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Hematopoietic Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network

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A B S T R A C T

The leukodystrophies are a heterogeneous group of inherited diseases characterized by progressive demyelination of the central nervous system leading to devastating neurologic symptoms and premature death. Hematopoietic stem cell transplantation (HSCT) has been successfully used to treat certain leukodystrophies, including adrenoleukodystrophy, globoid leukodystrophy (Krabbe disease), and metachromatic leukodystrophy, over the past 30 years. To date, these complex patients have primarily been transplanted at a limited number of pediatric centers. As the number of cases identified through pregnancy and newborn screening is increasing, additional centers will be required to treat these children. Hunter's Hope created the Leukodystrophy Care Network in part to create and standardize high-quality clinical practice guidelines to guide the care of affected patients. In this report the clinical guidelines for the care of pediatric patients with leukodystrophies undergoing treatment with HSCT are presented. The initial transplant evaluation, determination of patient eligibility, donor selection, conditioning, supportive care, and post-transplant follow-up are discussed. Throughout these guidelines the need for early detection and treatment and the role of the partnership between families and multidisciplinary providers are emphasized.

INTRODUCTION

The leukodystrophies are a heterogeneous group of inherited disorders that disrupt myelination in the central nervous system (CNS) and may also involve the peripheral nervous system. The onset and severity of symptoms differ between diseases and may correlate with genetic mutation(s). In the most severe forms, affected individuals experience rapid, progressive, and ultimately fatal neurologic symptoms. Without newborn screening (NBS) or a known family history, the diagnosis of the index case in a family is usually delayed until symptoms are present and progress to a stage where treatment with transplantation is no longer potentially beneficial.

Allogeneic hematopoietic stem cell transplantation (HSCT) has been used to treat patients with rapidly progressive forms of leukodystrophies for approximately 3 decades. This approach has been used in the cerebral form of X-linked adrenoleukodystrophy (cALD) [1-8], metachromatic leukodystrophy (MLD) [4,9-12], and Krabbe disease (also known as globoid cell leukodystrophy) [4,6,13]. Through engraftment with unaffected, healthy donor cells, HSCT has been effective in slowing neurologic progression and extending life in many patients, particularly when performed early in the course of the disease [14]. Cross-correction of the lysosomal disorders [15], MLD and Krabbe disease, occurs in the CNS through

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donor-derived engraftment of macrophages in the brain [16], replacing recipient microglia cells over time [17,18]. HSCT has also shown benefit in patients with ALD, but the mechanism of correction in this peroxisomal disorder is not fully understood [19,20]. Donor cells may also exert anti-inflammatory and/or proneurogenic effects through paracrine signaling [21]. Based on clinical observations, it is likely that sufficient brain engraftment of donor-derived cells occurs several months after HSCT. As a result, in many cases the rapid progression of cerebral disease is slowed months after transplant, with stabilization likely occurring at the end of the first post-transplant year. However, there may be slower, ongoing cerebral disease throughout the child's lifetime. In addition, transplant does not appear to prevent progression of peripheral nervous system disease.

Despite these limitations, transplantation has been shown to provide benefit to patients with presymptomatic and early disease. In an effort to extend the availability of this therapy and maintain quality, clinical care guidelines were formulated by the Treatment Working Group of the Leukodystrophy Care Network (LCN). This group, composed of pediatric transplant physicians, neurologists, advanced practice providers, scientists, physical therapist, and parent advocates, created evidence-based recommendations based on expert opinions, after agreement among the panel of experts.

METHODS

Guideline Development

The LCN is a consortium of patient advocates, affected families, physicians, other healthcare professionals, and medical centers committed to improving the care of individuals affected by leukodystrophies. The Treatment Clinical Practice Guidelines Working Group, representing 7 distinct LCN centers and a committee of parents with children affected by leukodystrophies, was tasked with creating these guidelines. The Treatment Clinical Practice Guidelines Working Group met in person 4 times between February 2017 and July 2018. The group also held multiple conference calls during this time to further develop and refine recommendations. Appropriate literature was identified from the PubMed library including, but not limited to, the terms "transplantation," "leukodystrophy(ies)," "metachromatic leukodystrophy," "Krabbe disease," "globoid cell leukodystrophy," "adrenoleukodystrophy," and "adrenomyeloneuropathy." In addition, abstracts from recent HSCT meetings were reviewed. A summary of the literature reviewed is presented in Supplementary Table 1. Guidelines presented represent a consensus of the members, and, when available, pertinent literature is cited. When consensus was not achieved, this was noted in the guidelines.

About the LCN

The LCN was founded in 2015 with the support of Hunter's Hope Foundation. The mission of the LCN is to improve the health and quality of life of individuals affected by leukodystrophies with proactive, innovative, and comprehensive medical care standards and specialized centers throughout the United States, Canada, and eventually the world. For more information please contact hope@huntershope.org or visit www.leukodystrophycarenetwork.org. At the time of publication, LCN Certified Centers include (*directly involved in the creation of these guidelines) *Ann & Robert H. Lurie Children's Hospital of Chicago, *Duke Children's Hospital, *Golisano Children's Hospital at University of Buffalo (Roswell Park Comprehensive Cancer Center), *Kennedy Krieger Institute, Massachusetts General Hospital, *Monroe Carell Jr. Children's Hospital at Vanderbilt, and *Primary Children's Hospital at the University of Utah. LCN Candidate and Affiliate Centers include *Children's Healthcare of Atlanta, Children's National Health System, Lucille Packard Children's Hospital at Stanford, Texas Children's Hospital, The Children's Hospital of Philadelphia, UF Health Shands Hospital, University of Minnesota Masonic Children's, and Weill Cornell Medicine.

DETERMINING WHETHER HSCT IS IN A PATIENT'S BEST INTEREST

HSCT should be offered to patients for whom the potential benefit outweighs the inherent risks. Infants and children who have already experienced severe neurologic deterioration have symptoms that compromise their ability to tolerate high-dose chemotherapy. The presence of these symptoms (Table 1) shifts the risk-to-benefit assessment in an unfavorable direction. In these cases, transplant will likely shorten the child's life without benefitting the course of the disease, and therefore HSCT is not indicated. In this setting, parents of children with leukodystrophies who were active members of the Treatment Clinical Practice Guidelines Working Group stressed the importance of meeting with the care team. This allows families to discuss results of assessments, understand what influenced the team's recommendations against proceeding with HSCT, and facilitates appropriate referrals (complex or chronic care team, palliative care, etc.) to optimize the child's quality of life.

Table 1
Clinical Contraindications to HSCT*

Inability to protect airway
Chronic aspiration
Uncontrolled seizures
Active or uncontrolled opportunistic infections
Severe scoliosis
Supplemental oxygen or need for assisted ventilation (ventilator support, bilevel positive airway pressure)
Coma

* Refer to Tables 5-7 for disease-specific guidelines for HSCT.

It is also important for all families to understand the limitations of HSCT as a therapy. Families should be counseled that although the goal is disease stabilization, progression can occur after HSCT (while waiting for donor cell engraftment or because the transplant slows but does not completely halt disease progression). The degree of progression is variable but in the most severe cases is neurologically devastating. It is important to describe these potential outcomes in concrete terms and to acknowledge that predictions regarding neurologic outcome may not be precise. Questions to raise include the following: What would the child's day-to-day life be like, including quality of life? How would they ambulate or communicate? Would they be able to "learn"? What would the impact be on the family to care for a child or adult with significant disabilities? Describing the best and worst case scenarios can be valuable for families and can facilitate discussions that explore how family members would define a "successful" transplant and what constitutes "quality of life" for their child.

GENERAL CONSIDERATIONS

It is well accepted that HSCT should be performed as early as possible in patients with leukodystrophies to maximize the likelihood of favorable outcomes, although the optimal timing differs somewhat between diseases. In the early infantile form of Krabbe disease (EIKD), HSCT is beneficial if performed in newborns in the first month of life who are clinically presymptomatic [6,13,22]. Access to NBS (or prenatal screening if there is a known family history) is critical to diagnose these infants as early as possible. In later onset diseases (ALD, MLD, and late-onset Krabbe disease [LOKD]), individuals with a suspected leukodystrophy must be evaluated promptly to establish the diagnosis, ideally at a center with expertise in these diseases. Once the diagnosis is made, other potentially affected family members should be evaluated and treated if indicated. Genetic counseling should be provided to at-risk family members to determine carrier status and to provide anticipatory guidance for future family planning. The decision to test an individual family member should consider the disease-specific inheritance pattern, relationship to the index case, and other clinical factors (ie, age, gender).

All patients should have a detailed history elicited that includes neurologic symptoms, in particular signs/symptoms

developing over the preceding 3 to 6 months to determine the pace of disease progression. Each patient should also undergo a full physical examination and comprehensive neurologic evaluation (Table 2). Disease-specific scoring systems, available for cALD, Krabbe disease, and MLD, can assist in assessing clinical disease burden (Table 3A-C). Further disease-specific guidelines are discussed below. The results of these studies should be reviewed, in discussion with the patient, his or her family, and consulting providers, to determine whether the individual is an appropriate candidate for HSCT. Patients proceeding to HSCT must also undergo standard pre-HSCT testing to determine final eligibility for the procedure (Supplementary Table 2). Additional disease-specific evaluations include adrenal function and gallbladder ultrasonography in cALD [8] and MLD patients [23,24], respectively.

Donor Selection

An HLA-matched, noncarrier sibling is the optimal donor choice for patients undergoing HSCT but is not available for most patients. Cord blood (CB) donors, when available, are preferred over unrelated bone marrow and peripheral blood stem cells. Benefits of CB include rapid procurement, permissive HLA mismatching, and low rates of acute and chronic graft-versus-host disease (GVHD). Because the use of peripheral blood stem cells in pediatric recipients is associated with a higher incidence of acute and chronic GVHD [25,26], this donor source should only be used if other sources are unavailable or if the donor cannot undergo bone marrow harvest for medical reasons. To date, the use of haploidentical donors has been limited because of concerns of using a carrier and lower rates of sustained full donor chimerism [27]. Haploidentical related donors can be evaluated in a timely manner, but carrier status will limit potential donors to include noncarrier siblings; in cALD patients, fathers may also be considered. Additional experience using the haploidentical approach is needed.

To determine donor availability, all full biologic siblings should have HLA typing and testing for donor carrier status performed. Disease screening should include enzyme levels (for Krabbe disease and MLD) and/or mutation testing (for cALD and in some cases Krabbe disease and MLD). Very-long-chain fatty acid (VLCFA) assays can be used to screen male siblings for cALD, but 15% of female carriers will have normal VLCFA testing [28]. To determine carrier status for ALD, female carriers should have *ABCD1* mutation analysis performed. Given that female carriers of ALD mutations can commonly develop milder neurologic symptoms (adrenomyeloneuropathy [AMN]) as adults and rarely adrenal insufficiency [29,30], female carrier donors should be avoided.

All donors should undergo standard donor evaluation. The cell dose for bone marrow grafts should be $\geq$3 to 10 $\times$ 10^8 total nucleated cells/kg recipient body weight (Table 4) [31-33]. Unrelated CB unit selection should be based on standard criteria (Table 4). Disease-specific enzyme testing (galactocerebrosidase [GALC] or arylsulfatase A) can be performed on potential CB units to ensure that affected or carrier donors are not selected [34-36]. The use of 2 CB units is appropriate in patients without a suitably dosed single unit [37]. CB grafts

Table 3A
Neurologic Function Score for ALD

Function	Score
Hearing/auditory processing problems	1
Aphasia/apraxia	1
Loss of communication	3
Vision impairment/field cuts	1
Cortical blindness	2
Swallowing difficulty	2
Tube feeding	2
Running difficulties/hyperreflexia	1
Walking difficulties/spasticity/spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair required	2
No voluntary movement	3
Episodes of urinary or fecal incontinence	1
Total urinary or fecal incontinence	2
Nonfebrile seizures	1
Possible Total	**25**

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Table 2
Baseline Disease-Related Evaluations in Leukodystrophy Patients under Consideration for HSCT

	Krabbe	MLD	cALD
Neurophysiologic testing			
Evoked potentials (visual and auditory)	X	X	X*
EEG	X	X	X†
NCS	X	X	X†
CSF	Cell count, protein, psychosine	Cell count, protein, inflammatory markers*	Cell count, protein, inflammatory markers*
Swallowing assessment	X†	X†	X†
MRI	With DTI	With DTI or spectroscopy*, Modified Eichler or Loes score	With Gadolinium (spectroscopy*), Loes score
Ophthalmology consultation	X	X	X‡
Neuropsychological and cognitive testing	X	X	X§
Motor function testing including physical therapy evaluation	X	X	X
Disease-specific testing		Gallbladder ultrasound	Adrenal function

EEG indicates electroencephalography; NCS, nerve conduction studies; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging.
* Certain centers.
† As clinically indicated.
‡ Including careful assessment of visual fields.
§ Including assessment of visual spatial skills.

Table 3B
Classification and Staging for Early and Late Infantile Krabbe Disease

Group Classification		Staging		
Group	Clinical Indicator	Stage	Early Infantile	Late Infantile
A	Mild thumb clasp (not fixed)	1	No detectable symptoms OR ≤2 of group A	No detectable symptoms OR ≤3 of group A
	Hypotonia of shoulder girdle			
	Weak feeding			
	Gastroesophageal reflux			
B	Fixed thumb clasp	2	All of group A OR any of group B	3 of group A AND >2 of group B
	Spasticity of extremities			
	Predominant trunk extensor tone (any age) or trunk hypotonia (>4 months of age), >1 of the following feeding abnormalities: (1) Difficulty latching to breast/nipple, (2) decreased rate of nutritive suck, (3) abnormal tongue, lip or chin movements, (4) uncoordinated suck and swallow.			
C	Clinical seizures	3	Spastic extremities with predominant extensor tone in trunk (any age) OR trunk hypotonia >4 months) AND ≥1 of group C	Spastic extremities with trunk hypotonia AND ≥1 of group C
	Absent deep tendon reflexes or other abnormal reflexes			
	Exaggerated startle			
	Visual tracking difficulties			
	Jerky eye movements			
	Abnormal pupillary response			
D	Severe weakness, unresponsive to stimuli, loss of primitive reflexes	4	Severe weakness with partial or complete loss of primitive reflexes AND/OR sensory impairment	
	Sensory impairment (blindness or deafness)			

Used with permission [89].

Table 3C
Gross Motor Function Classification Scale for Late Infantile and Juvenile MLD*

Stage	Description
M0	Walking without support with quality and performance normal for age
M1	Walking without support but with reduced quality of performance, ie, instability when standing or walking
M2	Walking with support; walking without support not possible (fewer than 5 steps)
M3	Sitting without support and locomotion such as crawling or rolling; walking with or without support not possible
M4	Sitting without support but no locomotion or sitting without support not possible, but locomotion such as crawling or rolling
M5	No locomotion or sitting without support, but head control is possible
M6	Loss of any locomotion as well as loss of any head and trunk control

* Validated in patients > 18 months of age.
Used with permission [111].

should target $>5 \times 10^7$total nucleated cells/kg, calculated from the total nucleated cells provided by the bank before cryopreservation [38].

Conditioning

Myeloablative conditioning regimens are currently considered to be standard of care (Supplementary Table 3). The experience using reduced-intensity conditioning regimens is limited and has been associated with higher rates of mixed chimerism and graft failure (Supplementary Table 1E). Total body irradiation should be avoided because of increased neurotoxicity and potential for long-term neurocognitive effects [1,39]. Preclinical data have demonstrated improved donor-derived brain engraftment with high-dose busulfan as compared with irradiation or treosulfan [40,41]. The most common myeloablative regimen includes busulfan and cyclophosphamide ± antithymocyte globulin [1,12,42,43], although fludarabine may be substituted for cyclophosphamide [44]. Standard chemotherapy supportive measures should be used, including the use of mesna and increased

Table 4
Donor Selection Criteria for Leukodystrophy Patients under Consideration for HSCT

	Matched Related Donor	Unrelated CB Donor
General	The use of carriers should be avoided. Bone marrow is the preferred stem cell source.	CB units should be procured from a public bank that has been inspected and accredited by FACT, AABB. or another accreditation program.
TNC dose	$\geq 3 \times 10^8$ TNC/kg recipient weight (bone marrow)	$\geq 5 \times 10^7$ TNC/kg recipient weight
HLA matching	High resolution matching for HLA-A, -B, -C, and -DRß1. Matched related donors should be fully matched at 8/8 loci.	High resolution matching for HLA-A, -B, -C, and -DRß1 is preferred when available [123]. The minimally acceptable matching would be 4/6 loci for -A, -B (intermediate resolution), and -DRß1 (high resolution).
Disease specific		
MLD or Krabbe disease	Highest enzyme level within the normal control range and meeting the above criteria	
cALD	Mutation analysis for *ABCD1* should be performed for any potential donor.	

FACT indicates Foundation for Accreditation of Cellular Therapy; AABB, American Association of Blood Banks; TNC, total nucleated cell.

hydration for cyclophosphamide, seizure prophylaxis and pharmacokinetic monitoring for busulfan [44,45], prophylactic medications during antithymocyte globulin, and stress dose hydrocortisone in patients with cALD during conditioning [44].

GVHD Prophylaxis and Treatment

GVHD is a significant barrier to success, leading to increased morbidity and mortality. Multiple regimens exist for GVHD prophylaxis based on the graft source, with a common regimen including a calcineurin inhibitor plus mycophenolate mofetil. Consider avoiding CNS toxic agents including methotrexate. Per standard of care, steroids are first-line treatment for GVHD. Steroid exposure should be minimized because of musculoskeletal complications that could compromise muscle strength and function [46,47]. Second-line GVHD treatment should be based on severity and location in the individual patient, avoiding agents with potential neurologic side effects.

Supportive Care during HSCT

Before the start of chemotherapy, all patients should undergo standard HSCT evaluations to assess basic organ function (cardiac, pulmonary, hepatic, renal) and infectious disease status (Supplementary Table 2). Standard supportive care measures should be used per institutional practice including antimicrobial prophylaxis (viral, fungal, and *Pneumocystis jirovec*iprophylaxis), empiric antibiotic therapy during high-risk periods, sinusoidal obstructive syndrome (veno-occlusive disease) prevention, granulocyte colony-stimulating factor for CB grafts starting in the first week post-transplant until durable neutrophil engraftment, and transfusion support. The use of intravenous immunoglobulin while patients are severely immunocompromised remains an area of discussion [48-50]. Comprehensive assessment and aggressive intervention with occupational therapy, physical therapy, and speech/language pathology should be provided. Therapies should address all categories of the international classification of function, including feeding, management of muscle tone, muscle extensibility, positioning and alignment, comfort, skin integrity, and support of optimal function and development [51]. Appropriate adaptive equipment, assistive technology, and orthotic intervention should be provided. Social work, child life, and complex care teams should be actively involved during the transplant period and beyond.

Nutrition and Growth

Adequate nutritional support is a key component of post-HSCT care. Patients should continue to receive enteral nutrition as tolerated. Placement of a nasogastric tube before transplant can be used to provide adequate nutrition and medication administration. Pretransplant gastrostomy tube placement should be strongly considered in patients, especially newborns and infants, who are likely to experience poor feeding and/or growth after HSCT. Parenteral nutrition can also be used to support nutrition during times where oral intake is poor. Symptomatic patients should be monitored closely for feeding or swallowing difficulties; feeding therapy may be helpful for these patients. Vitamin supplementation, including calcium and vitamin D, should be provided.

Neurologic

Seizure prophylaxis during busulfan administration must be used, with therapeutic drug level monitoring recommended for patients on long-term prophylaxis. Levetiracetam is the recommended agent based on its side effect profile and low potential for medication interaction [52]. If there is any evidence of seizure activity or risk for seizures (by electroencephalography), levetiracetam or other antiepileptic should be continued longer (eg, until the patient is off any drug [calcineurin inhibitor] that lowers seizure threshold or possibly longer). Neurologic changes during the peritransplant period should be aggressively evaluated, with the differential including subclinical seizures, medication side effects (eg, calcineurin inhibitor), posterior reversible encephalopathy syndrome, and CNS infection (particularly encephalitis caused by human herpesvirus-6).

SPECIAL CONSIDERATIONS FOR NEWBORNS UNDERGOING HSCT

There are unique aspects of care when newborns undergo HSCT, primarily for a diagnosis of EIKD, although this may also apply to asymptomatic infants with late infantile MLD (LI-MLD).

In Utero Diagnosis

In families with a previously affected child, prenatal diagnosis is recommended. Mothers carrying an affected child should be followed by a high-risk obstetric team, and HSCT consultation should occur before delivery. When possible, delivery should occur at the transplant center. For infants with EIKD, there is prior experience with inducing labor as soon as lung maturity is established, and this could be considered in consultation with the mother and obstetric and transplant teams. CB should be collected and sent for HLA typing and disease confirmation (as previously described). Standard newborn care should be provided during the first days of life.

NBS Diagnosis

Neonates diagnosed with EIKD, or LI-MLD when NBS becomes available, should be emergently referred, according to state-specific NBS algorithms, to centers with expertise in performing transplants in infants. An inpatient evaluation is strongly recommended to expedite studies. Newborns diagnosed with later onset diseases (ALD, juvenile onset MLD, etc.) should be referred for evaluation according to the state-specific NBS algorithms.

Evaluation of Newborns for Transplant

Confirmatory disease testing, including mutation analysis, should be performed as part of the disease evaluation to avoid delay in HSCT [53]. Pretransplant laboratory tests should be triaged to limit blood volumes withdrawn. Infectious disease testing may be performed using maternal blood samples, with PCR-based testing preferred. Infants should be evaluated for the presence of patent foramen ovale or ductus arteriosus to inform decisions about central line management. Common newborn findings, including patent ductus arteriosus or hyperbilirubinemia, are not contraindications to proceed to HSCT.

CB is the preferred donor source in this setting because of its rapid availability. Confirmatory HLA typing and/or enzyme testing on CB unit(s) may still be pending when chemotherapy is started, assuming multiple donors are tested to ensure at least 1 suitable donor is confirmed and available on the day of transplant. Transplant centers should strongly consider partnering with public CB banks to facilitate rapid testing and release of the CB unit.

Newborn Care During Transplant

Myeloablative busulfan-based conditioning regimens have most commonly been used in newborns undergoing HSCT. Pharmacokinetic data on intravenous busulfan in very young infants (particularly $\leq$1 month) are limited to those few

reported in larger studies [54-56]. Oral busulfan has been historically used in this population [36,57], but consensus was not obtained as to its current use. Cyclosporine has been historically used as GVHD prophylaxis in infants [36,43,58,59], although tacrolimus is used commonly in infants undergoing solid organ transplantation [60,61]. Most infants will not require viral prophylaxis but should be monitored for primary viral infections.

Breastfeeding should be encouraged and enabled for as long as possible. Cytomegalovirus transmission through breastmilk of cytomegalovirus-seropositive mothers has been shown in certain settings [62]. Despite this, the benefits of breastfeeding, including improved oral–motor strength, may outweigh the risk of cytomegalovirus transmission. If third-party breast milk is used, be cognizant that without adequate pasteurization, cytomegalovirus transmission can occur. Most infants will not be able to take in adequate enteral nutrition for months after transplant and benefit greatly from feeding therapy. Placement of a gastrostomy tube for medication administration and feeding for the first year post-transplant should be strongly considered. Growth including head circumference and length should be measured weekly in these young infants who are in a critical period of brain development. Infants who undergo HSCT also experience delays in developmental milestones for months and thus will benefit significantly from aggressive physical therapy, occupational therapy, and speech/language pathology.

DISEASE-SPECIFIC CONSIDERATIONS

Adrenoleukodystrophy

ALD is an X-linked peroxisomal disorder caused by mutations in the *ABCD1* gene leading to accumulation of VLCFAs primarily in the CNS and adrenal tissue. ALD has a complex clinical presentation that is progressive in nature and cannot be predicted by genotype [63,64]. Nearly all males with ALD will develop adrenal insufficiency, although the timing is variable [65,66]. Adrenal insufficiency (recognized or clinically silent) often precedes neurologic symptoms [8]. Cerebral disease is the most severe manifestation of ALD, occurring in approximately 40% of individuals during childhood or adolescence [63,67]. Early neurologic findings of cALD include behavior changes or attention issues and, if untreated, lead to rapid neurologic decline and death [8]. A second neurologic phenotype, AMN, typically occurs in men and is characterized by progressive spastic paraparesis [27,29]. A portion of men with AMN (approximately 20%) will also develop cALD with similarly poor outcomes [68]. Female carriers are at risk for developing AMN, but adrenal insufficiency and cerebral disease is rare [29].

State of the Art

HSCT is indicated only for patients with early cALD [1,3,69,70]. To facilitate early diagnosis, ALD was added to the recommended uniform screening panel in 2016 by the US Department of Health and Human Services. NBS for ALD is currently available in select states [71]. Asymptomatic male infants identified by NBS or family history should be followed every 6 to 12 months for early signs of adrenal insufficiency or preclinical cerebral disease [71]. Recognition of early cerebral disease is complicated, with signs or symptoms including behavior changes (eg, attention deficit/hyperactivity) or changes on neurophysiologic test (eg, brainstem auditory evoked responses) or neuroimaging (magnetic resonance imaging [MRI]) [72]. Diagnosis can be made by measuring serum VLCFA and confirmed by *ABCD1* mutation analysis as detailed above. ALD should be considered in males with new-onset adrenal insufficiency.

All patients with cALD being considered for HSCT should undergo a thorough neurologic assessment (Table 2). Moser et al. [73] developed the neurologic function score to classify disease severity based on clinical symptoms, with scores ≥ 2 reflecting advanced disease (Table 3A). Neuroimaging is a critical component of the diagnostic evaluation. Loes et al. [74] developed a disease-specific MRI severity score that assesses the degree of atrophy and extent and location of white matter disease on T1- and T2-weighted images. A Loes score $> .5$ and <10, assigned by a trained neuroradiologist, has been associated with more favorable neurologic outcomes after HSCT. In addition, the presence of gadolinium contrast enhancement is a very strong predictor of disease progression [75]. Brain magnetic resonance spectroscopy and diffusion tensor imaging have been shown to detect abnormalities beyond conventional brain MRI but remain exploratory [76-78]. Final eligibility for HSCT is determined through a combined assessment of MRI severity score and degree of clinical symptoms (ie, neurofunctional score < 2). Patients with higher Loes and/or neurologic function scores generally have higher morbidity and mortality post-HSCT [1,3,4,69,70,79].

It remains unclear whether AMN is responsive to HSCT. In natural history studies of boys without cerebral disease, nearly all develop AMN as adults, typically at age 20 to 30 years [80]. Long-term data in males who underwent HSCT for cALD are more limited. Van Geel et al. [81] observed that 3 of 5 transplanted males developed AMN after a median of 16 years (ages 22 to 25), but further studies are needed. The presence of AMN may also influence outcomes after HSCT. Kuhl et al. [82] reported on the outcomes of 15 men with cALD, most with clinical evidence of AMN at time of HSCT. The outcomes after HSCT were mixed but were improved in men with mild or no AMN and those transplanted more recently [83].

Recommendations

HSCT is recommended for patients with early-stage cALD (neurologic function score < 2 and Loes score < 10) (Table 5). Given the potential life-threatening complications related to adrenal insufficiency, adrenal function (glucocorticoid and mineralocorticoid) must be monitored. Stress dosed replacement therapy should be provided during cytoreduction and the immediate post-HSCT period [66]. HSCT does not correct adrenal insufficiency [65]; thus, patients with adrenal insufficiency will need lifelong replacement and stress dosed treatment as indicated.

Contraindications

Individuals with advanced disease (Table 3A) are at higher risk of transplant-related morbidity and mortality, without neurologic benefit. Therefore, it is not recommended that these patients undergo HSCT. Rather, patients may be eligible to participate in natural history studies, registries, or certain early-phase clinical trials studying novel agents and approaches. Chronic care and/or palliative care experts should be consulted. Partnering with an experienced leukodystrophy center can be helpful for the primary team in managing symptoms.

Early Infantile Krabbe Disease

Krabbe disease, or globoid cell leukodystrophy, is an autosomal recessive disease caused by mutations in the *GALC* gene, leading to deficiency of the lysosomal enzyme (GALC). Absent or very low enzyme activity causes toxic accumulation of

Table 5
Guidelines for Determining HSCT Candidacy for Patients with cALD

	Benefit > Risk	Benefit ~ Risk	Risk > Benefit
General	NFS = 0	NFS 1-2, depending on symptoms and presentation	NFS ≥ 3
Neuroimaging*	MRI severity score .5-9.5†	MRI severity score 10-13†	MRI severity score ≥ 14†
Mobility and tone	Normal	Subtle motor deficits	Spasticity present; requires assistance for walking or requires wheelchair
Oral motor function/feeding	Normal	Normal	Apraxia or aphasia; swallowing dysfunction; tube feeds required
Seizure+	None	None	Seizures
Neurocognitive	Mild or new attention, academic or behavioral issues	Moderate attention or behavioral issues; academic difficulties	Auditory processing delays; signs of neurocognitive decline

* Magnetic resonance spectroscopy can show abnormalities before MRI-detectable disease.

† Neuroimaging should be scored according to the system described by Loes et al. [74]. Location of lesions may also be informative [75]. Rapid progression is associated with posterior white matter involvement (parieto-occipital lobe or splenium of corpus callosum; common in younger boys), frontal involvement (frontal lobe or genu of corpus callosum; common in younger adolescents), or a combined parieto-occipital and frontal white matter involvement (younger boys). Primary cerebellar white matter involvement is more commonly seen in younger adolescents and generally progresses at a slower pace. Isolated projection fiber involvement is most common in adult patients and has been associated with a slower and more benign course [75]. An isolated seizure related to adrenal insufficiency/electrolyte disturbances or simple febrile seizures is not a contraindication to HSCT.

galactolipids, including psychosine, leading to neuroinflammation and demyelination in the CNS and peripheral nervous system. Although approximately 150 disease-causing mutations have been described, a subset including the common 30-kb deletion has been associated with the EIKD phenotype [84].

Infants with EIKD typically present before 6 months of age with crying and irritability, poor feeding, poor head control, increased tone, and thumb clasping. Diagnosis is made based on low or absent GALC enzyme activity, although new assays including psychosine (serum and cerebrospinal fluid) show promise [85-87]. EIKD progresses rapidly, causing loss of milestones, blindness, seizures, apnea, and death, in most cases before 3 years of age [88]. Less commonly, infants will present with symptoms > 6 months of age; this late infantile phenotype typically progresses at a slower rate than EIKD, but many management principles still apply (Table 6). Eligibility for HSCT in late infantile Krabbe disease should be assessed on a case-by-case basis based on the severity of clinical disease, including neurophysiologic testing and neuroimaging.

State of the Art

HSCT does not offer benefit to infants with EIKD after symptoms have developed [6]. A staging system developed by Escolar et al. [89] can be helpful to classify these infants based on exam findings (Table 3B). In infants diagnosed because of family history or by NBS, a survival and neurologic benefit has been demonstrated with HSCT [6,13,22]. To identify affected infants while HSCT is still an option, NBS has been instituted in certain states (in the United States) and countries. NBS programs have developed algorithms to rapidly confirm a diagnosis of EIKD and refer for evaluation within days of birth. Consensus guidelines have recently been published regarding NBS for Krabbe disease [53,90].

Recommendations

Diagnosis of EIKD can occur in utero (family history), at birth (through NBS when available), or several months later when clinical symptoms are present. Diagnostic testing includes GALC enzyme activity (very low or absent), mutation

Table 6
Guidelines for Determining HSCT Candidacy for Patients with EIKD (ie, age at onset of symptoms <6 months)

	Benefit > Risk	Risk > Benefit
General	Newborn* or stage 1	Symptomatic or stage 2-4 infant
Initial presentation	Positive newborn screen or known family history	Extreme irritability/inconsolability
Tone/spasticity	Normal, but may have subtle hypotonia of the shoulder girdle and/or intermittent thumb clasp	Overt spasticity or severe truncal hypotonia
Oral motor function/feeding	Slow feeding, mild feeding difficulties or evidence of GERD	Unable to maintain weight with oral feeding, signs or symptoms of aspiration; unable to clear secretions
Seizure or apnea	None	Present
Neuroimaging†	Normal or subtle evidence of demyelination	Evidence of moderate or severe demyelination
Development	Appropriate for gestational age	Regression or loss of developmental milestones
NCS‡	Normal or abnormal	Abnormal
EEG	Normal or abnormal	Seizures or regions of epileptic potential
VEP§	Normal or abnormal	Abnormal, documented vision loss
BAER¶	Normal or abnormal	Abnormal
Ophthalmological exam	Normal for age	Abnormal including optic atrophy

GERD indicates gastroesophageal reflux disease; VEP, visual evoked potential; BAER, brainstem auditory evoked response.

* Newborn is defined as <44 weeks estimated gestational age.

† For subtle evidence, neuroimaging can show abnormalities on T2-weighted imaging in internal capsule or dentate nucleus, accounting for gestational age [124,125]. DTI can demonstrate reduction of fractional anisotropy in corticospinal tracts [125,126]. As the disease progresses with moderate or severe demyelination, T2-weighted images will demonstrate hyperintensity in the dentate nucleus, cerebellar white matter, pyramidal tract posterior corpus callosal, or parieto-occipital white matter [100,127]; atrophy and/or tigroid appearance of white matter may also be present.

‡ NCS are considered abnormal if prolonged distal latency, low amplitude, no evoked response, or prolonged F-wave latency is present.

§ VEPs are considered abnormal if the P100 wave is absent or delayed [128].

¶ BAERs are considered abnormal if wave I to V interpeak latency is prolonged or if any of the obligate wave forms (I, III, V) are absent [129].

analysis, and, more recently, psychosine measurements. All patients considered for HSCT should undergo a thorough neurologic evaluation (Table 2). MRI with diffusion tensor imaging is preferred in these patients when available. Quantitative diffusion tensor imaging analysis can detect early disease in newborns and predict function after HSCT [91]. Most newborns with EIKD will exhibit at least 1 abnormality on neurophysiologic testing, with brainstem auditory evoked response abnormalities among the first indications of disease (Table 6) [89,92]. Newborns with a known homozygous 30-kb deletion (or heterozygous 30-kb deletion plus other severe mutation) should rapidly proceed to transplant irrespective of clinical testing, ideally within <30 days of life.

Contraindications

Infants diagnosed because of clinical symptoms are not eligible for HSCT (Table 7). Because of rapid disease progression, families should be referred for a palliative care consult. Partnering with a center experienced in caring for infants with symptomatic EIKD can be helpful for the primary medical team.

Late-Onset Krabbe Disease

LOKD is uncommon, occurring in only 5% to 10% of affected individuals based on current data, although higher rates are described in certain populations [93-95]. Children and adults with LOKD most commonly present with gait or visual disturbances [96]. The clinical course is variable and may include spastic paraparesis, cerebellar ataxia, vision problems, peripheral neuropathy, or seizures [6,97,98]. GALC enzyme levels are low but not undetectable [95]. The recommended diagnostic evaluation is similar to other leukodystrophies (Table 2), although visual evoked potentials and brainstem auditory evoked potentials are less helpful [92,99]. Characteristic MRI findings include increased signal in periventricular and deep cerebral white matter, often sparing U-fibers [98,100]. Prominent corticospinal involvement has also been seen in older patients [101].

The experience using HSCT in patients with LOKD is more limited, but disease stabilization on MRI and modest clinical improvements have been described [102-106]. The duration of effect remains unclear, especially with respect to peripheral disease. The decision to transplant LOKD patients should be based on the severity of clinical disease, including neurocognitive testing and neuroimaging.

Metachromatic Leukodystrophy

MLD is a lysosomal storage disease caused by mutations in the arylsulfatase A gene (*ARSA*), leading to deficiency of arylsulfatase, accumulation of sulfatides, and subsequent demyelination in the CNS and peripheral nervous system.

There are 3 subtypes of MLD based on age at onset of clinical symptoms: LI-MLD, <30 months; juvenile, 30 months to 15 years; and adult, ≥16 years. Age at onset is concordant within families, and genotype generally correlates with phenotype [107]. All subtypes present most commonly with gait abnormalities or weakness.

Children with LI-MLD invariably experience rapid progression, leading to severe neurologic compromise and death in 2 to 3 years [107]. Older children or adults may also present with decline in work/school performance or behavioral changes. Symptoms progress over months to years, leading to global neurologic regression. Diagnosis requires low enzyme activity, but it is not sufficient for diagnosis. Any preliminary diagnosis of MLD should be confirmed with mutation analysis and/or increased urinary sulfatides. Pseudodeficiency occurs in a small percentage of unaffected individuals who have low enzyme levels (~10% of normal) but without excess urine sulfatides [107,108].

State of the Art

Symptomatic patients with LI-MLD are unlikely to derive significant benefit from HSCT. Those transplanted before symptoms will experience some benefit, although most will

Table 7
Guidelines for Determining HSCT Candidacy for Patients with Juvenile and Adult MLD

	Benefit > Risk	Benefit ~ Risk*	Risk > Benefit
General	Pre- or mildly symptomatic	Mild to moderate symptoms	Moderate to severe symptoms and/or rapid progression of symptoms over previous 3 months
Motor function	M0, mildly increased tone or abnormal reflexes	M1-2, mild to moderately increased tone	M3-5, moderate to severely increased tone, abnormal reflexes
Oral motor function/feeding	Normal feeding	Can communicate in complete sentences; reduced quality for age; no signs or symptoms of aspiration	Cannot communicate in complete sentences; signs or symptoms of aspiration
Seizure	None	None	Present
Neuroimaging†	Minimal T2 hyperintensity	Moderate T2 hyperintensity with extension	Extensive T2 hyperintensity with further extension
Neurocognitive testing	IQ ≥ 85	IQ 70-84	IQ < 70
NCS‡	Normal or mildly abnormal	Moderately abnormal	Severely abnormal
EEG	Normal	Normal	Seizure activity or regions of epileptic potential
VEP§	Normal	Normal	Normal or abnormal
BAER¶	Normal or mildly abnormal	Abnormal	Abnormal

* For these patients, it is important to acknowledge that these guidelines are based on clinical experience and, to a lesser degree, published literature.

† Neuroimaging progression and severity well described [112,130]. Mild disease is characterized by T2 hyperintensity of the frontal, periventricular, corpus callosum, or central white matter. Moderate disease is additionally characterized by extension into subcortical white matter (U-fibers) or basal ganglia/thalamic regions. Severe disease is additionally characterized by involvement of projection fibers or cerebellar white matter, with tigroid appearance of white matter common.

‡ NCS were considered abnormal if prolonged distal latency, low amplitude, no evoked response, or prolonged F-wave latency was present [131]. Designation of severity is based on the neurologist interpretation.

§ VEPs are considered abnormal if the P100 wave is absent or delayed [128].

¶ BAERs are considered abnormal if wave I to V interpeak latency is prolonged or if any of the obligate wave forms (I, III, V) are absent [129].

later develop peripheral neuropathy [10,12,109]. Juvenile and adult MLD patients with early symptoms (Table 7) are appropriate candidates for HSCT, as reports have demonstrated potential benefit [9-11]. Cognitive function is generally preserved, but motor and expressive language functions are more variable. Peripheral nerve disease appears to be less responsive to HSCT [10,11]. MRI typically demonstrates increased white matter changes in the first 6 to 12 months post-HSCT, followed by stability or even slight improvement [9,110]. HSCT benefit in patients with advanced disease is minimal and therefore is not recommended with significant neurologic deficits (Table 7).

Recommendations

Diagnostic evaluation should include neuroimaging, cognitive testing, and neurophysiologic testing (Table 2). A gross motor function scale has been developed to assess function at baseline and over time (Table 3C) [111]. An MRI scoring system also exists for staging MLD patients [112]. Proton magnetic resonance spectroscopy can also be used in staging, because characteristic metabolic changes occur as disease progresses [113]. Elevated cerebrospinal fluid protein and cytokines have been described in MLD [114,115]. HSCT eligibility is primarily based on disease status, informed by a comprehensive neurologic evaluation and neurophysiologic or neuroimaging testing results (Table 7). Further research is needed to further understand and prioritize prognostic criteria.

Patients with MLD have a higher incidence of gallbladder disease [23,24]; therefore, pretransplant evaluation should include gallbladder imaging (eg, ultrasonography). Post-transplant, there should be a heightened awareness in patients experiencing abdominal symptoms or fever of unknown origin. Increased incidence of sinusoidal obstructive syndrome has not been reported in modern HSCT protocols [12], and prophylaxis should be per institutional practice. Mild elevations in liver transaminases can occur and may persist post-transplant. Patients with MLD also tend to develop metabolic acidosis (because of renal sulfatide accumulation) during times of physiologic stress [116]. Adequate monitoring and corrective measures should be considered. Patients benefit significantly from aggressive physical therapy and occupational therapy during transplant and in the long term.

Contraindications

Young children with symptomatic LI-MLD and older patients with advanced disease are unlikely to benefit from HSCT. Supportive care and symptom management should be provided.

LONG-TERM FOLLOW-UP AFTER HSCT

Leukodystrophy patients who have undergone HSCT require comprehensive, multidisciplinary care for months to years post-transplant. Transplant complications, including GVHD and organ dysfunction, require close monitoring to detect and treat late effects [117]. Consensus guidelines are available for long-term monitoring of children who have undergone HSCT for a variety of conditions [118,119]. Of note, patients transplanted as infants or very young children are at higher risk for certain post-HSCT complications [117,120] and should be followed accordingly.

In addition to the monitoring for post-HSCT complications, it is increasingly clear that additional disease symptoms will develop over time [10,12,13]. Infants transplanted for EIKD develop peripheral disease as young teenagers [22]. Similarly, individuals with MLD may have gradual worsening of peripheral disease [10]. The adult form of ALD, namely AMN, has been reported in a small number of patients previously transplanted, although the incidence remains unclear [81]. Therefore, continued supportive care and close monitoring should occur in collaboration with an experienced center. Recommendations for follow-up are presented briefly here (Supplementary Tables 4, 5, and 6) and in more depth in companion articles from the LCN.

CONCLUSION

The goal of these guidelines from the LCN is to provide evidence-based expert recommendations for transplant-related care of patients with leukodystrophies. We have focused on leukodystrophies where there is sufficient clinical experience and outcomes data supporting its use, specifically cALD, Krabbe disease, and MLD. In these diseases, HSCT is an established treatment aimed at slowing the disease and preserving neurologic function.

To facilitate rapid diagnosis and timely evaluation, our centers have a multidisciplinary team approach, including neurology, genetics, radiology, pathology/laboratory medicine, and stem cell transplantation, in partnership with allied health providers with expertise in leukodystrophies. Given the rarity of these diseases, we recommend partnering with experienced centers to supplement these guidelines. For example, subtle neuroimaging findings can be difficult to interpret, and efforts should be made to have neuroimaging reviewed by an experienced center. Furthermore, certain biochemical testing and CB enzyme assays are not commercially available. Coordination with research labs that perform these assays should be sought, particularly in suspected EIKD when urgent evaluation is needed.

The increasing availability of NBS has provided new challenges for families and treating providers. As more newborns are identified with EIKD, it is likely that there will be an increase in infants undergoing HSCT. There are unique considerations to performing HSCT in this very young population. Infants who undergo HSCT can experience chronic and unique issues, most notably feeding issues and developmental delays [22,117]. Well beyond infancy, these children benefit from aggressive therapies and require close monitoring for late effects of HSCT and their underlying disease.

Another consequence of NBS is the identification of new mutations and compound heterozygous states in which clinical disease severity is unknown. Although performing HSCT earlier in the disease course leads to better outcome, HSCT is not without risks. Therefore, HSCT should be reserved for neonates with a known severe genotype/phenotype. Those with new or complex mutations should be closely followed until the phenotype is better understood. A catalogue of ALD mutations is maintained by ALD Info (https://adrenoleukodystrophy.info), although registries are needed for Krabbe disease and MLD. Screening guidelines should be developed to better address these situations, analogous to what occurs in asymptomatic ALD patients. Under these unique circumstances, conveying the complexities of the diagnosis and treatment decision-making to a family facing a potential life-altering diagnosis becomes even more challenging. Establishing a comprehensive care team to partner with the family and follow these children longitudinally is of the utmost importance.

Finally, ongoing research in gene therapy, chaperone therapy, and enzyme replacement therapy provides further optimism for these patients. Most notably are promising results using autologous gene therapy for both MLD and cALD [121,122]. Advantages of autologous gene therapy include absence of GVHD and more rapid immune reconstitution. Myeloablative conditioning is still required for engraftment of transfected cells; therefore, conditioning-related toxicities can still pose significant risk. Furthermore,

data regarding the long-term efficacy of gene therapy are not yet available. As development of other treatment modalities continues, HSCT remains the primary therapeutic option and should be carefully considered for patients with cALD, Krabbe disease, and MLD. It is the goal of these guidelines to facilitate high-quality transplant-related care through a multidisciplinary, collaborative approach.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2019.09.003.

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