIGIBILITY

Evaluation of the related donor should be comprehensive and individualized, including a detailed clinical history, a complete physical examination, and an investigation of relevant comorbidities[2,12]. Unlike the criteria applied to unrelated donors, related donor eligibility may allow greater individualization based on risk–benefit analysis, considering the availability of alternatives, the urgency of the transplant, and the safety of both donor and recipient. Cardiovascular, pulmonary, autoimmune, hematologic, and neoplastic diseases should be carefully evaluated, since they may increase the risk during donation or affect recipient safety[2,12]. Conditions such as morbid obesity, uncontrolled infections, and systemic autoimmune diseases may represent relative contraindications or require individualized evaluation. In addition, clinical fitness should consider the type of collection (bone marrow or apheresis), including anesthetic evaluation when applicable[2]. For bone marrow collection, anesthetic and perioperative risks should be considered, whereas for apheresis collection, aspects related to venous access, granulocyte colony-stimulating factor (G-CSF) use, and the capacity to mobilize hematopoietic stem cells should be assessed.

The European Society for Blood and Marrow Transplantation (EBMT) and the Worldwide Network for Blood and Marrow Transplantation recommendations reinforce that donor eligibility should be based on an individualized risk–benefit analysis, especially in older donors[2,9,12]. Although there are no rigid age limits for related donors, advanced age is associated with lower CD34+ cell mobilization, a greater need for additional apheresis procedures, and a higher incidence of persistent symptoms and slower recovery after donation[2,9]. Laboratory investigation of the donor should include tests aimed at assessing organ function, collection safety, and clinical eligibility[2]. These tests generally include a complete blood count, biochemical assessment, ABO/Rh typing, and mandatory infectious disease testing, in addition to individualized supplementary tests according to the donor's clinical characteristics and the collection modality. These tests make it possible to identify cytopenias, organ dysfunction, and metabolic disturbances that may increase the risk during mobilization with hematopoietic growth factors or during the collection procedure, whether by peripheral blood progenitor cell apheresis or by bone marrow harvest. Laboratory evaluation should also consider particularities related to the collection method, including hematologic monitoring during G-CSF mobilization and assessment of the risk of anemia in bone marrow collections.

Infectious disease screening is mandatory and aims to reduce the risk of transmitting infections to the recipient, to inform post-transplant risk stratification and management, and to ensure the donor's own safety[2,12]. Testing should be performed for human immunodeficiency virus (HIV), hepatitis B and C, syphilis, and human T-lymphotropic virus (HTLV)-I/II, in addition to other epidemiologically indicated tests according to local guidelines and the donor's risk profile. In endemic regions, such as Brazil, screening for Chagas disease is also recommended[12]. Serologic testing for *Toxoplasma gondii* should likewise be included in the evaluation of donor and recipient, particularly in cases which seroprevalence is high. Post-transplant disease results mainly from reactivation in the seropositive recipient, and serostatus therefore guides prophylaxis and monitoring[2]. Additional epidemiologic assessment for malaria and arboviral infections may be necessary according to the donor's clinical history and recent exposure. EBMT and World Marrow Donor Association (WMDA) guidelines

emphasize the need for periodic updating of these tests close to the donation date[2,45], preferably within a period of up to 30 days before collection. The donor's clinical and epidemiologic assessment should also be reviewed immediately before donation, especially to identify recent infectious exposures or new clinical events.

DONOR SAFETY AND ETHICAL ASPECTS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem cell donation involves healthy individuals with no direct clinical benefit, which makes donor safety a non-negotiable ethical priority. Although serious events are uncommon, complications can occur both in bone marrow collection and in G-CSF mobilization and apheresis, whose long-term effects in healthy donors are not fully elucidated yet[46,47]. International standards, such as those of the WMDA, recognize that donor protection is an ethical imperative that should guide the entire transplant chain[45].

Donor care begins with the pre-donation evaluation, which includes a detailed history, complete physical examination, and comprehensive laboratory investigation, including screening for infectious diseases and relevant comorbidities[2,12]. Informed consent must be obtained, with adequate information about risks, benefits, and alternatives, respecting autonomy and confidentiality. Ensuring the absence of coercion is particularly important in related donors, who may be subject to implicit family pressure. In addition, eligibility criteria tend to be less restrictive for related than for unrelated donors, which require careful assessment of individual risk[12,46]. To reduce conflicts of interest, whenever possible the team responsible for donor evaluation should be independent from the team caring for the recipient[12,45,48].

The risk profile differs according to the collection modality. In bone marrow collection, the main risks are related to general anesthesia and anemia resulting from the volume collected, which may require iron supplementation or prior autologous collection. The main complications related to G-CSF mobilization are bone pain, constitutional symptoms, and complications from venous access. Strategies to minimize risks should be adopted, and adverse effects of mobilization and apheresis must be appropriately managed[46,47]. Clinical follow-up of the donor should be ensured until complete recovery[12,45,46].

Autonomy is harder to establish in the pediatric donor[46,48]. Pediatric donors should be used only when justified, after assessment of the donor's best interest and consideration of available donation alternatives[12,48]. From the standpoint of safety, most pediatric donors require a central venous catheter for apheresis, with risks of bleeding, pneumothorax, and complications of sedation or anesthesia; donors weighing less than 20 kg are frequently exposed to allogeneic blood products used to prime the cell separator, which can be associated with significant adverse events[46–48]. In this context, the choice of stem cell source should consider the recipient's indication but more importantly the donor's safety. Evaluation should be multidisciplinary, considering clinical, psychological, and social aspects, and should be conducted by a team independent of the recipient's care[12,48,49]. In addition to the legal guardian's consent, the child or adolescent's assent should be obtained whenever cognitive capacity is compatible, as an expression of respect for the minor's progressive autonomy[49]. HLA typing should not be performed when there is a medical contraindication to collection, so as not to expose the child to a process that cannot be completed[48]. In situations of relevant ethical conflict or disagreement regarding the eligibility of the pediatric donor, evaluation by an institutional ethics committee is recommended and, when applicable, judicial review in accordance with current legislation[12,48,50].

Table 2 summarizes the main recommendations related to donor safety.

Table 2. Recommendations related to donor safety and ethical aspects in hematopoietic stem cell transplantation.

#	Recommendation
	Assessment and consent
1	Pre-donation evaluation with a detailed history, complete physical examination, and comprehensive laboratory investigation, including screening for infectious diseases and relevant comorbidities[2,12].
2	Free and informed consent with adequate information about risks, benefits, and alternatives, respecting autonomy and confidentiality and ensuring the absence of coercion, especially in related donors[12,45].

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3	The team responsible for the donor should, whenever possible, be independent of the recipient's care team, to reduce conflicts of interest[12,45].
	Donor safety and well-being
4	The donor's well-being must be preserved regardless of the expected benefit to the recipient; it is ethically unacceptable to expose the donor to disproportionate risks or risks not justified by the potential benefit of the transplant[2,45–47].
5	Strategies to minimize risks during collection must be adopted: prevention of anemia in bone marrow donation and appropriate management of the adverse effects of growth factor mobilization and apheresis[46,47].
6	Donor's clinical follow-up should be ensured until complete recovery, with monitoring for early complications and appropriate support during the post-donation period[12,45,46].
	Pediatric donors
7	The use of pediatric donors should occur only when there is adequate clinical justification, after assessment of the donor's best interest, with minimization of physical and psychological risks and consideration of the available donation alternatives[12,48].
8	Multidisciplinary evaluation of the pediatric donor covering clinical, psychological, and social aspects, with a team independent of the recipient's care[12,48,49].
9	In addition to the consent of the legal guardians, the child or adolescent's assent must be obtained, whenever there is compatible cognitive capacity, as an expression of respect for the minor's progressive autonomy[49].
10	In situations of relevant ethical conflict or disagreement regarding the eligibility of the pediatric donor, evaluation by an institutional ethics committee is recommended and, when applicable, judicial review in accordance with current legislation[12,48,50].
11	Formal psychological evaluation, continuous support for the donor and family, and longitudinal follow-up after donation, especially in pediatric donors[2,12,48,49].

Source: Elaborated by the authors.

CONCLUSION

Donor selection in allogeneic HSCT can no longer be reduced to whether a matched-sibling donor is available. Once HLA typing is known, the variables discussed here should be weighted hierarchically. Donor age is the variable with the most consistent impact on survival and on chronic GVHD and should take precedence; in older patients whose siblings are equally old, a young unrelated donor is frequently a preferable alternative. CMV serostatus, ABO compatibility, and donor sex and parity are complementary tiebreakers between otherwise equivalent donors. Investigation of germline predisposition, although not universally available yet, should be pursued whenever there is clinical or molecular suspicion, since it may contraindicate an otherwise ideal related donor.

Throughout this process, donor safety and autonomy remain a non-negotiable ethical priority, particularly in related and pediatric donors, who may be exposed to family pressure. The algorithm presented in Fig. 1 organizes this hierarchy of priorities and is intended as practical support for decision-making but should take local resource availability into account and be individualized for each donor–recipient pair.

CONFLICTS OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Data will be provided upon request.

AUTHORS' CONTRIBUTIONS

Conception and design: Maradei SC and Rosemberg CW; **Acquisition of data:** Maradei SC and Mazzi MT; **Analysis and interpretation of data:** Maradei SC, Mazzi MT, Rosemberg CW and Bouzas LF; **Technical procedures:** Maradei SC, Mazzi MT, Rosemberg CW and Bouzas LF; **Manuscript preparation:** Maradei SC, Mazzi MT and Rosemberg CW; **Manuscript writing:** Maradei SC, Mazzi MT and Rosemberg CW; **Critical revision:** Maradei SC, Mazzi MT and Rosemberg CW; **Final approval:** Bouzas LF.

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