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Hematopoietic Cell Transplantation for Inherited Metabolic Disorders and Genetic Diseases

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

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Policy History

Last Review
12/18/2024
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Next Review: 10/09/2025

Review History

Definitions

Policy

Scope of Policy

This Clinical Policy Bulletin addresses hematopoietic cell transplantation for inherited metabolic disorders and genetic diseases.

Additional Information

Clinical Policy Bulletin Notes

I. Medical Necessity

Aetna considers allogeneic hematopoietic cell transplantation (HCT) medically necessary for the treatment of the following inherited metabolic disorders:

A. Alpha-mannosidosis
B. Childhood-onset adrenoleukodystrophy
C. Children and adolescents with Fanconi anemia who have failed supportive modalities, androgens, and hematopoietic growth factors, or those who cannot tolerate this approach, or who have developed severe bone marrow failure, myelodysplasia, or acute myeloid leukemia.
D. Erythropoietic protoporphyria with severe hepatopathy
E. Fucosidosis
F. Globoid cell leukodystrophy (Krabbe disease)
G. Metachromatic leukodystrophy
H. Mucolipidoses (e.g., adrenoleukodystrophy, Gaucher's disease, metachromatic leukodystrophy)
I. Mucopolysaccharidosis (e.g., Hunter's syndrome, Hurler's syndrome, Sanfillippo's syndrome, Maroteaux-Lamy syndrome, Morquio syndrome, Sly syndrome)
J. Wolman disease.

Aetna considers allogeneic HCT medically necessary for the treatment of children with infantile malignant osteopetrosis confirmed by bone biopsy and radiographic imaging and when they do not exhibit irreversible neurologic impairment and multi-organ failure.

II. Experimental, Investigational, or Unproven

The following procedures are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

- Allogeneic hematopoietic cell transplantation for Barakat syndrome (HDR syndrome)

- Autologous HCT for the treatment of infantile malignant osteopetrosis, mucopolysaccharidosis, or childhood-onset adrenoleukodystrophy
- Hematopoietic cell transplantation (autologous, allogeneic or cord blood) for the treatment of the following (not an all-inclusive list):

  - Hereditary corneal defects
  - Huntington's disease
  - TRNT1 (CCA-adding transfer RNA nucleotidyl transferase) enzyme deficiency.

III. **Related Policies**

- CPB 0140 Genetic Testing (../100_199/0140.html)
- CPB 0442 - Lysosomal Storage Disorders Treatments (../400_499/0442.html)
- CPB 0626 - Hematopoietic Cell Transplantation for Thalassemia Major and Sickle Cell Anemia (../600_699/0626.html)

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207 - 38215	Transplant preparation of hematopoietic progenitor cells
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions

Code	Code Description
38243	Hematopoietic progenitor cell (HPC); HPC boost
CPT codes not covered for indications listed in the CPB:	
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS codes covered if selection criteria are met:	
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition
ICD-10 codes covered if selection criteria are met:	
D61.09	Other constitutional aplastic anemia
E71.511	Neonatal adrenoleukodystrophy [childhood-onset adrenoleukodystrophy]
E75.23	Krabbe disease
E75.25	Metachromatic leukodystrophy
E75.5	Other lipid storage disorders [Wolman's disease]
E76.01 - E76.9	Disorders of glycosaminogiycan metabolism [Mucopolysaccharidosis]
E77.0	Defects in post-translational modification of lysosomal enzymes [Mucolipidosis II, Mucolipidosis III]
E77.1	Defects in glycoprotein degradation [Alpha-mannosidosis] [Fucosidosis] [Mucolipidosis I]
E80.0	Hereditary erythropoietic porphyria
Q78.2	Osteopetrosis [infantile malignant] [allogeneic only]

Code	Code Description
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
E88.09	Other disorders of plasma-protein metabolism, not elsewhere classified [TRNT1 (CCA-adding transfer RNA nucleotidyl transferase) enzyme deficiency]
G10	Huntington's disease
H18.501 - H18.591	Hereditary corneal dystrophies
Q87.89	Other specified congenital malformation syndromes, not elsewhere classified [Barakat syndrome]

Background

Alpha-Mannosidosis

Alpha-mannosidosis is a rare lysosomal storage disorder in which deficient alpha-mannosidase activity leads to lysosomal accumulation of mannose-rich oligosaccharides. Alpha-mannosidosis is characterized by mental retardation, skeletal changes, hearing impairment, and recurrent infections. HCT increases levels of alpha-mannosidosis, resulting in improvements in neurocognitive and sensorineural function as well as skeletal malformations (Yeskilipek, 2012).

Mynarek et al (2012) reported on the results of a retrospective multi-institutional analysis of 17 patients who underwent HCT. Median age at diagnosis was 2.5 years. After a median follow-up of 5.5 years 15 patients remained alive, 2 having died within the first 5 months after HCT. The investigators reported that t3 patients required re-transplantation due to graft failure. Following HCT, patients made developmental progress, although normal development was not achieved, including an improvement in hearing ability in some but not all patients.

Childhood-Onset Adrenoleukodystrophy

Adrenoleukodystrophy (ALD), an X-linked disorder which more severely affects males, is caused by a defect in the metabolism of long-chain fatty acids resulting in demyelination, neurological deterioration, and death. The majority of patients with ALD suffer from adrenal insufficiency, the neurological symptoms can appear either in childhood or adulthood. Childhood ALD, which is the most severe form of this disease, results in onset of neurological symptoms between ages 4 and 10. These symptoms include visual loss, hearing loss, learning disabilities, seizures, speech impairment, dysphagia, increased pigmentation of the skin, challenges in ambulation, abnormal withdrawal or aggression, poor memory and school performance, fatigue, and progressive dementia (NINDS, 2013).

Shapiro et al (2000) examined if bone marrow transplantation (BMT) can stop the progressive demyelination and neurodegeneration of patients with childhood-onset cerebral X-linked ALD (CCALD). A total of 12 patients were followed for 5 to 10 years after BMT. Electrophysiological, neurological, and neuropsychological studies, magnetic resonance imaging (MRI), as well as plasma very-long-chain fatty acid (VLCFA) measurements were used to evaluate the effect of BMT. Magnetic resonance imaging showed improvement in 1.patient and complete reversal of abnormalities in 2 patients. One patient showed no change from baseline to last follow-up. All 8 patients who showed an initial period of continued demyelination stabilized and remained unchanged thereafter. In 10 patients, motor function remained normal or improved after BMT. Verbal intelligence remained within the normal range for 11 patients; performance (non-verbal) abilities were improved or were stable in 7 patients. Decline in performance abilities followed by stability occurred in 5 patients. Plasma VLCFA concentrations decreased by 55 % and remained slightly above the upper limits of normal. The authors noted that 5- to 10-year follow-up of 12 patients with CCALD showed the long-term beneficial effect of BMT when the procedure is done at an early stage of the disease.

Beam et al (2007) evaluated outcomes of unrelated donor umbilical cord blood (UCB) transplantation after chemotherapy-based myeloablative conditioning and retrospectively determined if baseline studies correlated

and helped to predict outcome. A total of 12 boys with X-linked ALD who lacked human leukocyte antigen (HLA)-matched related donors were studied. Baseline studies of neuroimaging, neurophysiological, as well as neurodevelopmental status were performed and patients were subsequently evaluated for engraftment, graft-versus-host disease (GVHD), neurodevelopmental outcomes, and survival. A sub-study evaluated whether baseline neuroimaging and neurophysiological studies correlated with cognitive and motor function and if these studies were predictive of post-transplantation outcomes. The UCB grafts had normal levels of VLCFA. Three patients had grade II to IV acute GVHD; 2 had extensive chronic GVHD. Cumulative incidence of overall survival of the group at 6 months was 66.7 % (95 % confidence interval [CI]: 39.9 % to 93.3 %). Median follow-up was 3.3 years (range of 12 days to 6.3 years). As previously reported with BMT, symptomatic patients faired poorly with lower survival and rapid deterioration of neurological function. This study included 3 patients transplanted at a very young age (2.6 to 3.5 years) before the onset of clinical symptoms who continue to develop at a normal rate for 3 to 5 years post-transplant. Although baseline Loes scores correlated with cognitive and motor outcome, neurophysiological studies failed to show statistically significant differences. The authors concluded that transplantation of boys with X-linked ALD using partial HLA-matched UCB yielded similar results to those previously reported after BMT. Superior outcomes were seen in neurologically asymptomatic boys less than 3.5 years of age at the time of transplantation.

Mahmood and colleagues (2007) analyzed survival of CCALD patients who had not received HCT; and (ii) in a subgroup with early cerebral disease, compared survival in those who underwent HCT with those who did not. Retrospective survival analyses were done on 283 CCALD patients who had not received HCT, focusing on a 30-member early stage cerebral subgroup whose neurological disability and MRI severity scores matched those of a 19-member transplanted subgroup previously reported. A Kaplan-Meier survival curve and log-rank test were used for survival analysis and for estimating the difference between the survival probabilities of the groups with statistical significance set at p = 0.05. Mean age at onset of symptoms in the 283 non-transplanted group was 7 years (standard deviation [SD] = 2 years). A total of 131 (SD = 46 %) patients died during the mean follow-up period of 5.9 years (SD = 5.3) at a mean age of 12.3 years (SD = 4.9). The 5-year survival was 66 %; the

5-year survival probability of 54 % in the early stage group was significantly poorer (chi(2) = 7.47, p = 0.006) than the 5-year survival of 95 % in the transplanted group with early stage cerebral disease. The authors concluded that HCT done in the early and progressive stages of CCALD is beneficial, and these findings supported the recommendation that transplantation be offered to patients in the early stages of CCALD.

Miller et al (2011) presented findings on 60 boys who had undergone hematopoietic stem cell transplantation (HSCT) with varying conditioning regimens and allograft sources for cerebral ALD between 2000 and 2009. The median age at time of HSCT was 8.7 years with 50% demonstrating a Loes radiographic severity score ≥ 19 and 62% showing clinical evidence of neurologic dysfunction. Survival at a median 3.7 years after HSCT was 78% (n=47). Five year survival estimates for boys with Loes score < 10 at time of HSCT was 89% and for boys with a Loes score ≥ 10 at time of HSCT was 60% (p = .03). Among study participants who had not demonstrated clinical cerebral disease at the time of HSCT, the 5 year survival was 91% and for study participants who had exhibited neurologic dysfunction the 5 year survival was 66% (p = .08). Cumulative mortality incidence 100 days post HSCT was 8%. Thus, the investigators concluded that post-transplantation progression of neurologic dysfunction depended significantly on the pre-HSCT Loes score and clinical neurologic status.

Fanconi Anemia

Peffault de Latour and co-workers (2013) stated that although allogeneic HSCT (allo-HSCT) remains the only curative treatment for patients with Fanconi anemia (FA), published series mostly refer to single-center experience with limited numbers of patients. These investigators analyzed results in 795 patients with FA who underwent first HSCT between May 1972 and January 2010. With a 6-year median follow-up, OS was 49 % at 20 years (95 % CI: 38 to 65 years). Better outcome was observed for patients transplanted before the age of 10 years, before clonal evolution (i.e., myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML]), from a matched family donor, after a conditioning regimen without irradiation, the latter including fludarabine. Chronic GVHD and secondary malignancy were deleterious when considered as time-dependent co-variates. Age more than 10 years at time of HSCT,

clonal evolution as an indication for transplantation, peripheral blood as source of stem cells, and chronic GVHD were found to be independently associated with the risk for secondary malignancy. Changes in transplant protocols have significantly improved the outcome of patients with FA, who should be transplanted at a young age, with bone marrow as the source of stem cells.

Alhuraiji and associates (2016) noted that FA is a congenital bone marrow failure syndrome that is associated with congenital anomalies and increased risk of cancer; and HSCT is a potentially curative modality for bone marrow failure in FA patients. These researchers reported their center's experience regarding adolescent and young adult patients with FA and HSCT. They conducted a retrospective patient record analyses of patients who presented at their center from 1988 to 2014. They included patients greater than 14 years old with confirmed FA based on positive chromosome breakage study and who underwent HSCT at their institution. This study group comprised 12 patients with FA who underwent HSCT at their institution. The median age was 20 years (range of 14 to 31) with a female predominance of 83 %. Low-dose cyclophosphamide (20 to 80 mg/kg)-based conditioning regimens were used with different combinations that included fludarabine, anti-thymocyte globulin (ATG), or TBI. All patients had HLA-matched sibling grafts. In all patients, stem cell source was the bone marrow. All patients showed engraftment; 4 patients (33 %) developed acute GVHD; 3 patients (25 %) died early before day 100 after HSCT due to infectious complications, with 1 patient having steroid refractory acute GVHD; OS was 75 % at a median follow-up of 43 months. All patients who survived were well and remained transfusion independent without evidence of secondary malignancy. The authors concluded that these findings supported the feasibility of reduced intensity conditioning (RIC) allo-HSCT in older and more heavily pre-treated patients with FA, especially for those who were engrafted.

Ebens and co-workers (2017) stated that HSCT for FA has improved dramatically over the past 40 years. With an enhanced understanding of the intrinsic DNA-repair defect and pathophysiology of hematopoietic failure and leukemogenesis, sequential changes to conditioning and graft engineering have significantly improved the expectation of survival following allo-HSCT with incidence of graft failure decreased from 35 % to

less than 10 % and acute GVHD from greater than 40 % to less than 10 %. Today, 5-year OS exceeds 90 % in younger FA patients with bone marrow failure but remains about 50 % in those with hematologic malignancy. These researchers examined the evolution of allo-HSCT contributing to decreased rates of transplant-related complications; highlighted current challenges including poorer outcomes in cases of clonal hematologic disorders, allo-HSCT impact on endocrine function and intrinsic FA risk of epithelial malignancies; and described investigational therapies for prevention and treatment of the hematologic manifestations of FA. The authors concluded that current methods allow for excellent survival following allo-HSCT for FA-associated bone marrow failure irrespective of donor hematopoietic cell source. Alternative curative approaches, such as gene therapy, are being examined to eliminate the risks of GVHD and minimize therapy-related adverse effects.

Kesici and colleagues (2019) stated that FA is an inherited disease, characterized by congenital malformations, short stature, progressive bone marrow failure and predisposition to leukemia and solid tumors. In a single-center study, these researchers examined the clinical and prognostic features of patients with FA. The charts of FA patients were reviewed 35 years retrospectively and a total of 175 patients were included in the study in which 51.4 % of patients were male. The mean age at diagnosis was 6.3 ± 4.1 years. The incidence of microcephaly was 92.6 %, skin findings were 88.0 %, eye abnormality was 74.3 %, thumb and radius abnormality was 53.1 %, urinary system abnormality was 30.9 %, skeletal system abnormality other than thumb and radius was 18.9 %, genital system abnormality was 11.4 %, cardiovascular system abnormality was 11.4 %, ear and hearing abnormalities were 9.7 %, and gastro-intestinal (GI) system abnormality was 5.7 %. Short stature was present in 75.4 % of the patients. Of the 175 patients 167 (95.4 %) developed bone marrow failure during follow-up and the mean age of bone marrow failure was 7.1 ± 3.7 years (1 month-old to 19.8 years). The 1st clinical symptom was thrombocytopenia in 83.4 % of patients. Malignancy developed in a total of 23 (13.1 %) patients (20 leukemia, 3 solid tumors) during follow-up. Of 175 patients, 35 (20 %) underwent HSCT. Fatality rate among patients who underwent HSCT was 31.4 % (11/35) and fatality rate among other patients was 63.4 % (83/131; $p < 0.05$). Of 94 patients who deceased, death was due to bleeding in 44.7 %, infection in 34 %, leukemia progression in 16.0 % and GVHD in 5.3 %.

The authors concluded that in terms of the number of patients included, this study was one of the largest cohorts with a remarkable duration of follow-up time; and HSCT was found to have a good impact on survival of patients. However, it is important to employ less toxic regimens, regimens without TBI are especially important.

Doval and co-workers (2020) noted that HSCT is the only therapeutic option for the hematological manifestations of FA. Fludarabine-based RIC regimens have helped in improving outcomes significantly in FA patients. These investigators retrospectively analyzed the outcomes of FA patients who underwent allogeneic-HSCT at BLK Super-Specialty Hospital, New Delhi from June 2011 to September 2019. A total of 20 FA patients underwent 23 transplants at the authors' center; OS and disease free survival (DFS) were 65 % and 50 %, respectively at a median of 23 months; overall mortality was 30 %. The authors concluded that HSCT for FA is a feasible option even in developing countries although children presented late to transplant centers after multiple transfusions and infections.

Furthermore, an UpToDate review on "Hematopoietic cell transplantation for idiopathic severe aplastic anemia and Fanconi anemia in children and adolescents" (Khan and Negrin, 2020) states that "Management of children with Fanconi anemia (FA) consists of supportive modalities, androgens, and hematopoietic growth factors, which can achieve a transient improvement in hematopoietic function. For those who cannot tolerate this approach, or who have developed severe bone marrow failure, myelodysplasia, or acute myeloid leukemia, allogeneic HCT is the only treatment option that can restore normal hematopoiesis. If an HLA-identical sibling donor (the best choice) is not available, children receiving HCT from an HLA-matched unrelated donor may do well when fludarabine is part of the conditioning regimen".

Fucosidosis

Approximately 100 cases of fucosidosis have been reported worldwide. Fucosidosis is a rare autosomal recessive lysosomal disorder and is caused by mutations in the FUCA1 gene, which is key in production of the alpha-L-fucosidase enzyme. Alpha-L-fucosidase is involved in the breakdown of oligosaccharides attached to certain glycolipids and

glycoproteins. Absence of alpha-L-fucosidase results in incomplete breakdown of glycolipids and glycoproteins. The incomplete compounds gradually accumulate within various cells, particularly brain cells, but can accumulate throughout the body, causing cell malfunction. Fucosidosis results in intellectual disability that worsens with age, delayed motor skills development, impaired growth, dysostosis multiplex, seizures, spasticity, angiokeratomas, visceromegaly, recurrent respiratory infections, and distinctive or coarse facial features. Individuals with severe disease typically live into late childhood while mildly affected individuals can live until mid-adulthood (Genetics Home Reference, 2008).

Krivit (2004), in a review of the clinical responses and prospectus of new therapies following use of HCT for a number of disorders including fucosidosis report that over 500 patients with lysosome and peroxisomal metabolic storage diseases due to deficiency of primary enzymes have been treated with HCT since the treatment option became available. Krivit stated that normal enzymatic activity has been robust in these patients along with excellent engraftment rates.

Globoid Cell Leukodystrophy (Krabbe disease)

Globoid cell leukodystrophy is a neurodegenerative disorder caused by a deficiency of the lysosomal enzyme galactosylceramidase, resulting in an accumulation of incompletely metabolized galactocerebroside, which is a component of myelin. The resulting galactocerebroside accumulation leads to progressive white matter disease (Pastores, 2009). Duffner et al (2009) stated that although most globoid cell leukodystrophy patients present within the first 6 months of life, some can present into adolescence and adulthood. He further notes that the only available treatment for infants with early infantile disease is HCT, typically using umbilical cord blood. Duffner further reports that globoid cell leukodystrophy patients receiving HCT perform better neurologically than those following the typical fulminant course of early infantile globoid cell leukodystrophy.

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is an autosomal recessive lysosomal disorder due to the deficiency of arylsulfatase A causing impaired degradation of sulfatide, which manifests in affected individuals as progressive demyelination and subsequent debilitating neurological symptoms. HCT has been used to treat metachromatic leukodystrophy utilizing both umbilical cord blood and bone marrow sources (Patil et al, 2013). Biffi et al (2013) reported on 3 patients who received HCT pre-symptomatically. Following HCT, the patients showed extensive and stable ARSA gene replacement, leading to high enzyme expression throughout hematopoietic lineages and in cerebrospinal fluid. The three patients showed no disease progression 7 to 21 months beyond the predicted age of symptom onset.

Martin et al (2013) reported the longitudinal outcome following umbilical cord blood transplantation in 27 pediatric metachromatic leukodystrophy patients. Seven patients died of infection, regimen-related toxicity, or disease progression. Twenty patients were followed for a median of 5.1 years, and the results showed that patients with motor function symptoms at the time of transplant did not improve after transplantation. The investigators also found that brainstem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities stabilized or improved in juvenile patients but continued to worsen in most patients with the late-infantile presentation. The investigators concluded that children who were asymptomatic at the time of transplantation benefited most from the procedure, while children with juvenile onset and minimal symptoms showed stabilization or deterioration of motor skills but maintained cognitive skills.

Mucolipidoses

The mucoipidoses (ML) are lysosomal storage diseases. Symptoms of ML can be congenital or begin in early childhood or adolescence; there are four types of ML and symptoms can range from mild to severe. Symptoms of ML I are either present at birth or develop within the first year of life, often presenting with excessive swelling throughout the body noted at birth. These infants are often born with coarse facial features, gum enlargement, macroglossia, liver and spleen enlargement,

hypotonia, mental retardation and skeletal malformations. Many patients suffer from failure to thrive and from recurrent respiratory infections. Most infants with ML I die before the age of 1 year (NINDS, 2011).

ML II is a particularly severe form of ML that resembles Hurler syndrome. Abnormal skeletal development, coarse facial features, and restricted joint movement may be present at birth and affected children often fail to grow and develop in the first months of life, with delays in motor skills being more pronounced than delays in cognitive skills. Children with ML II usually have enlargement of certain organs, such as the liver or spleen, or even the heart valves and have recurrent respiratory tract infections; children with ML II eventually develop a clouding on the cornea of their eyes and an underdeveloped trunk. Children with ML II generally die before their seventh year of life, often as a result of congestive heart failure or recurrent respiratory tract infections (NINDS, 2011).

ML III is a milder form and has symptoms which are often not noticed until the child is 3-5 years of age. ML III also results from a deficiency or defect of the enzyme N-acetylglucosamine-1-phosphotransferase but produces less severe symptoms and progresses more slowly, probably because the deficient enzyme retains some of its activity, resulting in a smaller accumulation of carbohydrates, lipids, and proteins in the inclusion bodies. Individuals with ML IV can present with delays in movement development and coordination, clouding of the cornea of the eye, and severely reduced vision. These patients often have an unsteady gait, do not walk independently. and speech is usually severely impaired. More mildly affected ML IV patients can walk and have better speech. Rarely, ML IV patients may even have only an eye abnormality resulting in vision impairment, but remain without mental impairment (NINDS, 2011).

Martin et al (2006) reported results of the Cord Blood Transplantation Study (COBLT), a phase II multicenter study in 69 patients with lysosomal and peroxisomal storage diseases designed to evaluate the use of cord blood in allogeneic transplantation. The study included patients with mucopolysaccharidoses I to III, mucolipidoses (ML) II (n = 36), adrenoleukodystrophy (n = 8), metachromatic leukodystrophy (n = 6), Krabbe disease (n = 16), and Tay-Sachs disease (n = 3) and all patients received the same preparative regimen, graft-versus-host disease (GVHD) prophylaxis, and supportive care. Sixty-nine patients (64% men;

81% white) with a median age of 1.8 years underwent transplantation with a median cell dose of 8.7 x 10(7)/kg and one-year survival was 72% (95% confidence interval, 61%-83%). The cumulative incidence of neutrophil engraftment by day 42 was 78% (95% confidence interval, 67%-87%) at a median of 25 days and grade II to IV acute GVHD occurred in 36% of patients. The investigators concluded that cord blood transplantation should be considered as frontline therapy for young patients with lysosomal and peroxisomal storage diseases.

Mucopolysaccharidoses

The mucopolysaccharidoses are a group of inherited metabolic diseases that are caused by the absence or malfunctioning of specific enzymes needed to break down molecules called glycosaminoglycans, which are long chains of sugar carbohydrates in human cells that help build bone, cartilage, tendons, corneas, skin, and connective tissue. Individuals with a mucopolysaccharidosis (MPS) either do not produce enough of one of the 11 enzymes required to break down sugar chains into proteins and simpler molecules or they produce enzymes that do not work properly, resulting in permanent, progressive cellular damage affecting the individual's appearance, physical abilities, organ and system functioning. In most cases, mental development is also affected. An estimated one in every 25,000 babies born in the United States will have some form of the mucopolysaccharidoses. They are autosomal recessive disorders, meaning that only individuals inheriting the defective gene from both parents are affected. (The exception is MPS II, or Hunter syndrome, in which the mother alone passes along the defective gene to a son.) When both people in a couple have the defective gene, each pregnancy carries with it a one in four chance that the child will be affected. The parents and siblings of an affected child may have no sign of the disorder. Unaffected siblings and select relatives of a child with one of the mucopolysaccharidoses may carry the recessive gene and could pass it to their own children (NINDS, 2013). MPS V, which was also referred to as Scheie syndrome, is a designation which is no longer in use (Dekabon et al, 1976).

Noh and Lee (2014) reviewed the classification and pathophysiology of MPS and discussed current therapies and new targeted agents under development. A Medline search through PubMed was performed for

relevant articles and treatment guidelines on MPS published in English for years 1970 to September of 2013 inclusive. The references listed in the identified articles, prescribing information of the drugs approved for the treatment of MPS, as well as recent clinical trial information posted on Clinicaltrials.gov website, were reviewed. Until recently, supportive care was the only option available for the management of MPS. In the early 2000s, enzyme replacement therapy (ERT) was approved by the Food and Drug Administration (FDA) for the treatment of MPS I, II and VI. Clinical trials of ERT showed substantial improvements in patients' somatic symptoms; however, no benefit was found in the neurological symptoms because the enzymes do not readily cross the blood-brain barrier (BBB). Hematopoietic stem cell transplantation, another potentially curative treatment, is not routinely advocated in clinical practice due to its high risk profile and lack of evidence for efficacy, except in preserving cognition and prolonging survival in young patients with severe MPS I. In recent years, substrate reduction therapy (SRT) and gene therapy have been rapidly gaining greater recognition as potential therapeutic avenues. The authors concluded that (i) ERT is effective for the treatment of many somatic symptoms, particularly walking ability and respiratory function, and remains the mainstay of MPS treatment, (ii) the usefulness of HSCT has not been established adequately for most MPS, and (iii) although still under investigation, SRT and gene therapy are promising MPS treatments that may prevent the neurodegeneration not affected by ERT.

Mucopolysaccharidoses I (Hurler's Syndrome)

Hurler's syndrome causes progressive deterioration of the central nervous system and death in childhood.

Staba and co-workers (2004) examined the feasibility of using cord blood transplants from unrelated donors and a myeloablative preparative regimen that did not involve total-body irradiation (TBI) in young children with Hurler's syndrome. A total of 20 children with Hurler's syndrome were given conditioning regimens before receiving cod blood transplants from unrelated donors. The children were subsequently evaluated for engraftment, side effects, and effects on disease symptoms. Cord blood donors were discordant for up to 3 of 6 HLA markers. Neutrophil

engraftment occurred a median of 24 days after transplantation. Five patients had grade II or grade III acute GVHD; none had extensive chronic GVHD. Seventeen of the 20 children were alive a median of 905 days after transplantation, with complete donor chimerism and normal peripheral blood alpha-L-iduronidase activity (event-free survival rate of 85 %). Transplantation improved neurocognitive performance and decreased somatic features of Hurler's syndrome. The authors concluded that cord blood from unrelated donors appears to be an excellent source of stem cells for transplantation in patients with Hurler's syndrome. Sustained engraftment can be achieved without TBI. They stated that cord blood transplantation favorably altered the natural history of Hurler's syndrome and thus may be important to consider in young children with this form of the disease.

Boelens et al (2007) analyzed data on Hurler's syndrome patients transplanted in Europe to identify the risk factors for graft failure. These investigators compared outcomes of 146 Hurler's syndrome patients transplanted with various conditioning regimens and grafts. Risk factor analysis was performed using logistic regression. "Survival" and "alive and engrafted" rates after first HCT were 85 % and 56 %, respectively. In multi-variable analysis, T-cell depletion (odds ratio [OR] 0.18; 95 % CI: 0.04 to 0.71; p = 0.02) and reduced-intensity conditioning (OR 0.08; 95 % CI: 0.02 to 0.39; p = 0.002) were the risk factors for graft failure. Busulfan targeting protected against graft failure (OR 5.76; 95 % CI: 1.20 to 27.54; p = 0.028). No difference was noted between cell sources used (bone marrow, peripheral blood stem cells, or UCB); however, significantly more patients who received UCB transplants had full-donor chimerism (OR 9.31; 95 % CI: 1.06 to 82.03; p = 0.044). The authors concluded that cord blood increased the likelihood of sustained engraftment associated with normal enzyme levels and could therefore be considered as a preferential cell source in HCT.

Hansen et al (2008) reported transplant outcomes following a reduced intensity, highly immunosuppressive preparative regimen in 7 patients with Hurler's syndrome. A total of 6 patients received grafts from unrelated donors and 1 received a sibling donor graft. The preparative regimen was well-tolerated. All patients had initial donor engraftment at 100 days; 1 patient had delayed loss of donor chimerism. There was no severe acute graft versus host disease. Six of the 7 children survived a

median of 1,014 days (726 to 2,222 days) post-transplant. The authors concluded that this reduced intensity preparative regimen has the potential to support engraftment and improve survival and outcome in patients with Hurler's syndrome undergoing HCT.

Sauer et al (2009) stated that allogeneic HSCT can achieve long-term survival in patients with Hurler's syndrome by correcting the enzymatic deficiency. In an attempt to improve long-term engraftment and to reduce regimen-related toxicity (RRT), these investigators used a fludarabine-based TBI-free preparative regimen. A total of 12 children were studied. Median age at HCT was 14 months (range of 4 to 31 months). CD34 positively selected peripheral blood hematopoietic stem cell were used in 10 children with a matched unrelated donor. Two children with a matched sibling donor received non-manipulated bone marrow. Donor lymphocyte infusions were given in 6/12 children for mixed hematopoietic chimerism. At a median follow-up of 29 months (range of 2 to 85 months), all children engrafted and had either stabilized or improved neurological function. In total, 12/12 patients showed donor-derived engraftment with 9/12 having full and 3/12 having mixed hematopoiesis. One developed acute GVHD greater than or equal to grade II; RRT greater than or equal to grade II was observed in 2 patients.

Guidelines from the International Consensus Panel on the Management and Treatment of Mucopolysacchardosis I (Muenzer et al, 2009) stated that when it is successful, HCT using either bone marrow or UCB cells can prevent and/or reverse many but not all of the clinical features of severe MPS I. It must be performed early in the disease course, before developmental deterioration begins.

Mucopolysaccharidosis II (Hunter Syndrome)

Hunter syndrome, an X-linked, recessive, lysosomal storage disease, is caused by a defect of the iduronate-2-sulfatase gene. It is diagnosed in approximately 1 out of 65,000 to 132,000 births. In the absence of sufficient enzyme activity, glycosaminoglycans (GAG) accumulate in the lysosomes of many tissues and organs; thus contributing to the multi-system (e.g., cardiovascular, musculo-skeletal, nervous, and respiratory systems) progressive pathologies in these patients. Hunter syndrome usually becomes apparent in children 1 to 3 years of age. Symptoms

include growth delay, joint stiffness, and coarsening of facial features. In severe cases, patients experience neurological deficits, enlargement of the liver and spleen, cardiac as well as respiratory problems, and death.

Guffon et al (2009) evaluated the effect of bone marrow transplant (BMT) in children with Hunter syndrome. A total of 8 boys (aged 3 and 16 years) received BMT. In 6 cases, the donor was a sibling with identical HLA status, in 1 case the donor was unrelated but HLA-compatible, and in 1 case the donor was unrelated and mismatched. Successful engraftment was achieved in all patients, with the proportion of donor cells reaching greater than or equal to 95 % 1 month after transplantation in all patients. Patients were followed for 7 to 17 years and all were still alive, except for 1 boy who died at the age of 10 from unrelated causes. Cardiovascular abnormalities stabilized in all patients, hepato-splenomegaly resolved, and joint stiffness improved, perceptual hearing defects remained stable, and transmission hearing defects improved. Only 1 child required subsequent surgery to correct kyphosis. Neuropsychological outcome was variable and appeared to be related to the severity of the syndrome.

Mucopolysaccharidosis III (Sanfilippo Syndrome)

Sanfilippo syndrome (MPS III) causes severe neurological symptoms, including progressive dementia, aggressive behavior, hyperactivity, seizures, some deafness and loss of vision, and an inability to sleep for more than a few hours at a time. MPS III affects children differently, and its progress will be faster in some than in others. Affected children show a marked decline in learning between ages 2 and 6, followed by eventual loss of language skills, and in some children an inability to speak at all. MPS III is also characterized by loss of some or all hearing. Aggressive behavior, hyperactivity, profound dementia, and irregular sleep may make children, particularly those who retain normal physical strength, difficult to manage. As the disease progresses, children become increasingly unsteady on their feet. Most are unable to walk by age 10 with height growth ceasing. Also, thickened skin and mild changes in facial features, bone, and skeletal structures become noticeable with age. Children with MPS III may also experience narrowing of the airway passage in the throat and enlargement of the tonsils and adenoids, making it difficult to eat or swallow, and recurring respiratory infections are common. There are four distinct types of MPS III, due to alteration of a different enzyme

for breakdown of the heparin sulfate sugar chain. Although there is little differentiation clinically between the four types, children with type A present with more severe symptoms and progress more quickly. Some individuals with MPS III may live into their teenage years, or even into their twenties or thirties (NINDS, 2013).

Mucopolysaccharidosis IV (Morquio Syndrome)

MPS IV, also known as Morquio syndrome, has an estimated occurrence of 1 in every 200,000 births, with an onset between the ages 1 and 3. Neurological complications include spinal nerve and nerve root compression resulting from extreme, progressive skeletal changes, conductive hearing loss, neuro-sensitive hearing loss, and clouded corneas. If hydrocephalus develops and is not treated intelligence can be adversely affected but is otherwise normal. Physical growth slows and often stops around age 8 with skeletal abnormalities including a bell-shaped chest, a flattening or curvature of the spine, shortened long bones, and dysplasia of the hips, knees, ankles, and wrists. In more severe cases of MPS IV children may not live beyond their twenties or thirties (NINDS, 2013).

Mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome)

MPS VI, Maroteaux-Lamy syndrome, does not affect normal intellectual development but includes many of the physical symptoms found in severe MPS I. MPS VI, which has a variable spectrum of severe symptoms, is caused by the deficient enzyme *N*-acetylgalactosamine 4-sulfatase,. Neurological complications include pain caused by compressed or traumatized nerves and nerve roots, clouded corneas, deafness, and thickening of the dura. Growth stops suddenly around age 8 and by age 10 children have developed a shortened trunk, crouched stance, and restricted joint movement. Children with MPS VI may also, in severe cases, develop a protruding abdomen and forward-curving spine. These skeletal changes are progressive and limit movement. Most children with MPS VI have some form of heart disease, usually involving valve dysfunction (NINDS, 2013).

Mucopolysaccharidosis VII (Sly Syndrome)

MPS VII, also known as Sly syndrome, is one of the least common forms of the mucopolysaccharidoses, with an estimated occurrence of fewer than 1 in 250,000 births. In its rarest form, MPS VII causes children to be born with hydrops fetalis, in which extreme amounts of fluid are retained in the body, and in these cases survival is usually a few months or less. Most children with MPS VII are less severely affected, but do experience neurological symptoms including mild to moderate mental retardation by age 3, communicating hydrocephalus, nerve entrapment, corneal clouding, and some loss of peripheral and night vision. These children often present with short stature, skeletal irregularities, joint stiffness, and umbilical and/or inguinal hernias, and may experience repeated bouts of pneumonia during their first years of life, and generally live into the teenage or young adult years (NINDS, 2013).

The NINDS "Mucopolysaccharidoses fact sheet" (NINDS, 2013) states that BMT and UCB transplantation are high-risk procedures and are usually performed only after family members receive extensive evaluation and counseling.

Wolman Disease

Wolman disease is a fatal lysosomal storage disease caused by a deficiency in lysosomal enzyme acid lipase. Wolman disease typically presents in early infancy with diarrhea, massive hepatospenomegaly, failure to thrive, and calcification of adrenal glands, with HCT the only therapy reported to prevent hepatic failure and death, which would otherwise occur during the first year of life (Tolar et al, 2009). Three cases of successful treatment with HCT were reported by Yanir et al (2013), but they also reported on two cases of fatality from hepatic complications.

Infantile Malignant Osteopetrosis

Osteopetrosis is a rare genetic disorder and infantile malignant osteopetrosis (IMO), also known as Albers-Schonberg disease/syndrome or marble bone disease, is the worst subtype of this disease; 70 % of

patients die in 6 years of life without proper treatment. Hematopoietic stem cell transplantation (HSCT) offers the only chance of cure for IMO (Zhu et al, 2012).

Driessen et al (2003) performed a retrospective analysis of 122 children who had received an allogeneic HSCT for autosomal recessive osteopetrosis between 1980 and 2001. The actuarial probabilities of 5 years disease free survival were 73 % for recipients of a genotype HLA-identical HSCT (n = 40), 43 % for recipients of a phenotype HLA-identical or 1 HLA-antigen mismatch graft from a related donor (n = 21), 40 % for recipients of a graft from a matched unrelated donor (n = 20) and 24 % for patients who received a graft from an HLA-haplotype-mismatch related donor (n = 41). In the latter group, a trend towards improvement was achieved at the end of the study period (17 % before 1994, 45 % after 1994, p = 0.11). Causes of death after HSCT were graft failure and early transplant-related complications. Severe visual impairment was present in 42 % of the children before HSCT. Conservation of vision was better in children transplanted before the age of 3 months. Final height was related to height at the time of HSCT and better preserved in children transplanted early. Most children attended regular school or education for the visually handicapped. The authors concluded that at present, HSCT is the only curative treatment for autosomal recessive osteopetrosis and should be offered as early as possible.

Tsuji et al (2005) stated that the only curative therapy for IMO is HSCT. Because the number of patients is limited, the conditioning regimen and the use of alternative donors for HSCT have been controversial and not established. The authors reported a case of successful cord blood transplantation (CBT) with a non-myeloablative regimen (NMR) for IMO. The patient was a 9-month old girl with IMO. Before this diagnosis, she had received chemotherapy under the tentative diagnosis of juvenile myelomonocytic leukemia. She was on mechanical ventilation with tracheotomy due to the progression of IMO when she underwent CBT with NMR. The conditioning regimen included fludarabine, melphalan, and anti-thymocyte globulin. Cyclosporine A and methylprednisolone were used for prophylaxis for graft-versus-host disease (GVHD). Neutrophil engraftment was achieved on day 26 after HSCT and had been fully maintained up to the present. Although grade 3 GVHD and hepatic veno-occlusive disease (VOD) occurred, both were controllable.

The authors noted that although the pre-transplant condition of the patient was somewhat unusual, this was the first reported case of successful CBT with NMR for IMO. Because of the urgent need, CBT can be considered as one of the HSCT sources for IMO, especially in a severe, life-threatening setting.

Corbacioglu et al (2006) noted that IMO is a rare hereditary disorder of osteoclast function, which can be reversed by HSCT. These investigators observed a high incidence of hepatic VOD in transplanted patients and explored the prevention of this complication by using defibrotide (DF) as a prophylaxis. A total of 20 children with IMO were consecutively transplanted in the authors' center between 1996 and 2005; 11 of these patients were transplanted between 1996 and 2001 and experienced an overall incidence of VOD of 63.6 % (7/11). Veno-occlusive disease was severe in 3 patients and 1 patient succumbed to VOD-related multi-organ failure. Owing to this very high incidence of VOD, DF prophylaxis was initiated in 9 patients consecutively transplanted between 2001 and 2005. In this group, only 1 patient (11.1 %) was diagnosed with moderate VOD. The authors reported a very high risk in patients with IMO to develop VOD after transplantation; and prophylactic DF was implemented in their current transplant protocol and reduced the VOD rate significantly in this high-risk population.

Mazzolari et al (2009) reported on the clinical and molecular findings and treatment in 20 consecutive patients (9 females and 11 males) with IMO, diagnosed at a single center in the period of 1991 to 2008. Mean age at diagnosis was 3.9 months, and mean follow-up was 66.75 months. Mutations in ClCN7, TNFRSF11A, OSTM1, and TCIRG1 genes were detected in 1, 1, 3, and 9 patients, respectively. Six patients remain genetically undefined; OSTM1 and ClCN7 mutations were associated with poor neurologic outcome. Among 9 patients with TCIRG1 defects, 6 presented with hypo-gammaglobulinemia, and 1 showed primary pulmonary hypertension. A total of 14 patients received HSCT; of these, 9 are alive and 8 of them have evidence of osteoclast function. The authors concluded that these data may provide a basis for informed decisions regarding the care of patients with IMO.

Gassas et al (2011) noted that HSCT has been used as therapy for selected inherited metabolic and genetic diseases (IMGDs). The primary objective of HSCT for these disorders has been to promote long-term survival, optimize quality of life, and improve neurocognitive performance. These researchers performed 45 HSCTs for 44 children with IMGDs (13 related and 32 unrelated); 24 HSCTs for 23 children with Hurler syndrome, 8 for IMO, 6 for X-linked adrenoleukodystrophy, 2 for metachromatic leukodystrophy, 2 for Gaucher disease, 1 for ganglioside mono-sialic acid (GM) gangliosidosis, 1 for sialiosis (type 2), and 1 HSCT for Niemann-Pick type A. At a median follow-up of 7.2 years (range of 2.2 to 17.6 y) 18 of 23 patients with Hurler syndrome are alive, 15 attended regular school; 13 of 18 were ambulatory, 2 had mobility difficulties, and 1 uses wheelchair. For non-Hurler patients, 5 children suffered secondary graft failure and 4 of them died from progressive disease. The remaining children with IMO are alive and most children attended regular school. One out of the 4 survivors with adrenoleukodystrophy has been transferred to the adult follow-up clinic and he is in full-time employment. Parents' perspectives and expectations of HSCT in these IMGDs were positive and supportive to continue to offer HSCT for these disorders.

Usta and colleagues (2012) stated that IMO presents early in life with extreme sclerosis of the skeleton and reduction of bone marrow spaces. Since there is a defect in the bone marrow, the disease can cause anemia, extra-medullary hematopoiesis secondary to anemia leading to hepato-splenomegaly, cranial nerves compression and severe growth failure. This disorder is often lethal within the first decade of life because of secondary infections. Stem cell transplantation remains the only curative therapy. These investigators reported on the case of a 2-month old male infant, diagnosed as IMO while investigating the cause of hepato-splenomegaly. The patient was referred for HSCT. The authors concluded that IMO should be kept in mind as a rare cause of hepato-splenomegaly and the patient should be referred for stem cell transplantation before neurologic or visual impairment develops.

Zhu and colleagues (2012) performed a retrospective analysis on 8 patients with IMO who underwent HSCT during the period from 2006 to 2011. Eight cases (4 females and 4 males, mean age of 13.5 months at HSCT) were diagnosed as IMO. Conditioning regimen included fludarabine, busulfan and cyclophosphamide. All patients received

cyclosporine for prophylaxis of GVHD. A UMD recipient underwent CD34(+) cell selection. ATG/ALG, mycophenolate mofetil (MMF) and methotrexate (MTX) used for recipients with unrelated cord donor (n = 2) and recipients with haplo-identical donors n = (5). Average time for neutrophil engraftment was 15.7 day (9 to 36), platelet engraftment was 43.3 day (10 to 68). Patients were followed-up from 47 days to 5 years; 1 patient died of post-transplant complications. Seven cases presented better in clinical manifestation. Acute GVHD Ⅰ° to Ⅱ° was observed in 6 patients, Ⅲ° to Ⅳ° in 2 patients. It was controlled by anti-GVHD therapy. The authors concluded that non-allogeneic HSCT treatment of infantile IMO showed high survival rate and restoration of hematopoiesis in haploid transplant patients, therefore, non-allogeneic HSCT may be an option to treat IMO in children.

Buchbinder and associates (2013) stated that IMO is a congenital disorder of osteoclast differentiation or dysfunction. Inadequate bone resorption by osteoclasts results in a spectrum of complications including hypocalcemia, osteosclerosis, marrow failure, extra-medullary hematopoiesis, hydrocephalus, visual deficits, and eventual mortality. Early diagnosis and timely HSCT is a recommended treatment approach for select patients prior to the development of end-organ damage. A co-morbid bleeding disorder presents a unique challenge in the setting of IMO and cord blood HSCT given the additional risk factors for bleeding including delayed engraftment, a high risk of developing sinusoidal obstruction syndrome, and potential need for emergent invasive procedures. To the authors' knowledge, this was the first report of a patient with an autosomal recessive form of IMO who successfully underwent a cord blood HSCT complicated by the presence of mild hemophilia A and HSCT-related complications including delayed engraftment, sinusoidal obstruction syndrome, and need for multiple invasive procedures (e.g., ventriculostomy, tracheostomy) without clinically significant bleeding.

Ott and associates (2013) stated that autosomal recessive osteopetrosis (ARO, MIM 259700) is a genetically heterogeneous rare skeletal disorder characterized by failure of osteoclast resorption leading to pathologically increased bone density, bone marrow failure, and fractures. In the neuronopathic form neurological complications are especially severe and progressive. An early identification of the underlying genetic defect is

imperative for assessment of prognosis and treatment HSCT. These researchers describe for the first time homozygous microdeletions of different sizes affecting the OSTM1 gene in 2 unrelated consanguineous families with children suffering from neuronopathic IMO. Patients showed an exceptionally severe phenotype with variable CNS malformations, seizures, blindness, and deafness. Multi-organ failure due to sepsis led to early death between 6 weeks and 5 months of age in spite of intensive care treatment. Analysis of the break-points revealed different mechanisms underlying both re-arrangements. Microdeletions seem to represent a considerable portion of OSTM1 mutations and should therefore be included in a sufficient diagnostic screening.

Essabar et al (2014) reported on the case of a 13-month old male patient, diagnosed as IMO while investigating the cause of hepato-splenomegaly associated with hydrocephalus. His medical history revealed non consanguineous parents and 1 brother's death at the same age of unknown etiology (similar symptoms). Systemic examination showed hepato-splenomegaly, growth failure, developmental milestones delay, and rickets features. Ophthalmic exam yielded bilateral optic atrophy. Skeleton radiographs detected generalized dense bone and rickets. Cerebral CT scan revealed hydrocephalus. Histological examination showed hypoplastic bone marrow and extra-medullary hematopoiesis. Diagnosis was confirmed by genetic testing that showed 2 heterozygote mutations within the TCIRG1 gene. The patient received supportive treatment. He died from an acute respiratory distress. The authors concluded that IMO should be kept in mind as a rare cause of hepato-splenomegaly. Timely HSCT is the only curative approach for an otherwise fatal disease; it should be performed early before the irreversible neurologic impairment. Hematopoietic stem cell transplantation replaces abnormal osteoclasts with normal cells, given the high associated morbidity and mortality it is reserved only for the most severe cases of osteopetrosis. Successful results have been achieved in patients transplanted with allogeneic donor stem cells. Furthermore, non-allogeneic HSCT may be an option to treat IMO, it showed high survival rate and restoration of hematopoiesis in haploid transplant patients.

There was a phase II/III clinical trial on “Hematopoietic Stem Cell Transplantation for Malignant Infantile Osteopetrosis”. However, the status of this trial is unclear because the information has not been verified

since May 2012. Inclusion criteria were (i) diagnosis of osteopetrosis confirmed by bone biopsy and radiographic imaging, and (ii) age up to 5-year old. Exclusion criteria were (i) bilirubin greater than or equal to 3 mg/dL, (ii) carbonic anhydrase II deficiency osteopetrosis variant, (iii) creatinine clearance less than or equal to 40 ml/min/1.73 m2 or renal tubular acidosis, (iv) current severe infection, (v) evidence of CNS involvement, (vi) morbidity such as blindness or deafness, and (vii) serum glutamic pyruvic transaminase (SGPT) greater than or equal to 500 U/L.

Steward et al (2005) noted that autosomal recessive osteopetrosis (OP) is a rare, lethal disorder in which osteoclasts are absent or nonfunctional, resulting in a bone marrow cavity insufficient to support hematopoiesis. Because osteoclasts are derived from hematopoietic precursors, allogeneic hematopoietic cell transplantation can cure the bony manifestations of the disorder. However, high rates of graft failure have been observed in this population. It is not possible to harvest bone marrow from these patients for reinfusion should graft failure be observed. Steward, et al. reported that 8 of 10 patients with OP had high numbers of circulating CD34(+) cells (3% +/- 0.9%). This increased proportion of peripheral CD34(+) cells made it possible to harvest 2 x 10(6) CD34(+) cells per kilogram with a total volume of blood ranging from 8.3 to 83.7 mL (1.3-11.6 mL/kg). In addition, colony-forming assays documented significantly more colony-forming unit-granulocyte-macrophage and burst-forming unit-erythroid in the blood of osteopetrotic patients compared with controls; the numbers of colony-forming units approximated those found in control marrow. The investigators concluded that OP patients with high levels of circulating CD34(+) are candidates for peripheral blood autologous harvest by limited exchange transfusion. These cells are then available for reinfusion should graft failure be observed in patients for whom re-transplantation is impractical.

Acyl-CoA Oxidase Deficiency

Wang et al (2014) stated that acyl-CoA oxidase (ACOX1) deficiency is a rare disorder of peroxisomal very-long chain fatty acid oxidation. No reports detailing attempted treatment, longitudinal imaging, or neuropathology exist. These researchers described the natural history of

clinical symptoms and brain imaging in 2 siblings with ACOX1 deficiency, including the younger sibling's response to allogeneic unrelated donor HSCT. These investigators conducted retrospective chart review to obtain clinical history, neuro-imaging, and neuropathology data. ACOX1 genotyping were performed to confirm the disease. In-vitro fibroblast and neural stem cell fatty acid oxidation assays were also performed. Both patients experienced a fatal neurodegenerative course, with late-stage cerebellar and cerebral gray matter atrophy. Serial brain MRI in the younger sibling indicated demyelination began in the medulla and progressed rostrally to include the white matter of the cerebellum, pons, midbrain, and eventually subcortical white matter. The successfully engrafted younger sibling had less brain inflammation, cortical atrophy, and neuronal loss on neuro-imaging and neuropathology compared to the untreated older sister. Fibroblasts and stem cells demonstrated deficient very long chain fatty acid oxidation. The authors concluded that although HSCT did not halt the course of ACOX1 deficiency, it reduced the extent of white matter inflammation in the brain. Demyelination continued because of ongoing neuronal loss, which may be due to inability of transplant to prevent progression of gray matter disease, adverse effects of chronic corticosteroid use to control GVHD, or intervention occurring beyond a critical point for therapeutic efficacy.

I-Cell Disease (Mucolipidosis Type II)

Lund et al (2014) stated that mucolipidosis type II (MLII), or I-cell disease, is a rare but severe disorder affecting localization of enzymes to the lysosome, generally resulting in death before the 10th birthday. While HSCT has been successful in treating some lysosomal storage diseases (LSD), only 2 cases have been reported on the use of HSCT to treat MLII. These investigators described the combined international experience in the use of HSCT for MLII in 22 patients. Although 95 % of the patients engrafted, overall survival (OS) was low, with only 6 patients (27 %) alive at last follow-up. The most common cause of death post-transplant was cardiovascular complications, most likely due to disease progression. Survivors were globally delayed in development and often required complex medical support, such as gastrostomy tubes for nutrition and tracheostomy with mechanical ventilation. The authors concluded that although HSCT has demonstrated effectiveness in treating some LSD,

the neurologic outcome and survival for patents with MLII were poor. Thus, they stated that new medical and cellular therapies should be sought for these patients.

Combined Haploidentical Stem Cell Transplantation with Umbilical Cord Blood for Cerebral X-Linked Adrenoleukodystrophy

Jiang et al (2015) noted that childhood cerebral X-linked adrenoleukodystrophy is a rapidly progressive neurodegenerative disorder that affects central nervous system myelin and the adrenal cortex. Hematopoietic stem cell transplantation is the best available curative therapy if performed during the early stages of disease. Only 30 % of patients who might benefit from a HSCT will have a full human leukocyte antigen-matched donor, which is considered to be the best choice. These investigators presented the case of a 5-year old boy with cerebral X-linked adrenoleukodystrophy whose brain MRI severity score was 7 and who needed an immediate transplantation without an available full HLA-matched donor. These researchers combined haploidentical and UCB sources for transplantation and observed encouraging results. After transplantation, the patient showed neurological stability for 6 months and the level of very long chain fatty acids had decreased. By 1 year, the patient appeared to gradually develop cognition, motor, and visual disturbances resulting from possible mix chimerism. The authors concluded that transplantation of haploidentical stem cells combined with the infusion of UCB is a novel approach for treating cerebral X-linked adrenoleukodystrophy. It is critical to monitor post-transplant chimerism and carry out anti-rejection therapy timely for a beneficial clinical outcome. These preliminary findings need to be validated by well-designed studies.

Hereditary Corneal Defect

Rocca and associates (2015) noted that cystinosis is caused by a deficiency in the lysosomal cystine transporter, cystinosin (CTNS gene), resulting in cystine crystal accumulation in tissues. In eyes, crystals accumulate in the cornea causing photophobia and eventually blindness. Hematopoietic stem progenitor cells (HSPCs) rescue the kidney in a mouse model of cystinosis. These researchers examined the potential for HSPC transplantation to treat corneal defects in cystinosis. These

investigators isolated HSPCs from transgenic DsRed mice and systemically transplanted irradiated Ctns-/- mice. A year post-transplantation, these researchers investigated the fate and function of HSPCs by in-vivo confocal and fluorescence microscopy (IVCM), quantitative reverse transcription polymerase chain reaction (RT-qPCR), mass spectrometry, histology, and by measuring the IOP. To determine the mechanism by which HSPCs may rescue disease cells, these investigators transplanted Ctns-/- mice with Ctns-/- DsRed HSPCs virally transduced to express functional CTNS-eGFP fusion protein. They found that a single systemic transplantation of wild-type HSPCs prevented ocular pathology in the Ctns-/- mice. Engraftment-derived HSPCs were detected within the cornea, and also in the sclera, ciliary body, retina, choroid, and lens. Transplantation of HSPC led to substantial decreases in corneal cystine crystals, restoration of normal corneal thickness, and lowered intra-ocular pressure (IOP) in mice with high levels of donor-derived cell engraftment. These researchers found that HSPC-derived progeny differentiated into macrophages, which displayed tunneling nanotubes capable of transferring cystinosin-bearing lysosomes to diseased cells. The authors concluded that to their knowledge, this was the first demonstration that HSPCs can rescue hereditary corneal defects, and supported a new potential therapeutic strategy for treating ocular pathologies.

TRNT1 (CCA-Adding Transfer RNA Nucleotidyl Transferase) Enzyme Deficiency

Wedatilake and colleagues (2016) stated that TRNT1 (CCA-adding transfer RNA nucleotidyl transferase) enzyme deficiency is a new metabolic disease caused by defective post-transcriptional modification of mitochondrial and cytosolic transfer RNAs (tRNAs). These researchers investigated 4 patients from 2 families with infantile-onset cyclical, aseptic febrile episodes with vomiting and diarrhea, global electrolyte imbalance during these episodes, sideroblastic anemia, B lymphocyte immunodeficiency, retinitis pigmentosa, hepatosplenomegaly, exocrine pancreatic insufficiency and renal tubulopathy. Other clinical features found in children include sensorineural deafness, cerebellar atrophy, brittle hair, partial villous atrophy and nephrocalcinosis; WES and bioinformatic filtering were utilized to identify recessive compound heterozygous TRNT1 mutations (missense mutation c.668T>C,

p.Ile223Thr and a novel splice mutation c.342+5G>T) segregating with disease in the 1st family. The 2nd family was found to have a homozygous TRNT1 mutation (c.569G>T), p.Arg190Ile, (previously published). These investigators found normal mitochondrial translation products using passage matched controls and functional perturbation of 3' CCA addition to mitochondrial tRNAs (tRNA(Cys), tRNA(LeuUUR) and tRNA(His)) in fibroblasts from 2 patients, demonstrating a pathomechanism affecting the CCA addition to mt-tRNAs. Acute management of these patients included transfusion for anemia, fluid and electrolyte replacement and immunoglobulin therapy. These investigators described 3-year follow-up findings after treatment by BMT in 1 patient, with resolution of fever and reversal of the abnormal metabolic profile. The authors concluded that this report highlighted that TRNT1 mutations caused a spectrum of disease ranging from a childhood-onset complex disease with manifestations in most organs to an adult-onset isolated retinitis pigmentosa presentation. They stated that systematic review of all TRNT1 cases and mutations reported to-date revealed a distinctive phenotypic spectrum and metabolic and other investigative findings, which will facilitate rapid clinical recognition of future cases. The effectiveness of BMT in the treatment of TRNT1 needs to be further investigated in well-designed studies.

Haploidentical Allogeneic Hematopoietic Stem Cell Transplantation for X-Linked Adrenoleukodystrophy

Chen and colleagues (2019) noted that X-linked ALD is a severe inherited disorder leading to rapid neurological deterioration and premature death; and allogeneic HSCT is still the only treatment that halts the neurologic symptoms in ALD. However, many patients lack suitable HLA-matched related donors and must rely on alternative donors for a source of stem cells. These researchers examined the outcomes of haploidentical allogeneic SCT for ALD patients. Between December 2014 and December 2018, a total of 8 children with ALD lacking HLA-matched related or unrelated donors were treated with haploidentical allogeneic HSCT. Subjects received conditioning regimen with busulfan 9.6 mg/kg, cyclophosphamide 200 mg/kg and fludarabine 90 mg/m2; GVHD prophylaxis consisted of anti-human thymocyte globulin, cyclosporine A, mycophenolate mofetil and short course of methotrexate. All 8 participants received allogeneic SCTs from their fathers. The median age

of the recipients was 8 years (range of 5 to 12). The median age of the donors was 36 years (range of 32 to 40). All the recipients received granulocyte colony-stimulating factor (G-CSF) mobilized bone marrow and peripheral blood-derived stem cells. The median number of total mononuclear cells dose and CD34+ dose was 10.89 (range of 9.40 to 12.16)×108/kg and 7.06 (range of 0.74 to 7.80)×106/kg, respectively. Neutrophil engraftment occurred a median of 11 days (range of 8 to 13) after transplantation. Platelet engraftment occurred a median of 10 days (range of 8 to 12) after transplantation. All subjects achieved complete donor chimerism at the time of engraftment; 4 patients had grades II to IV acute GVHD and 1 had chronic GVHD. No severe chronic GVHD occurred. Among all the children, 2 had cytomegalovirus (CMV) DNAemia and 2 Epstein-Barr virus (EBV) DNAemia. Overall, 7 of the subjects survived and had no major complications related to transplantation; 1 died of cerebral hernia after epilepsy 125 days after transplantation. The authors concluded that these preliminary findings showed that haploidentical allogeneic SCT with this novel regimen could successfully achieve full donor chimerism in ALD patients. These researchers stated that haploidentical allogeneic HSCT is safe and feasible in the treatment of X-linked ALD.

Stem Cell Transplantation for Huntington's Disease

Colpo and colleagues (2019) noted that Huntington's disease (HD) is an autosomal-dominant neurodegenerative disorder encoding a mutant form of the huntingtin protein (HTT). Huntington disease is pathologically characterized by loss of neurons in the striatum and cortex, which resulted in progressive motor dysfunction, cognitive decline and behavioral symptoms. Stem cell-based therapy has emerged as a feasible therapeutic approach for the treatment of neurodegenerative diseases and may be effective in alleviating and/or halting the pathophysiological mechanisms underlying HD. Several pre-clinical studies have used stem cells in animal models of HD. These researchers carried out a systematic review of pre-clinical studies to examine the treatment efficacy of stem cells in animal models of HD. Based on this systematic review, treatment with stem cells significantly improved neurological and behavioral outcomes in animal models of HD. The authors concluded that although promising results were found, the design

of animal studies, the types of transplanted cells and the route of administration are poorly standardized and this greatly complicates comparative analysis.

Erythropoietic Protoporphyria

Smiers et al (2010) reported on the case of a 9-year-old boy with erythropoietic protoporphyria (EPP) who suffered from severe skin burns and liver failure caused by progressive cholestasis and fibrosis. Orthotopic liver transplantation (OLT) was carried out without major complications. Four months following LT, the subject underwent parental haploidentical HSCT. The myeloablative conditioning regimen was relatively well-tolerated and hematological engraftment was rapid (on day 10). Protoporphyrin concentrations returned to normal following HSCT; however, immune recovery was significantly delayed. Varicella zoster virus reactivation resulted in impaired vision, prolonged hospitalization and eventually in multi-organ failure and death. The authors concluded that sequential liver and haploidentical HSCT proved feasible though a high-risk procedure in this EPP patient. The management of post-immunosuppressive therapy (IST) after these combined transplantations remains a challenge and needs to be further established.

Wahlin et al (2011) noted that LT is an established life-saving treatment for patients with severe protoporphyric liver disease; however, disease recurrence in the graft occurs in the majority of transplant recipients. Severe burn injuries may occur when protective light filters were not used with surgical luminaires; and motor neuropathy with an unclear pathogenesis was a frequent complication. These researchers retrospectively studied 35 transplants performed for protoporphyric liver disease in 31 European patients between 1983 and 2008. Most of the patients were male (61.3 %), and the mean age at the time of primary transplantation was 39 years (range of 9 to 60 years). The overall patient survival rates were 77 % at 1 year and 66 % at 5 and 10 years. The overall rate of disease recurrence in the graft was 69 %; 43 % of the patients experienced recurrence within 1 year, but this was often a transient finding that was associated with other graft complications. Phototoxic injuries due to surgical luminaires were observed in 25.0 % of the patients who were not protected by filters, but these injuries were not observed in the 9 patients who were protected by filters. Significant

motor neuropathies requiring prolonged ventilation complicated the post-operative course for 5 of the 31 patients (16.1 %); HSCT was carried out for 3 patients to prevent graft loss due to disease recurrence. The authors stated that prognostic markers are needed to identify patients prone to severe protoporphyric liver disease so that curative HSCT can be offered to select patients instead of LT.

Butler et al (2015) stated that X-linked protoporphyria (XLP) is an erythroid porphyria that leads to variable cutaneous photosensitivity due to accumulation of protoporphyrin. The genetic defect in XLP is mutation of the gene ALAS2, resulting in gain of function for the erythroid enzyme 5-aminolevulinate synthase 2. Previous reports have shown that protoporphyrin-induced liver disease may also occur in XLP, occasionally severe enough to warrant LT; however, transplantation may be followed by injury to the graft due to continued presence of the underlying metabolic disorder in the bone marrow. These investigators presented a case of XLP with severe liver disease successfully treated with hematopoietic progenitor cell transplant (HPCT) to avoid LT. The case also showed the feasibility of reduced intensity transplant to provide engraftment sufficient for correction of porphyria and tolerability of RIC containing total lymphoid irradiation (TLI) in the face of severe liver injury. Allogeneic stem cell transplantation and erythropoietic protoporphyria were key words in this study.

Windon et al (2015) noted that EPP is a rare inherited disorder of the heme biosynthesis pathway resulting in the accumulation of protoporphyrins in the blood, red blood cells (RBCs), and other tissues. Because of a gene mutation in the FECH gene, ferrochelatase, the enzyme involved in the final step of heme synthesis, is deficient in these patients. Although the major symptom of this disorder is photosensitivity, rarely, it can cause progressive liver disease requiring LT. However, LT is not curative and only BMT can correct the underlying enzymatic defect. Because liver disease results from accumulation of protoporphyrin in the liver, LT without HSCT leaves the new liver at risk for similar EPP-related damage. A handful of pediatric patients undergoing sequential LT and HSCT have been described in the literature; however, to-date none has been described in detail in adults. These investigators reported a case of a man with EPP and liver failure who successfully underwent a sequential LT and HSCT.

Ardalan et al (2019) stated that EPP is an inherited metabolic disorder of heme synthesis resulting from over-production of protoporphyrin IX (PPIX), which could result in progressive liver disease characterized by recurrent EPP crises and end-stage liver disease (ESLD). These researchers employed the Australian Transplant Registry to identify 5 patients referred for LT between 2008 and 2017. A total of 4 patients had EPP secondary to ferrochelatase deficiency, and 1 patient had X-linked EPP. No patient had follow-up with a specialist before the diagnosis of progressive liver disease. There were 3 patients who underwent OLT, whereas 2 died while on the transplant waiting list. Parenteral PPIX-lowering therapy was used in 4 patients and was effective in 3 patients, although 2 of these had rebound porphyria and worsening liver function following a decrease in the intensity of therapy. Early disease recurrence in the allograft following LT occurred in 2 patients requiring red cell exchange (RCE) to successfully attain and maintain low PPIX levels; however, RCE was associated with hemosiderosis in 1 patient. Allogeneic stem cell transplantation (AlloSCT) was carried out in 2 patients. One failed engraftment twice, whereas the other subject rejected the 1st graft but achieved full donor chimerism with a 2nd graft and increased immunosuppression. The authors concluded that these findings suggested that progressive liver disease needs parenteral PPIX-lowering treatment with the intensity adjusted to achieve a target Erc-PPIX level. Because EPP liver disease is universally recurrent, AlloSCT should be considered in all patients with adequate immunosuppression to facilitate engraftment; RCE appeared to be effective for recurrent EPP liver disease but is associated with an increased risk of iron overload.

Hashmi et al (2021) noted that EPP is a rare disorder of heme biosynthesis in which patients present with disabling photosensitivity. A subset of patients will develop severe liver disease with progressive liver failure necessitating an OLT. A HSCT can potentially cure EPP by replacing the native bone marrow, which is the primary site of heme synthesis. However, due to concerns for inherent risks of treatment-related toxicities, the use of HSCT has been reserved for patients undergoing an OLT to avoid disease recurrence in the hepatic graft. Data for HSCT in EPP are lacking, especially in the pediatric population. These investigators presented the case of a 12-year-old patient with EPP photosensitivity and cirrhosis, whom the authors successfully treated with pre-emptive allogeneic HSCT, significantly improving the patient's quality

of life (QOL). They employed a matched-unrelated donor bone marrow-derived graft. The patient achieved full donor peripheral blood chimerism and has not had any evidence of GVHD. In addition to resolution of photosensitivity, the subject had reversal of liver fibrosis that these researchers felt was largely due to intervention at an early stage of compensated cirrhosis. The authors concluded that this case highlighted the successful application of a known RIC regimen to this rare disorder that was well-tolerated with sustained donor engraftment. It also emphasized the importance of timing for HSCT in patients with EPP and liver fibrosis. These investigators stated that HSCT should be considered early in pediatric patients with EPP-hepatopathy to prevent progression to liver failure and need for OLT with lifelong immunosuppression.

Wang et al (2021) stated that cutaneous, hematopoietic, and hepatic manifestations of congenital erythropoietic porphyria (CEP) and EPP can be debilitating. These investigators presented their institution's experience with 5 patients with porphyria who underwent HSCT -- 4 patients with CEP, including 3 under the age of 2 years, received myeloablation. One patient with EPP, with prior LT, received (RIC. Four patients were alive without porphyria symptomology and with full donor chimerism. The authors concluded that HSCT corrected the defective heme pathway and should be considered early in patients with severe EPP to minimize end-organ damage; and RIC regimens could minimize toxicity in patients with co-morbidities.

GeneReviews' webpage on "X-Linked Protoporphyria" (Balwani and Desnick, 2019) stated that "Bone marrow transplantation has also been attempted without liver transplantation in some instances. A child aged 2 years with XLP and stage IV hepatic fibrosis was treated with a hematopoietic progenitor cell transplantation that stabilized his liver disease, thus avoiding liver transplantation".

Furthermore, an UpToDate review on "Erythropoietic protoporphyria and X-linked protoporphyria" (Mittal and Anderson, 2023) states that "A combination of treatments is often used for patients with decompensated hepatopathy. Any patient with EPP who develops cirrhosis or severe protoporphyric hepatopathy should be referred for evaluation for possible

liver transplantation. In some individuals with severe hepatopathy, sequential liver transplantation and hematopoietic stem cell transplantation (HSCT) may be appropriate".

Allogeneic Hematopoietic Cell Transplantation for Barakat Syndrome (HDR Syndrome)

Spennato et al (2023) noted that Barakat syndrome is a rare genetic disorder encompassing hypoparathyroidism (H), sensorineural deafness (D) and renal disease (R); thus, it is also known as the HDR syndrome. These investigators presented the case of a 64-year-old woman who was referred to the authors' endocrinology clinic for a switch in treatment (from dihydrotachysterol to calcitriol). The subject exhibited progressive sensorineural deafness since the age of 18 and idiopathic hypoparathyroidism diagnosed at age of 36. Her medical history included osteoporosis with hip/spine fractures, nephrolithiasis and a family history of hearing loss, osteoporosis and kidney disease. The subject's clinical presentation indicated Barakat syndrome. Genetic analysis found a GATA3:c.916C>T nonsense variant. Further tests such as audiometry, labs and renal imaging supported the diagnosis. Due to rarity and manifold symptoms, diagnosis can be challenging. Optional GATA3 testing was suggested in 2018, except in cases of isolated sensorineural deafness or renal disease with pertinent family history. In isolated "H'" cases without "D" and "R", GATA3 studies are not required, as no haplo-insufficiency cases were reported. The authors concluded that given the rise in genetic disorders, physicians should consistently consider rare genetic disorders in patients with suggestive symptoms, even decades after onset. These researchers stated that although diagnosis might not always impact management directly, it would assist patients in accepting their condition and has broader family implications.

An UpToDate review on "Autosomal dominant tubulointerstitial kidney disease" (Bleyer, 2024) states that "Hypoparathyroidism, deafness, and renal dysplasia (HDR) syndrome, also known as Barakat syndrome, is another autosomal dominant condition due to mutations in GATA3. Patients may have cystic kidneys, kidney hypoplasia, and nephrocalcinosis. Approximately 10 % proceed to ESKD". However, this UTD review does not mention allogeneic stem cell transplant as a therapeutic option in this setting.

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