Clinical Policy Bulletin:
Hematopoietic Cell Transplantation for Inherited Metabolic Disorders and Genetic Diseases

Number: 0871

Policy

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

- Alpha-mannosidosis
- Childhood-onset adrenoleukodystrophy
- Fucosidosis
- Globoid cell leukodystrophy (Krabbe disease)
- Metachromatic leukodystrophy
- Mucolipidoses (e.g., adrenoleukodystrophy, Gaucher's disease, metachromatic leukodystrophy)
- Mucopolysaccharidosis (e.g., Hunter's syndrome, Hurler's syndrome, Sanfilippo's syndrome, Maroteaux-Lamy syndrome, Morquio syndrome, Sly syndrome)
- Wolman disease

Aetna considers hematopoietic cell transplantation (autologous, allogeneic or cord blood) 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.

Aetna considers autologous HCT experimental and investigational for the treatment of mucopolysaccharidosis or childhood-onset adrenoleukodystrophy because its effectiveness for these indications has not been established.

See also CPB 0140 Genetic Testing, CPB 0442 - Enzyme-Replacement Therapy for Lysosomal Storage Disorders, and CPB 0626 - Hematopoietic Cell Transplantation for Thalassemia Major and Sickle Cell Anemia.
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 3 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 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 substudy 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 fared 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 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.

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, angiookeratomas, visceromegaly, recurrent respiratory infections, and distinctive or coarse facial features.
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 presymptomatically. 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 mucolipidoses (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 $8.7 \times 10^7$/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).

**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 cord 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 chimism. 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 Mucopolysaccharidosis 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 mis-matched. 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, hepatosplenomegaly 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, may be difficult to manage due to aggressive behavior, hyperactivity, profound dementia, and irregular sleep. 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).

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Mucopolysaccharidosis IV (Morquio syndrome)

MPS IV, also known as Morquio syndrome, has an estimated occurrence of one 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, neurosensitive 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 one 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 hepatosplenomegaly, 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 CICN7, TNFRSF11A, OSTM1, and TCIRG1 genes were detected in 1, 1, 3, and 9 patients, respectively. Six patients remain genetically undefined; OSTM1 and CICN7 mutations were associated with poor neurologic outcome. Among 9 patients with TCIRG1 defects, 6 presented with hypogammaglobulinemia, 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 monosialic 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, osteo-sclerosis, 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 breakpoints 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.


CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

38204
38205
38207 - 38215
38230
38240
38242
38243

**CPT codes not covered for indications listed in the CPB:**

38206
38232
38241

**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-9 codes covered if selection criteria are met:**

- **271.8** Other specified disorders of carbohydrate transport and metabolism [Fucosidosis and Mannosidosis]
- **272.7** Lipidoses [Wolman’s disease]
- **277.5** Mucopolysaccharidosis
- **277.86** Peroxisomal disorders [childhood-onset adrenoleukodystrophy]
- **330.0** Leukodystrophy

**The above policy is based on the following references:**


