Inborn errors of metabolism and osteopetrosis

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ABSTRACT

Allogeneic hematopoietic cell transplantation (HCT) remains the standard and potentially curative therapy for certain inborn errors of metabolism (IEM) and for osteopetrosis. This paper updates the Brazilian consensus guidelines for HCT indications in pediatric patients with IEM, specifically focusing on mucopolysaccharidosis, X-linked adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy, and osteopetrosis. We emphasize the importance of early diagnosis, timely referral, and multidisciplinary follow-up to optimize patient outcomes. Additionally, we discuss the evolving landscape of conditioning regimens and donor selection criteria, underscoring the critical need for genetic testing to guide therapy. Future directions in research, including gene therapy and novel therapeutic strategies, are also highlighted.

Keywords: Hematopoietic Stem Cell Transplantation. Mucopolysaccharidosis. Adrenoleukodystrophy. Leukodystrophy, Globoid Cell. Leukodystrophy, Metachromatic. Osteopetrosis.

INTRODUCTION

Inborn errors of metabolism comprise a large group of diseases caused by defects in genes that code for proteins (enzymes) involved in metabolic pathways, resulting in accumulation of toxic metabolites in different human cells and tissues. Hematopoietic cell transplantation (HCT) is a treatment option for a selected number of patients with inborn errors of metabolism. In most cases, HCT provides donor-derived cells capable of producing the missing enzyme, helping to prevent further neurological deterioration and other systemic complications. Since HCT does not reverse established damage, early diagnosis and timely referral are critical for better outcomes. Here we update the recommendations from the last Brazilian consensus guidelines, published in 2021, focusing on the most common HCT indications for these diseases (Table 1)[1–4].

Table 1. Hematopoietic cell transplantation indications for pediatric patients: Brazilian Society of Bone Marrow Transplantation and Cellular Therapy Consensus recommendations for inborn errors of metabolism.

Disease	Allogeneic				Autologous
	Familiar		Unrelated		
	MSD	MMFD	MUD	MMUD	
MPS type I (Hurler)	Yes*	Yes*	Yes	Yes	No
MPS type II (Hunter)	Yes*	Yes*	Yes	Yes	No
MPS type IV	Yes*	Yes*	Yes	Yes	No
MPS type VI	Yes*	Yes*	Yes	Yes	No
cALD	Yes*	Yes*	Yes	Yes	No
Krabbe	Yes*	Yes*	Yes	Yes	No
MLD	Yes*	Yes*	Yes	Yes	No
Osteopetrosis	Yes*	Yes*	Yes	Yes	No

*Non-carriers; MSD: matched sibling donor, MMFD: mismatched family donor: MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MPS: mucopolysaccharidosis; cALD: cerebral leukodystrophy; MLD: metachromatic leukodystrophy. Source: Elaborated by the authors.

MUCOPOLYSACCHARIDOSIS

Mucopolysaccharidosis (MPS) is a heterogeneous group of lysosomal storage disorders that result in the accumulation of glycosaminoglycans. There is progressive multiorgan dysfunction, including psychomotor retardation, severe skeletal abnormalities, life-threatening cardiopulmonary complications, and premature death[5,6]. HCT is indicated for patients with central nervous system involvement (MPS-IH and MPS-II) or for those who are refractory to enzyme replacement therapy (ERT) (MPS-IV and MPS-VI) (Table 2)[7–9].

Table 2. Transplant indication, donor type, and cell source.

Disease	Transplant indication	Preferential donor type and cell source
MPS type I (Hurler)	Preferrable in the first 1–2 years of life	non-carrier MSD > UCB > URD BM
MPS type II (Hunter)	Preferrable in the first 1–2 years of life in case of high risk of developing central nervous system phenotype either on the basis of genotype or a predictive family history	non-carrier MSD > UCB > URD BM
MPS type IV	ERT refractory	non-carrier MSD > UCB > URD BM
MPS Type VI	ERT refractory	non-carrier MSD > UCB > URD BM
cALD	Loes score > 1 and < 9; NFS 0 or 1	non-carrier MSD > MUD > haplo or MMUD
Krabbe	Early infantile — presymptomatic; late infantile — symptoms developing after 12 months	non-carrier MSD > MUD > UCB or MMUD
MLD	Juvenile or adult forms, late infantile only when presymptomatic	non-carrier MSD > MUD > UCB or MMUD
Osteopetrosis	Infantile malignant osteopetrosis: excluding neurodegenerative osteopetrosis (all OSTM1 and about half of CLCN7 cases) and RANKL mutations Intermediate osteopetrosis: severe forms with hematological insufficiency and (imminent) visual impairment after individual assessment. We strongly recommend genetic testing or discussing indication with a specialist if gene mutation not available.	non-carrier MSD > MUD > haplo or MMUD

ERT: enzyme replacement therapy; MSD: matched sibling donor; UCB: unrelated cord blood; URD: unrelated donor; BM: bone marrow; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; MPS: mucopolysaccharidosis; cALD: cerebral leukodystrophy; MLD: metachromatic leukodystrophy. Source: Elaborated by the authors.

Unlike ERT, HCT provides a lifelong source of enzyme-producing donor-cells, which can cross the blood-brain barrier, and deliver the enzyme to the brain in a mechanism known as cross-correction, thereby improving neurological symptoms[10]. In MPS-IH, the recommended approach is to start ERT at diagnosis with many groups suggesting that it can be continued until complete chimerism is achieved. Umbilical cord blood (UCB) units are a rapidly available stem cell source and offer great flexibility in human leukocyte antigen (HLA) matching, allowing nearly uniform access to HCT[11].

Before 2010, myeloablative conditioning regimens using busulfan and cyclophosphamide (BuCy) were standard. Since then, they have been largely replaced by reduced-toxicity regimens (RTC), primarily based on busulfan (with PK levels) and fludarabine (Bu-Flu). These RTC regimens demonstrate similar efficacy with lower toxicity.

However, despite their potential to reduce treatment-related mortality, RTC regimens are associated with higher rates of graft failure, especially when busulfan PK levels are not available[3,12]. Rituximab is often included in cord blood transplant protocols to help reduce post-transplant autoimmune cytopenias and graft rejection (Tables 3 and 4)[13]. Multidisciplinary follow-up is very important for improving quality of life (Table 5). Early HCT after diagnosis through newborn screening in Hurler (MPS-1H) patients is currently being studied and may help to improve transplant long-term outcomes[14].

Table 3. Conditioning regimens.

MPS / cALD — CB	MPS / cALD — BM	Osteopetrosis
Cyclophosphamide 50 mg/kg/day, D-6 Fludarabine 40 mg/m2/day, D-6, D-5, D-4, D-3 Busulfan (based on weight or MAC AUC — total AUC 85–95 ng/Lxh), D-8, D-7, D-6, D-5 rATG 5–10 mg/kg/total dose Rituximab 375 mg/m2/day, D-9, D-2 Imunoglobulin 500 mg/kg/day, D-1	Fludarabine 40 mg/m2/day Busulfan (based on weight or MAC AUC) rATG 5–10 mg/kg/total dose	Fludarabine 30 mg/m2/day, D-7 to D-3 Busulfan* (based on weight or MAC AUC — total AUC 85–95 ng/Lxh), D-8, D-7, D-6, D-5 rATG 5–10 mg/kg/total dose D-3 to D0 Thiotepa 5 mg/kg/day twice, D-4

MPS: mucopolysaccharidosis; cALD: cerebral leukodystrophy; CB: cord blood; BM: bone marrow; *initial busulfan dose is based on weight: 3 to 15 kg, 5.1 mg/kg/day (reference for once daily IV infusion – 3 hours); 15 to 25 kg, 4.9 mg/kg/day; 25 to 50 kg, 4.1 mg/kg/day; 50 to 75 kg, 3.3 mg/kg/day; and 75 to 100 kg, 2.7 mg/kg/day. Source: Elaborated by the authors.

Table 4. Graft-*versus*-host-disease immunoprophylaxis.

GvHD immunoprophylaxis according to donor type	
Matched sibling donor	CsA 3 mg/kg/day since D-2 plus MMF 40–45 mg/kg/day since D+1
Unrelated donor (bone marrow)	CsA 3 mg/kg/day since D-2 plus MMF 40–45 mg/kg/day since D+1 rATG 5–10 mg/kg/total dose, D-5, D-4, D-3, D-2
Unrelated cord blood	CsA 3 mg/kg/day starting on D-2* CTC 1 mg/kg/day starting on D-2 or MMF 40–45 mg/kg/day since D+1 rATG 5–10 mg/kg/total dose, D-8, D-7, D-6, D-5
Haploidentical donor	Cyclophosphamide 50 mg/kg D+3 and +4 CsA 3 mg/kg/day since D+5* and MMF 40–45 mg/kg/day since D+5

*Csa levels 200–300 ng/mL. Source: Elaborated by the authors.

X-LINKED ADRENOLEUKODYSTROPHY

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by pathogenic variants in *ABCD1 gene*, provoking deficient β-oxidation of saturated very-long-chain fatty acids. It is a progressive metabolic disorder with three main presentations: adrenal insufficiency, cerebral inflammatory demyelination (cerebral ALD, or cALD), and axonal myeloneuropathy.

Table 5. Multidisciplinary follow-up for patients with mucopolysaccharidosis (MPS)-1H.

	Screening	Time after hematopoietic stem cell transplantation
Neurologist	Neurocognitive delay, hydrocephalus, brain magnetic resonance Imaging especially for MPS type 2	Six months, one year and annually
Orthopedist	Dysostosis multiplex, skeletal dysplasia, chronic orthopedic problems needing surgical interventions	Six months, one year and annually
Ophthalmologist	Corneal clouding, retinal involvement	Annually
Otorhinolaryngologist	Recurrent ear infections, rhinosinusitis, conductive or sensorineural hearing impairment, airway obstruction, tonsil/adenoid hypertrophy, snoring, rhinorrhea, hoarseness and swallowing disorders	Annually
Pulmonologist	Sleep apnea syndrome, upper respiratory tract infections and pneumonia	Six months, one year and annually
Cardiologist	Cardiac valve disease, aortic root dilatation, cardiomyopathy, arrhythmia, and hypertension	Annually

Source: Elaborated by the authors.

Cerebral ALD is an inflammatory, demyelinating, progressive leukodystrophy occurring in approximately 40% of males with ALD and leading to severe disability and death[15]. There is not known association between genotype and phenotype[15,16]. The main role of HCT is to halt the progression of early cALD. However, it does not influence other manifestations, such as adrenal insufficiency, nor does it prevent the development of later axonal myeloneuropathy. The gold standard for the diagnosis of cALD is brain magnetic resonance imaging (MRI). Gadolinium enhancement may indicate active disease. The extent of brain involvement on MRI can be assessed using the MRI severity scoring system (Loes score), ranging from 0 (no abnormalities) to 34 (severely abnormal).

Allogeneic HCT is the standard treatment for cALD and can halt progression. Transplantation eligibility should be determined by an ALD transplantation expert. Outcome is poor in advanced disease (Loes score[17] > 9 and/or neurologic function NFS score[18] > 1). Indications for HCT includes patients with demyelination with gadolinium enhancement (Loes score > 0.5 and ≤ 9) and a NFS score of 0 or 1[16].

Donor choice includes non-carrier matched family donors (female family donors must be tested for heterozygous mutations) and matched unrelated donors. Myeloablative conditioning with busulfan (with PK levels when available), fludarabine and ATG is the most recommended regimen. Cell source is preferably bone marrow[2,3]. The use of unrelated cord blood, haploidentical donors (non-carriers) or mismatched unrelated donors might be considered in urgent situations, but optimal conditioning regimen is still not determined, with a significant portion of patients developing primary graft failure or secondary rejection[7]. Although it is not available in Brazil, lentivirus gene therapy (elivaldogene autotemcel) has been approved by regulatory agencies in the United States of America and may be an option (if available) in patients with poor donor options[19]. However, the recent reports of myeloid cancer associated with insertional mutagenesis in patients treated with this product are of concern[20].

GLOBOID CELL LEUKODYSTROPHY (KRABBE DISEASE)

Krabbe disease is a rare, inherited neurodegenerative disorder caused by a deficiency in the enzyme galactosylceramidase. This deficiency leads to the accumulation of psychosine, a cytotoxic compound, resulting in demyelination in both the central and peripheral nervous systems. The disease most commonly presents in its infantile form, which is characterized by rapid progression and severe neurological decline, often leading to death between 2 and 4 years of age if untreated[3].

HCT is currently the only established treatment for Krabbe disease, particularly effective when performed in presymptomatic patients. Early intervention with HCT can significantly improve survival and

neurodevelopmental outcomes. For early infantile Krabbe disease, HCT is indicated for presymptomatic infants diagnosed through newborn screening, ideally in the first few weeks of life. Early intervention has been shown to improve cognitive and language development, although gross motor function may still be affected[21–23]. In late-infantile Krabbe disease, HCT may also be beneficial, particularly for asymptomatic patients or those with symptom onset after 12 months of age, as it can prolong lifespan and improve functional abilities[3]. The efficacy of HCT in symptomatic patients is limited, with minimal neurologic improvement observed in those who undergo transplantation after symptoms have developed[3,21]. Therefore, the timing of HCT is critical, and early diagnosis through newborn screening is essential to optimize outcomes. HCT can be performed using related non-carrier or unrelated donors, with bone marrow or cord blood being the preferred hematopoietic cell source. Conditioning regimens are myeloablative and typically include busulfan (with PK monitoring), fludarabine, and ATG[3]. Recent research has explored additional therapeutic strategies, such as gene therapy, which has shown promise in preclinical models.

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency in the enzyme arylsulfatase A (ARSA), leading to the accumulation of sulfatides and subsequent demyelination in the central and peripheral nervous systems. This results in progressive neurological impairment. MLD is classified into late-infantile, juvenile, and adult forms, based on the age of onset, with varying clinical presentations and progression rates. HCT is currently the most established treatment for MLD, particularly in presymptomatic or early symptomatic patients. HCT can stabilize neurological function and normalize ARSA levels in some patients, especially when performed early in the disease course[3,24]. However, the effectiveness of HCT is limited in patients who are already symptomatic, particularly in the late-infantile form, due to the rapid progression of the disease[25]. HCT can be performed using related non-carrier or unrelated donors, with bone marrow being the preferred hematopoietic cell source. Conditioning regimens are myeloablative and typically include busulfan (with PK monitoring), fludarabine, and ATG[3]. Gene therapy and enzyme replacement therapy have been studied as potential future treatments, but these are not standard clinical practice yet[24,25].

OSTEOPETROSIS

Osteopetrosis is a group of rare monogenic disorders characterized by skeletal sclerosis, and currently at least nine distinct phenotypes are recognized. The etiology of osteopetrosis is primarily linked to diminished or absent osteoclast activity, resulting in a variety of clinical manifestations including craniofacial abnormalities, fractures, visual impairment, hematological complications (bone marrow failure and extramedullary hematopoiesis), and central nervous system symptoms, like hydrocephalus and neurodegeneration[2]. Genetic mutation analysis is recommended, as some genetic mutations do not respond to treatment with HCT. Infantile malignant osteopetrosis is an urgent indication of HCT with the intent of preservation of remaining auditory and visual function, except in patients with neurodegenerative forms (OSTM1 mutation, and some patients with CLCN7 mutation) or RANKL mutation[3,26,27]. Patients with osteopetrosis have particular risks of specific complications post-HCT, including high risk of pulmonary hypertension, increased incidence of veno-occlusive disease, high risk of graft failure (with frequent need for second procedures) and calcium disturbances (hypocalcemia pre-HCT and hypercalcemia post-engraftment)[28]. HCT is indicated with the best available donor, including matched sibling donor, matched unrelated donor or haploidentical donors. Bone marrow is the preferred cell source, and high cellularity is recommended (total nucleated cells targeting $> 5 \times 10\text{^}8$ cells/kg). Conditioning regimen includes myeloablative busulfan (with AUC monitoring), fludarabine, thiotepa, and ATG[29,30]. Continuous follow-up is essential to manage complications and evaluate improvements in the quality of life for these patients.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Fernandes JF, Rodrigues AM, Daudt LE, Klinger P and Bonfim C. **Conception and design:** Fernandes JF and Bonfim C. **Manuscript writing:** Fernandes JF, Rodrigues AM, Daudt LE, Klinger P and Bonfim C. **Final approval:** Fernandes JF and Bonfim C.

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