



CIGNA MEDICAL COVERAGE POLICY

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Subject Stem-Cell Transplant for Sickle Cell Disease and Thalassemia Major

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Coverage Policy

CIGNA covers myeloablative allogeneic hematopoietic stem cell transplant (HSCT) from a human leukocyte antigen (HLA)- matched donor (at least five of six HLA-match) as medically necessary for the treatment of children and young adults at increased risk of complications of sickle cell disease (SCD) or thalassemia major.

CIGNA does not cover myeloablative allogeneic HSCT for adults with SCD or thalassemia major because it is considered experimental, investigational or unproven.

CIGNA does not cover non-myeloablative allogeneic HSCT for children or adults with SCD or thalassemia major because it is considered experimental, investigational or unproven.

General Background

The hemoglobin molecule is a protein with four subunits (tetramer) made of two pairs of globin chains. Normal adult hemoglobin is made of two alpha chains and two beta chains. Approximately 1200 natural mutations are known; additional novel globin mutations are continually being discovered (Chui, 2005). Most of these mutations are clinically insignificant; however, a small number causes some of the most common hereditary diseases (Chui, 2005).

Hemoglobinopathies are a group of rare, inherited disorders involving abnormal structure of the hemoglobin molecule. Abnormal hemoglobins can result from several circumstances, including structural defects in the hemoglobin molecule, diminished production of the hemoglobin molecule, and the abnormal association of otherwise normal subunits. Some hematologists refer to qualitative structural abnormalities (i.e., sickle hemoglobins) and quantitative production (i.e., thalassemia, hemolytic anemia) abnormalities to be more precise (Quirolo, 2004). Clinically significant variants include hemoglobin S-C disease, sickle cell anemia, various types of thalassemia, hemoglobin C and hemoglobin E. (National Institutes of Health [NIH], 2008; NIH, 2007; Chiu, 2005; Sickle Cell Disease Association of America [SCDAA], 2005).

Sickle Cell Disease

Sickle cell disease (SCD) is the most common inherited blood disorder in the U.S., affecting about 72,000 Americans (NIH, 2007). Individuals with African descent exhibit the highest frequency of hemoglobin S (Hb S); however, individuals with Mediterranean, Caribbean, South and Central American Arab and East Indian ancestry also have increased incidence of the Hb variant. (Santharajah, 2005). In the U.S., the expected incidence of sickle cell anemia is one in 500 African Americans (NIH, 2007).

This disorder encompasses many sickling syndromes caused by abnormal sickle hemoglobin (Quinn, 2005); the most common are sickle cell anemia (Hb SS), sickle-hemoglobin C disease (Hb SC), sickle-beta plus thalassemia, and sickle-beta zero thalassemia (NIH, 2007). Autosomal recessivity is required for the disease to be expressed. Persons having one copy of the sickle hemoglobin gene and one normal hemoglobin gene are considered carriers of the disease but do not exhibit symptoms. These persons have what is known as sickle cell trait (Wang, 2004). Sickle cell trait affects about two million Americans (NIH, 2007).

Normal red blood cells (RBCs) are smooth, round and bi-concave in shape. In the case of individuals who have the Hb S mutation, RBCs may cluster together and sickle, or become crescent in shape when exposed to certain conditions, such as low levels of oxygen or high concentrations of hemoglobin. This frequently results in the inability of the cells to move easily through small blood vessels, and occlusion occurs. Additionally, because of an increased susceptibility to hemolysis, these abnormal cells have a decreased life cycle of 10 to 20 days compared to the 120-day cycle of a normal RBC.

Although disease attributed to Hb S has been observed in early infancy, affected individuals characteristically are without symptoms until the second half of the first year of life (Wang, 2004). This can be explained by the production of fetal hemoglobin (Hb F) which limits sickling of the RBCs. As the child ages, the amount of Hb F is reduced, erythrocytes contain increasing amounts of Hb S, and the sickling phenomenon increases (Wang, 2004).

SCD is widely variable in its clinical expression, even among affected members of the same family. While many individuals will have recurrent, severe complications, others may experience a relatively symptom-free course (Wang, 2004). Persons with more symptomatic disease, such as those who exhibit fetal hemoglobin below the 75th percentile, hemoglobin levels below the tenth percentile, elevated white blood cell counts, renal insufficiency, acute chest syndrome, and seizures are at greater risk of death. Early mortality is highest among individuals whose disease is symptomatic (Wang, 2004). Mortality in children is primarily due to bacterial infection and stroke; in adults, causes of mortality are more varied. In an analysis by Quinn (2004) of 711 children with SCD who were followed from birth to age 18, cumulative overall survival was estimated to be 86%.

The prognosis for persons with sickle cell disease has dramatically improved as a result of early diagnosis, patient education and medical intervention. In recent years, newborn screening, better medical care, parent education and penicillin prophylaxis have successfully reduced morbidity and mortality. Currently, the average lifetime of an individual with SCD is estimated to be between 40–50 years (Locatelli, 2004).

Complications / Standard Treatment Options

Common complications of SCD include chronic anemia, acute chest syndrome (ACS), stroke, splenic sequestration, episodes of severe musculoskeletal pain, known as painful crises, and increased susceptibility to infection. Treatment is specific to the complication and may include intermittent or chronic red cell transfusion programs, hydroxyurea, pharmacologic therapy for pain control, corticosteroids, and supportive care. Previously, infection was the most frequent cause of death in children with sickle cell disease during the first three years of life; however, penicillin prophylaxis and pneumococcal vaccines have helped decrease mortality in this age group.

Thalassemia

Thalassemia is among the most common genetic disorders worldwide; 4.83% of the world's population carries globin variants (Rund, 2005). According to Yesilipek (2007), there are over 200,000 beta thalassemia patients in the Mediterranean area alone. Thalassemia is a hereditary anemia resulting from defects in hemoglobin production (Rund, 2005). These defects result in low levels of hemoglobin being produced and the excessive destruction of red blood cells. There are two types of thalassemia, alpha and beta, depending on which one of the two hemoglobin chains is affected. Alpha and beta have both mild (minor) and severe (major) forms; the severity of the disease depends on the number and combination of genes affected.

Thalassemia minor is a milder form of hemolytic anemia. Red blood cells are small (microcytic), pale (hypochromic) and vary in shape (poikilocytosis). Due to the decreased size and irregular shape, they are less able to carry oxygen. This form of thalassemia does not usually result in a decreased lifespan. Hematopoietic stem-cell transplantation (HSCT) it is not considered an appropriate therapy for thalassemia minor.

Thalassemia major has a much greater clinical impact. Persons with thalassemia major may present with fatigue, shortness of breath, jaundice and bone deformities of the face. Oxygen depletion becomes apparent within the first six months of life. Additionally, individuals generally have an enlarged spleen and microcytic, hypochromic poikilocytosis, which is seen on blood smear. Growth failure, bone deformities, hepatomegaly, splenomegaly and an increased susceptibility to infection are some of the complications that may occur. If left untreated, death occurs within a few years. Due to complications of iron overload caused by frequent blood transfusions, death from heart failure may occur during the third or fourth decades of life.

Alpha Thalassemia: This disorder is caused by a deletion or variance of one or more of the four genes from the alpha globin chain. If one gene is affected, individuals are called silent carriers and they have no signs of the disease. If two genes are affected, individuals have mild anemia. They are considered carriers, and their disorder is referred to as alpha thalassemia trait or alpha thalassemia minor. Individuals with three genes affected have moderate to severe anemia and have Hemoglobin H disease. Moderate to severe anemia can result when two or more of the genes are missing. Hydrops fetalis, or alpha thalassemia major, is a result of the deletion of four genes. This affects babies who usually die before or shortly after birth. Persons from Southeast Asia, India, China and the Phillipines have an increased incidence of alpha thalassemia (National Heart Lung and Blood Institute [NHLBI], 2008).

Beta Thalassemia: Beta thalassemia is caused by any of more than 200 mutations in one or more of the two genes in the beta globin chain (Rund, 2005). Persons of Mediterranean ancestry and, to a lesser extent, those of Chinese, other Asians and African descent have an increased risk for this disease (NHLBI, 2008). Beta thalassemia is considered an autosomal recessive disorder, which means that an individual must inherit a variant gene from both parents to have the major form of the disease. The severity of the disease depends on the number of genes affected and the abnormality.

If only one gene is inherited, the individual will have the minor form of the disease and is considered a carrier. Although small blood cells are present on exam, there are no symptoms. This form of the disease is known as beta thalassemia trait or beta thalassemia minor. If both genes are affected, the anemia can range from moderate to severe. Moderate beta thalassemia is also known as beta thalassemia intermedia, thalassemia intermedia or mild Cooley's anemia. The severe form of this disease is known as Cooley's anemia, which is the most common severe form of thalassemia in the U.S. It is also known as beta thalassemia major, thalassemia major or Mediterranean anemia (NHLBI, 2008).

Standard Treatment Options

Persons who have thalassemia trait usually have no symptoms and require no treatment. Moderate anemia, or thalassemia intermedia requires occasional blood transfusions, especially when the body is under physical stress such as with the presence of infection. If the need for transfusions increases, the individual is usually considered to have thalassemia major or Cooley's anemia.

Thalassemia major requires frequent, lifelong blood cell transfusions and folate supplements; however, the effects of iron overload may damage the heart, liver and endocrine systems. Viral infections are common post-transfusion. Ongoing chelation therapy is commonly used to remove the excessive iron buildup. Without treatment, children with the severe form of the disease usually do not live beyond early childhood; individuals

with successfully treated thalassemia may live until their forties or beyond (NHLBI, 2008). Successful allogeneic HSCT is considered as curative for children and young adults with this disorder.

Other Hemoglobinopathies

In 1989, several hundred unusual hemoglobins were identified. In addition to hemoglobin S (sickle) and hemoglobin beta Thal (thalassemia), hemoglobins C and E are most commonly seen in the population (Genetics Home Reference [GHR], 2007; SCDA, 2005). Inherited in a homozygous manner where two copies of the same variant are inherited (e.g., Hb CC), there are few physical symptoms, and a normal lifespan is expected. Because of the morbidity and mortality associated with HSCT, it is not considered an appropriate therapy for these homozygous disorders. Clinical significance occurs when the individual inherits two different beta gene variants (i.e., doubly or compound heterozygous) and has no normal hemoglobin. The resulting gene combinations can produce mild or severe clinical symptoms.

Hemoglobin C disease, also known as clinical hemoglobin C or Hb CC, is a rare inherited disease caused by a mutation in the beta globin gene. It is most commonly seen in individuals of West African descent. This disease leads to a type of anemia due to a premature breakdown of red blood cells (NIH, 2007). Most individuals do not develop symptoms, although mild hemolytic anemia, an enlarged spleen, jaundice, gallstones, hip or vision problems may be present. Treatment is not usually given; however, folic acid supplementation may improve the production of normal red blood cells (NIH, 2007). People with this disorder may expect to lead a normal life (NIH, 2007).

Hemoglobin E disease, also known as Hb EE, is another mutation of the gene which creates the beta chain. It is more commonly found in individuals of Southeast Asian ancestry (GHR, 2007). Red blood cells are small; there is a mild hemolytic anemia and mild enlargement of the spleen. There are usually no related health problems.

Stem-Cell Transplantation

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into an individual. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSC transplantation (HSCT) can be either autologous (using the individual's own stem cells) or allogeneic (using stem cells from a donor). HSCT is provided to persons with hematological disorders to rescue them from treatment-induced aplasia, after high-dose chemotherapy and/or radiotherapy has been administered to eliminate the defective hematologic system.

Many factors affect the outcome of a tissue transplant. The selection process is designed to obtain the best result for each individual. There are several relative contraindications. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction < 45%)
- poor liver function (bilirubin > 2.0mg/dl and transaminases greater than two times normal)
- poor renal function (creatinine clearance < 50ml/min)
- poor pulmonary function [diffusion capacity (DLCO) < 60% of predicted]
- presence of human immunodeficiency virus OR an active form of any ONE of the following:
 - hepatitis B virus (HBV)
 - hepatitis C virus (HCV)
 - human T-cell lymphotropic virus (HTLV)-1
- Karnofsky rating < 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status > 2**

**EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE AND CORRESPONDING KARNOFSKY RATING

ECOG-PS GRADE	DESCRIPTION	KARNOFSKY RATING
0	Fully active, able to carry on all predisease activities without restriction	100
1	Restricted in physically strenuous activity, but ambulatory	80–90

****EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE AND CORRESPONDING KARNOFSKY RATING**

ECOG-PS GRADE	DESCRIPTION	KARNOFSKY RATING
	and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60–70
3	Capable of only limited self-care; confined to bed or chair 50% or more of waking hours	40–50
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	30 or less

(Niederhuber, 2000)

Allogeneic Transplant: Allogeneic HSCT involves using HSCs from a donor. In order for such a transplant to be successful, the donated cells must be similar, or a match, to the recipient's. Human leukocyte antigen (HLA) typing can identify donors who may be a perfect match. HLAs are proteins on the surface of cells. These proteins help the immune system identify a cell as either belonging to the body or from outside the body. There are three types each of class I and class II HLA. Increased survival is associated with a match between recipient and donor HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 (Morishima, et al., 2002).

For any given individual, there is a 25% chance that a sibling is an HLA-identical match. A sibling who has a class I and class II HLA match is called a related donor. An identical twin is termed a syngeneic match. For an individual who does not have a matched, related donor, a search for someone with matching HLA types is initiated through donor banks. In most cases, a matched, unrelated donor (MUD) can be found by searching the National Marrow Donor Program (NMDP). Historically, the outcome after HSCT from unrelated donors has been poorer than that using matched-sibling-donors primarily because of increased rates of graft rejection and graft-versus-host disease (GVHD). Depletion of T cells from the transplant is associated with a significantly lower incidence of both acute and chronic GVHD (Bhushan and Collins, 2003).

Myeloablative conditioning regimens prepare the recipient for HSCT by eliminating any remaining recipient stem cells, suppressing the host immunity, and creating space to facilitate engraftment of donor stem cells.

Non-Myeloablative Conditioning: Non-myeloablative preparative regimens (also called mini-transplants) are designed to reduce regimen-related toxicities and allow allogeneic HSCT in persons who are older, have comorbid conditions or have toxicities from previous treatment. Non-myeloablative conditioning regimens fall into two categories: reduced intensity and minimally myelosuppressive. Conditioning regimens vary by study protocol and may include a purine analog, an alkylating agent, or low-dose total-body irradiation. The purine analogs (including fludarabine, cladribine, and pentostatin) are broadly cytotoxic, as well as immunosuppressive.

The reduced-intensity, non-myeloablative preparative regimen relies on cytotoxic conditioning to maintain an anti-tumor effect and eliminate GVHD. The recipient becomes aplastic before engrafting donor cells. This regimen retains the toxic side effects of high-dose treatments, although to a lesser degree. This strategy is more likely to be tried in rapidly progressive diseases, in which a certain amount of cytoreduction is necessary to minimize residual disease, and the graft-versus-leukemia effect is less potent.

The minimally-myelosuppressive regimen uses immunosuppression before and after transplant to reduce GVHD and allow donor engraftment. Recipient cells may not be completely eliminated by the conditioning regimen; therefore, a state of mixed chimerism (defined as the concurrent presence of donor and recipient hematopoietic cells) may be created. Eventually, the immune response of the donor cells may eradicate any remaining recipient cells.

Source of Cells

HSCs are available in the peripheral blood, bone marrow, and umbilical cord.

Peripheral-Blood Stem-Cell (PBSC) Transplant: Stem cells are present in the peripheral blood but in such small numbers that ordinary blood tests cannot identify them. However, a medication (i.e., filgrastim) can be given to the donor to induce stem cells to leave the marrow and enter the blood, where they can be collected (harvested). Several studies have demonstrated faster neutrophil and platelet engraftment, reduced early toxicity, and superior immune reconstitution after allogeneic PBSC transplantation as compared to bone-marrow transplantation (Bensinger, et al., 2001; Madero, et al., 2001; Ringden, et al., 1999; Hagglund, et al., 1998; Mifflin, et al., 1997). Because of the relative ease of the donation process and the success of PBSC transplant, most HSCTs use PBSCs as the cell source.

Bone-Marrow Transplant (BMT): Bone marrow is used for HSCT because it contains a relatively large number of HSCs. Bone marrow is removed from the top of the donor's hip bone. The bone marrow is then filtered, treated, and either transplanted immediately or frozen and stored for later use. When the recipient is ready for the transplant, the transplant material is transfused into the individual through a vein (IV line) and is naturally transported back into the bone cavities, where it grows to replace the old bone marrow. Because of the relative difficulty of the donation process and the increased risk to the donor from anesthesia, BMT is performed less commonly than PBSC transplantation.

Umbilical-Cord Blood Transplant (UCBT): Blood in the umbilical cord contains a high proportion of stem cells. The umbilical cord itself, however, yields only a small volume of blood. Therefore, a donation of stem cells from one umbilical cord yields fewer stem cells than a donation from bone marrow or from peripheral blood. This lower stem-cell yield limits the usefulness of UCBT in adults. The single most important factor influencing time to hematopoietic recovery in adults appears to be the nucleated-cell content of the graft relative to the recipient size (Grewal, et al., 2003; Rubinstein, et al., 1998). Studies are being conducted to evaluate the feasibility of ex vivo expansion of umbilical cord blood (UCB) stem cells for use in adults or larger children.

Potential advantages of UCBT over marrow or blood stem-cell transplants include (Hayes, 2005; The Leukemia & Lymphoma Society, 2005; Barker, et al., 2001; Laughlin, et al., 2001; Gluckman, et al., 1997):

- large potential donor pool
- rapid availability, since the cord blood has been prescreened, tested and frozen and is ready to use
- no donor attrition, since the UCB stem cells are already stored
- no risk or discomfort for the donor
- low incidence of contamination by viruses
- lower risk of GVHD, even for recipients with a less-than-perfect tissue match

Disadvantages of UCBT include:

- potential for diseases that have not developed in the donor to be transmitted to the recipient
- unclear long-term success
- slower engraftment rate, potentially leaving the recipient at risk for life-threatening infections

Allogeneic Stem-Cell Transplantation for Sickle Cell Disease

Myeloablative allogeneic HSCT is the only curative therapy for SCD (Steinberg, 1999; Quinn, 2004; Walters, 2004; Iannone, 2005). HSCT is a suitable treatment option that can be applied with a curative intent when an HLA-matched sibling donor is available (Panepinto, 2007). Research to date has demonstrated that successful engraftment of normal donor hematopoietic stem cells prevents additional pathological effects of SCD (Iannone, 2005). Additionally, full donor chimerism is not necessary to achieve this effect. The optimal timing of marrow transplantation in the course of sickle cell disease remains uncertain, in part, because of the unpredictable nature of the disease (Walters, 2004). For individuals with sickle cell anemia, the decision to undergo HSCT, complicated by the unpredictability of outcomes, must be weighed against the risks of morbidity and mortality of this intervention (Hoppe, 2004). Selection of optimal candidates is made difficult by the clinical heterogeneity of SCD (Hoppe, 2004). Published data argue for early referral and HSCT in persons with sickle cell disease who have an HLA-matched sibling donor so that HSCT may be performed in younger individuals with minimal exposure to red blood cell transfusions (Panepinto, 2007).

Children and young adults who have severe complications (e.g. stroke, recurrent ACS, refractory pain) and have an HLA-matched donor are the best candidates for transplantation. It is increasingly being used in children with early signs of SCD morbidity (Walters, 2005). It is estimated that about 38% of persons with SCD may meet these requirements (Hoppe, 2004).

Very few adults are considered for transplantation (Walters, 2005), and there are scarce published data. For this population, the role of myeloablative allogeneic HSCT has not been established.

The finding that mixed chimerism can cure SCD has prompted recent studies using reduced toxicity conditioning regimens that do not ablate host hematopoiesis (Iannone, 2004). In these studies, pre-transplant conditioning relies on immunosuppression to facilitate engraftment of donor cells (Horan, 2004). Study populations include very small numbers of older individuals (both adults and children) who have evidence of organ damage from vaso-occlusion or iron-overload as a result of chronic transfusion therapy. Mortality related to GVHD and graft rejection continues to be a complication related to this therapy. Although investigations are continuing, it has been difficult to identify a regimen that is sufficiently immunosuppressive to ensure stable engraftment of donor cells, yet also meets the objective of reduced toxicity with a risk that is distinguishable from conventional allografting (Walters, 2005). Published reports of nonmyeloablative SCT for SCD have confirmed improved safety, but the majority of such transplants were unsuccessful because of graft failure (Horwitz, 2007). Novel strategies for promoting host-donor tolerance are currently under development (Iannone, 2004). At this time, non-myeloablative conditioning remains investigational for both children and adults.

Stem-Cell Transplantation for Thalassemia Major

Allogeneic HSCT is considered a potentially curative therapy for selected individuals with thalassemia major who have an appropriate donor (National Human Genome Research Institute [NHGRI], 2007; NIH, 2006; Hongeng, 2006; Jaing, 2005). Despite this, HSCT is associated with a non-negligible risk of both transplant-related mortality and morbidity. This risk must be taken into account, considering the relevant improvements achieved with conventional therapy (Locatelli, 2005).

The outcome of allogeneic HSCT using an HLA-identical family donor is largely dependent on the age of the recipient as well as on pretransplant parameters reflecting the degree of organ damage from iron overload (Resnick, 2007). As proposed by Lucarelli (Yesilipek, 2007) three risk factors such as the presence of hepatomegaly greater than two cm, liver fibrosis and irregular chelation therapy in the pretransplant correlates with outcomes post-transplantation. Individuals categorized as Class I have no risk factors, Class II have one or two risk factors and Class III, who have the poorest outcomes post-transplantation, have three risk factors.

Adults generally have a worse outcome than children, especially in the presence of chronic viral hepatitis (Locatelli, 2005). In children who do not have liver disease and have received regular chelation therapy, the probability of survival with transfusion independence is over 90% (La Nasa, 2005; Locatelli, 2005). For individuals with good-risk disease with an HLA-compatible sibling donor, the probability of disease-free survival is 85–90% (La Nasa, 2005; Locatelli, 2005). Worse results have been obtained in high-risk individuals where the probability of disease-free survival with transfusion independence after the allograft is approximately 58% (La Nasa, 2005). However, Sevilla (2005) reports that hypertransfusion and intensive iron chelation prior to transplantation has increased the probability of overall survival (OS) to 93%, and thalassemia-free survival can be improved to 85% in the high-risk group. Data strongly suggest that the optimal timing of HSCT of an individual with an HLA-identical sibling donor is at a very early age (Yesilipek, 2007).

Because of the difficulty of eradicating the endogenous thalassemic bone marrow, it has been considered essential to administer full myeloablative conditioning regimens for transplantation (Rund, 2005). Non-myeloablative regimens have been used less frequently. Follow-up is short, and it is unclear whether this therapy will be beneficial; however, mixed chimerism can sometimes result in an acceptable clinical outcome as long as anemia is corrected (Rund, 2005)

Although good outcomes have been reported by some, the use of HLA-mismatched-related or HLA-matched-unrelated donors is associated with a greater risk of graft rejection and GVHD, and is generally not recommended. Recently the use of umbilical cord blood (CBT) has been reported to result in lower rates of GVHD; however, graft failure and recurrence of disease are seen as major problems with the use of CBT in hemoglobinopathies (Yesilipek, 2007). The use of high-resolution molecular immunotyping techniques has improved the post-transplantation outcomes of recipients using alternatives to these donor sources. Several

multicenter trials are ongoing to address the ideal conditions necessary to reduce graft rejection and improve disease-free survival.

Literature Review

Sickle Cell Disease

Myeloablative Conditioning with Allogeneic HSCT

On behalf of the Center for International Blood and Transplant Research, Panepinto et al. (2007) reported outcomes after myeloablative allogeneic HSCT using HLA-matched sibling donors in 67 patients with SCD who were transplanted between 1989 and 2002 in 30 transplant centers worldwide. The most common indications for transplant were stroke and vaso-occlusive crisis. Median patient age was 10 years. Twenty-seven percent of patients had a poor performance score (i.e. $\leq 90\%$) at transplantation. Most patients had received >10 red blood cell transfusions prior to transplantation. Five-year probabilities of acute and chronic GVHD were 10% and 22%, respectively. Median follow-up among surviving patients was 61 months. Five-year probabilities of disease-free survival (DFS) and overall survival (OS) were 85% and 95%, respectively. The authors note that this report confirms and extends earlier reports that HCT from HLA-matched related donors offers a very high survival rate, with few transplant-related complications and the elimination of sickle-related complications in the majority of patients who undergo this therapy.

Bernauldin et al. (2007) reported the results of 87 consecutive patients with severe SCD who received myeloablative allogeneic HSCT between 1988 and 2004. Mean patient age was 9.5 years. Cerebral vasculopathy was the most common indication for transplantation (n=55); after transplantation the median risk of recurrence was 5.6%. Graft source was a matched sibling donor for all patients. The graft rejection rate was 22% before the addition of antithymocyte globulin (ATG) in 1992 and 2.9% thereafter. With a median follow-up of six years the overall and event-free survival rates were 93% and 86.1%, respectively. EFS rate for patients receiving transplantation after 2000 was 95.3%. GVHD was the main cause of treatment-related mortality (TRM). The authors note that these results indicate that HLA-identical allogeneic HSCT should be considered standard of care for children with SCD who are at high-risk of stroke. The authors also noted that the conditioning regimen was well tolerated. Considering the very high risk of rejection after nonmyeloablative procedures, the authors note that only myeloablative transplantations should be used in children without organ failure. There was a significant relation between GVHD and older age, suggesting that HSCT should be performed before the age of 15 years.

Adamkiewicz et al. (2004) evaluated the use of unrelated placental blood cells (URPBCs) and myeloablative conditioning in three children with SCD who had cerebral vascular accidents (CVAs) and did not have HLA-matched sibling donors. All patients experienced graft-versus-host disease, either acute or chronic. One patient did not engraft and had spontaneous autologous recovery. Two patients had complete donor chimerism and were without detectable hemoglobin S or symptoms of SCD at 40 and 61 months, respectively, after transplantation. The authors noted that allogeneic HSCT with URPBCs is feasible in patients with SCD, but that this therapy should be restricted to children with high-risk manifestations of the disease.

Locatelli et al. (2003) analyzed the results of 44 pediatric s who received an allogeneic HSCT for thalassemia (n=33) or SCD (n=11) using umbilical cord blood. Prior to transplant, SCD patients had experienced cerebral vasculopathy, recurrent bone pain, acute chest syndrome, and splenic sequestration. Median age was five years. There were no deaths; therefore, overall survival probability was 100%. Probability of two-year event-free survival for SCD was 90%. At a median follow-up of 24 months, 36 of 44 patients remain free of disease. Two-year probability of event-free survival is 90% for patients with SCD.

Walters et al. (2000) reported the results of 50 children with symptomatic SCD who received a matched sibling allograft between 1991 and 1999. Median age was 9.9 years. Prior to transplantation, patients not receiving chronic transfusion therapy underwent a partial exchange transfusion to achieve a fraction of Hb S=30%. The six-year probabilities of survival and disease-free survival are 94% and 84%, respectively. The cumulative incidence of graft rejection or disease recurrence was 10%. Among the 47 surviving patients, five have recurrent sickle cell disease, four have stable mixed chimerism and 38 have full donor chimerism. Twenty-two of these patients had complete resolution of sickle cell complications. The authors note that results encourage continued study to determine the appropriate role and eligibility for transplantation amid other available medical therapies.

Walters et al. (1996) investigated the risks and benefits of allogeneic HSCT in 22 children with complications of SCD. Children were under 16 years of age. The indications for transplant included a history of stroke, recurrent

ACS and recurrent, painful crises. Allografts were from HLA-identical siblings. Four-year estimates of overall and event-free survival were 91% and 73%, respectively. Sixteen patients had stable engraftment with donor hematopoietic cells. The authors noted that myeloablative allogeneic HSCT can be curative in young patients with symptomatic disease.

Van Besien et al. (2000) discussed the results of two adult patients who received myeloablative conditioning with allogeneic HSCT for end-stage SCD. Donors were sibling HLA-identical. Donor engraftment was 100%; however, both patients died of GVHD-related complications; one patient died at day +142 after transplantation and the other patient died at day +355 after transplantation.

Nonmyeloablative Conditioning with Allogeneic HSCT

Horwitz et al. (2007) reported the outcomes of two adult patients with SCD who underwent total-body irradiation (TBI) followed by fludarabine-based nonmyeloablative conditioning and allogeneic HSCT from HLA-identical matched sibling donors. One patient had end-stage renal disease (ESRD) and underwent daily dialysis and a 20% reduction in fludarabine dose prior to transplantation. Both patients achieved complete donor chimerism, have normal blood counts and are on no immunosuppressive drugs. Although neither patient developed acute GVHD or chronic GVHD at a median follow-up of 20 months, the patient with ESRD developed symptomatic heart failure with moderate left heart dilatation, epicardial effusion, and decreased ejection fraction. The authors noted that fludarabine-based nonmyeloablative allogeneic HSCT is feasible, even in the setting of ESRD.

Horan et al. (2005) reported the results of four consecutive patients who received allogeneic hematopoietic stem-cell transplantation with non-myeloablative conditioning between 2001 and 2002 to induce full or partial stable engraftment. Patient age range was nine to 30 years. To be eligible, patients must have experienced significant sickle-cell related complications (e.g., clinical stroke, recurrent acute chest syndrome, sickle cell nephropathy), have thalassemia major or another red blood cell disorder dependent upon red blood cell (RBC) transfusions or a platelet-transfusion-dependent disorder. Three patients had SCD (two patients had Hb SS; one patient had Hb C), and one patient had thalassemia major. Donors were HLA-identical siblings in all cases. At three months post-transplantation, all patients had evidence of donor myeloid chimerism (range 15–100%); however, after post-transplantation, immunosuppression was discontinued; graft rejection occurred in three recipients. At 27 months' follow-up, one patient was doing well, with full donor chimerism. One patient received a second HSCT for graft failure and died at 52 days post-HSCT due to pneumonia and intractable heart failure. The other patients remained alive but without significant donor chimerism. The authors noted that stable donor engraftment after non-myeloablative HSCT is difficult to achieve in immunocompetent patients with hemoglobinopathies. They also noted that new approaches will need to be developed before wider application of this transplantation method for this subset of patients.

Iannone et al. (2003) analyzed the outcomes of six patients with SCD and one patient with thalassemia major who received non-myeloablative conditioning with allogeneic HSCT to induce partial or full stable donor engraftment. Transplantation occurred between 1999 and 2001 at four medical centers. Median age was nine years. Prior complications before transplantation in patients with SCD included cerebral infarct (n=3), frequent painful crises (n=2) and acute chest syndrome (n=1). Four patients received regular red blood cell transfusions. All donors were HLA-identical siblings; of these, four had sickle cell trait. Two months after transplantation, six of seven patients had evidence of donor chimerism; one patient did not engraft. There were no complications attributable to SCD during the period of transient donor chimerism. After post-transplantation, immunosuppression was tapered; however, there was a nonfatal loss of donor graft. All patients experienced autologous hematopoietic recovery, and there was disease recurrence. The authors noted even partial donor engraftment was sufficient in most patients to suppress clinical expression of the underlying hemoglobinopathy. They also noted that stable donor chimerism is more difficult to achieve in immunocompetent pediatric patients with hemoglobinopathies compared to adults with hematologic malignancies, perhaps because of previous transfusions.

Thalassemia Major

Myeloablative Conditioning with Allogeneic HSCT

To explore the use of alternative donors, Hongeng et al. (2006) retrospectively reviewed the outcomes of 49 consecutive children who received allogeneic HSCT for severe thalassemia using related (n=28) and unrelated (n=21) marrow donors between 1992 and 2005. The median age of patients receiving a related marrow graft were 7.2 years and four years for patients receiving an unrelated marrow graft. More females were included in the related donor group, according to the authors. Forty-five patients received myeloablative conditioning, while

four received nonmyeloablative conditioning prior to transplant. Mean time to myeloid engraftment was identical in both groups (16 days). Frequencies of GVHD were similar as were frequencies of other post-transplantation complications. Karnofsky or Lansky performances in patients who survived > one year were similar; related donor mean score was 98/100, and unrelated donor mean score was 95/100. The two-year thalassemia-free survival was 77% (95% confidence interval, 61–86). Overall survival (OS) was 89% (95% confidence interval, 72–94) for all recipients. Estimated two-year OS in the related donor recipient group was 92% (95% confidence interval, 70–97) compared to 82% in the unrelated donor group (95% confidence interval, 53–94). The rejection rate after transplantation was 14% in both the related and unrelated donor groups. The authors noted that this study demonstrates comparable outcomes using related and unrelated donors for the HSCT of children with severe thalassemia. They note that this may be because of the younger age of the unrelated cohort. They also noted that this study provides additional evidence to support the view that it is reasonable to consider use of unrelated donor allografts as an acceptable therapeutic option, at least for younger patients who are not fully compliant with conventional therapy and do not yet exhibit irreversible severe complications of iron overload.

Jaing et al. (2005) reported the results of five patients with beta thalassemia major who underwent allogeneic HSCT between 2003 and 2004. The median age at transplantation was 3.7 years. The cell source was unrelated banked umbilical cord blood with varying loci of HLA-mismatching. All patients with myeloid engraftment displayed complete donor chimerism by day +17, and had sustained engraftment. All patients developed GVHD. The authors noted that the results of their study suggest that ideal candidates for the use of UCB are young patients without underlying complications of their disease or transfusional iron overload.

La Nasa et al. (2005) evaluated whether bone marrow transplantation using an unrelated donor in high-risk adult thalassemia patients can offer a probability of cure comparable to the outcomes from the use of an HLA-compatible sibling donor. From 1992 to 2003, 27 high-risk adult patients underwent bone marrow transplantation using an unrelated donor. The median age was 22 years. Risk factors included the presence of hepatomegaly, liver biopsy revealing portal fibrosis and irregular pretransplantation iron chelating therapy. Nineteen patients (70%) had complete, donor-derived hematological and immunological reconstitution. Median follow-up of surviving patients was 43 months. OS and event-free survival (EFS) was 70.4%; cumulative incidence of TRM was 30%. The incidence of grade II–IV acute and chronic GVHD was 37 and 27%, respectively. The authors noted that unrelated donor bone marrow transplantation in high-risk adult patients with donors selected through high-resolution molecular typing offers an outcome comparable to that historically reported in patients with similar prognostic characteristics, using an HLA-identical sibling donor.

Non-myeloablative Conditioning with Allogeneic HSCT

Few peer-reviewed studies addressing the outcomes of the use of non-myeloablative conditioning and allogeneic HSCT were found. The majority of studies were limited by small populations and study design.

Sixty-nine patients with thalassemia major underwent allogeneic HSCT at a single transplant facility between 1982 and 2005. Resnick et al. (2007) reported the results of a cohort of 20 patients who underwent reduced toxicity fludarabine-based conditioning followed by allogeneic HSCT using matched-related and unrelated donors between 1996 and 2005. Median patient age was 5.6 years. All patients had previously received blood cell transfusions. The incidence of acute and chronic GVHD was 25% and 25%, respectively. With a median follow-up of 39 months, 16 of 20 patients have sustained engraftment and are transfusion independent. The OS and thalassemia-free survival were 100% and 80%, respectively, at a median follow-up of 39 months. The authors note that although the results of this study look promising, larger cohorts of patients and prospective clinical trials are required to confirm the benefits of this approach as a possible better alternative to the existing protocols.

In one study, Hongeng et al. (2004) reported on an 18 year-old female patient with beta-thalassemia who received non-myeloablative conditioning with an allogeneic HSCT with stem cells from her mother. With regard to HLA typing, her mother was a haploidentical match to the patient. The patient developed acute grade II GVHD and chronic GVHD involving the skin. She experienced multiple post-transplant complications which resolved with treatment. The patient achieved full chimerism at one month and maintained it at a follow-up of 18 months. The patient has good quality of life and no features of thalassemia. The authors state that the use of non-myeloablative conditioning permits engraftment of donor stem cells by creating marrow space, not by myeloablative chemotherapy or radiation therapy. They also note that this therapy with haploidentical stem cells was well tolerated, allowed stable engraftment and can ameliorate symptoms of thalassemia.

Hongeng et al. (2002) also reported the outcomes of a 10 year-old female with beta-thalassemia who received non-myeloablative conditioning and allogeneic HSCT. The patient achieved 100% chimerism by day +23. The patient did not experience GVHD. The authors report that one year after transplantation, the patient had no clinical features of thalassemia or chronic GVHD. The patient continued to maintain 100% donor chimerism.

Professional Societies/Organizations

The National Marrow Donor Program (2008) lists hemoglobinopathies, including SCD and thalassemia major, as diseases which are treatable by allogeneic HSCT. The National Heart, Lung and Blood Institute (NHLBI, 2007) notes that bone marrow transplant can be a very effective treatment for sickle cell anemia, but because of its risks, only some individuals can or should have this procedure. It is usually used only for younger individuals with severe sickle cell anemia, but the decision is made on a case-by-case basis. In 2002, they recommended that HSCT for SCD should be considered for children who experience significant, noninfectious complications caused by vaso-occlusion. If full siblings are available, HLA typing should be performed. Families should be counseled about the collection of umbilical cord blood from prospective siblings. For severely affected children who have HLA-identical sibling donors, families should be informed about the benefits, risks and treatment alternatives, such as HSCT.

The NHLBI (2008) notes that a stem cell transplant is the only treatment that can cure thalassemia; it is most successful in children. Although numerous guidelines were found regarding newborn screening for sickle cell disease and for management of the complications of SCD, no guidelines regarding stem cell transplantation were found.

Summary

Allogeneic hematopoietic stem-cell transplant (HSCT) is potentially curative for sickle cell disease (SCD) and thalassemia major. The peer-reviewed, published medical literature supports this therapy in the treatment of children and young adults with SCD and thalassemia major who have a human leukocyte antigen (HLA)-matched donor. Outcomes are better for young children who have not developed the cardiac, liver and endocrine toxicities associated with iron overload from chronic blood transfusions. The use of HLA-matched sibling donors for transplantation results in improved overall- and disease-free survival; however, more sophisticated immunotyping techniques allow the increasing use of matched-unrelated and umbilical cord blood donors, with acceptable results.

There is scarce data regarding the use of myeloablative allogeneic HSCT in adults for the treatment of SCD and thalassemia major and the role of this therapy has not been established for that population.

Use of non-myeloablative conditioning and allogeneic HSCT for the treatment of SCD and thalassemia major is a subject of clinical study; however, study populations remain small and outcomes are poor. The role of non-myeloablative allogeneic HSCT for these indications has not been established at this time.

In combination with other red blood cell mutations, hemoglobinopathies such as hemoglobin C and hemoglobin E diseases may result in more serious disorders, such as sickling syndromes and thalassemias. Individually these mutations do not usually result in life-threatening disorders. Treatment is symptomatic and supportive.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT [®] * Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously

	frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
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

† Note: Covered when medically necessary when used to report allogeneic bone marrow or blood-derived stem cell procedures.

ICD-9-CM Diagnosis Codes	Description
282.41	Sickle-cell thalassemia without crisis
282.42	Sickle-cell thalassemia with crisis
282.49	Other thalassemia
282.5	Sickle-cell trait
282.60	Sickle-cell disease, unspecified
282.61	Hb-SS disease without crisis
282.62	Hb-SS disease with crisis
282.63	Sickle-cell/Hb-C without crisis
282.64	Sickle-cell/Hb-C with crisis
282.68	Other sickle-cell disease without crisis
282.69	Other sickle-cell disease with crisis

*Current Procedural Terminology (CPT®) © 2007 American Medical Association: Chicago, IL.

References

1. Amado RG, Schiller GJ. Nonmyeloablative approaches to the treatment of sickle hemoglobinopathies. *Semin Oncol.* 2000 Apr;27(2 Suppl 5):82-9.
2. American Association for Clinical Chemistry. Lab tests online: hemoglobin variants. Updated 2007 Nov 10. Accessed 2008 May 27. Available at URL address: http://www.labtestsonline.org/understanding/analytes/hemoglobin_var/glance-2.html

3. American Sickle Cell Association, The. What is sickle cell anemia? Updated 2005. Accessed 2006 Sep 15. Available at URL address: <http://www.ascaa.org/educ.asp>
4. Bernaudin F, Socie G, Kuentz M, Chevret S, Duvall M, Bertrand Y, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood*. 2007 Oct 1;110(7):2749-56. Epub 2007 Jul 2.
5. Bridges KR. Management issues in sickle cell disease. In: Rakel RE, Bope ET, editors. *Conn's Current Therapy* 2006, 58th ed. St Louis, Mo: Saunders. 2006. p.492-502.
6. Brunetti M, Cohen J. Hematology. In: Robertson J, Shilkofski N., editors. *Johns Hopkins: the Harriet Lane handbook: a manual for pediatric house officers*, 17th ed. Philadelphia, PA: Mosby. 2005.
7. Buchanan GR, DeBaun MR, Quinn CT, Steinberg MH. Sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2004;35-47.
8. Chakrabarti S, Bareford D. Will developments in allogeneic transplantation influence treatment of adult patients with sickle cell disease? *Biol Blood Marrow Transplant*. 2004 Jan;10(1):23-31.
9. Chui DHK, Steinberg MH. Laboratory diagnosis of hemoglobinopathies and thalassemias. In: Hoffman R, Benz, Jr. EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. *Hematology: basic principles and practice*, 4th ed. Orlando: Churchill Livingstone; 2005.
10. Cooley's Anemia Foundation. What is thalassemia? Updated 2001. Accessed 2007 Jun 12. Available at URL address: <http://www.cooleysanemia.org/sections.php?sec=1>
11. Gaziev J, Sodani P, Polchi P, Andreani M, Lucarelli G. Bone marrow transplantation in adults with thalassemia: Treatment and long-term follow-up. *Ann N Y Acad Sci*. 2005;1054:196-205.
12. Hongeng S, Chuansumrit A, Hathirat P, Rerkamnaychoke B, Chaisiripoomkere W, Jootar S. Full chimerism in nonmyeloablative stem cell transplantation in a beta-thalassemia major patient (class 3 Lucarelli). *Bone Marrow Transplant*. 2002 Sep;30(6):409-10
13. Hongeng S, Pakasama S, Chaisiripoomere W, Ungkanont A, Jootar S. Nonmyeloablative stem cell transplantation with a haploidentical donor in a class 3 lucarelli severe thalassemia patient. *Bone Marrow Transplant*. 2004 Aug;34(3):271-2.
14. Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Kitpoka P, Udomsubpayakul U, et al. Outcomes of transplantation with related- and unrelated-donor stem cells in children with severe thalassemia. *Biol Blood Marrow Transplant*. 2006 Jun;12(6):683-7.
15. Hoppe CC, Walters MC. Bone marrow transplantation in sickle cell anemia. *Curr Opin Oncol*. 2001 Mar;13(2):85-90.
16. Horan JT, Liesveld JL, Fenton P, Blumberg N, Walters MC. Hematopoietic stem cell transplantation for multiply transfused patients with sickle cell disease and thalassemia after low-dose total body irradiation, fludarabine and rabbit anti-thymocyte globulin. *Bone Marrow transplant*. 2005 Jan;35(2):171-7.
17. Howard SC, Willimas JA, Flores A, Pacheco C, de Reves G, Machim S. Treatment for children with severe aplastic anemia and sickle cell disease in low income countries in Latin America: a report on the recent meetings of the Monzo International School of Pediatric Hematology/Oncology (MISPHO): part III. *Pediatr Blood Cancer*. 2006 Aug 1;[Epub ahead of print]
18. Horwitz ME, Spasojevic I, Morris A, Telen M, Essell J, Gasparetto C, et al. Fludarabine-based nonmyeloablative stem cell transplantation for sickle cell disease with and without renal failure: clinical outcome and pharmacokinetics. *Biol Blood Marrow Transplant*. 2007 Dec;13(12):1422-6.

19. Iannone R, Casella JF, Fuch EJ, Chen AR, Jones RJ, Woolfrey A. Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and beta-thalassemia. *Biol Blood Marrow Transplant*. 2003 Aug;9(8):519-28.
20. Iannone R, Ohene-Frempong K, Fuchs EJ, Casella JF, Chen AR. Bone marrow transplantation for sickle cell anemia: progress and prospects. *Pediatr Blood Cancer*. 2005 May;44(5):436-40.
21. Jaing TH, Hung IJ, Yang CP, Chen SH, Sun CF, Chow R. Rapid and complete donor chimerism after unrelated mismatched cord blood transplantation in 5 children with beta-thalassemia major. *Biol Blood Marrow Transplant*. 2005 May;11(5):349-53.
22. Kean LS, Durham MM, Adams AB, Hsu LL, Perry JR, Dillehay D. et al. A cure for murine sickle cell disease through stable mixed chimerism and tolerance induction after nonmyeloablative conditioning and major histocompatibility complex-mismatched bone marrow transplantation. *Blood*. 2002 Mar 1;99(5):1840-9.
23. Kramer K, Cohen HJ. Antenatal diagnosis of hematologic disorders. In: Hoffman R, Benz, Jr. EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. *Hematology: basic principles and practice*, 4th ed. Orlando: Churchill Livingstone; 2005.
24. La Nasa G, Caocci G, Argioli F, Giardini C, Locatelli F, Vacca A, et al. Unrelated donor stem cell transplantation in adult patients with thalassemia. *Bone Marrow Transplant*. 2005 Dec;36(11):971-5.
25. Locatelli F, De Stephano P. Innovative approaches to hematopoietic stem cell transplantation for patients with thalassemia. *Haematologica*. 2005 Dec;90(12):1592-4.
26. Miller ST, Sleeper LA, Pegelow CH, Enos LE, Wang WC, Weiner SJ, et al. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med*. 2000. Jan 13;342(2):83-9.
27. National Heart, Lung and Blood Institute. Diseases and Conditions Index: Sickle cell disease. Updated 2007 Nov. Accessed 2008 May 27. Available at URL address: http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_Causes.html
28. National Heart, Lung and Blood Institute. The management of sickle cell disease, 4th ed. Final version 2002 Jul 12. Accessed 2008 May 27. Available at URL address: <http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>
29. National Institutes of Health, Center for Biotechnology Information: Genes and Diseases. NIH Publications: sickle cell anemia. Updated 2005 August. Accessed 2008 May 27. Available at URL address: <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.section.98&ref=sidebar>
30. National Institutes of Health, Genetics Home Reference: beta thalassemia. Updated 2007 Feb. Accessed 2008 May 27. Available at URL address: <http://ghr.nlm.nih.gov/condition=betathalassemia>
31. National Institutes of Health, Genetics Home Reference: sickle cell disease. Updated 2007 Feb. Accessed 2008 May 27. available at URL address: <http://ghr.nlm.nih.gov/condition=sicklecelldisease>
32. National Institutes of Health, Medical Encyclopedia. Thalassemia. Updated 2008 Apr 28. Accessed 2008 May 27. Available at URL address: <http://www.nlm.nih.gov/medlineplus/ency/article/000587.htm>
33. National Institutes of Health, National Human Genome Research Institute. Learning about thalassemia. Updated 2007 Nov 25. Accessed 2008 May 27. Available at URL address: <http://www.genome.gov/10001221>
34. National Institutes of Health, National Heart Lung and Blood Institute. Diseases and Conditions Index: What is thalassemia? Updated 2008 Jan. Accessed May 27, 2008. Available at URL address: http://www.nhlbi.nih.gov/health/dci/Diseases/Thalassemia/Thalassemia_WhatIs.html

35. National Marrow Donor Program. Physician resources: diseases treatable by hematopoietic cell transplant. Updated 2008 Jan. Accessed 2008 May 27. Available at URL address: http://www.marrow.org/PHYSICIAN/Tx_Indications_Timing_Referral/Diseases_Treatable_by_HCT/index.html
36. National Organization of Rare Diseases. Sickle cell disease. Updated 2006. Accessed 2008 May 27. Available at URL address: http://www.rarediseases.org/search/rdbdetail_abstract.html?disname=Sickle%20Cell%20Disease
37. Nietert P, Abboud MR, Silverstein MD, Jackson SM. Bone marrow transplantation versus periodic prophylactic blood transfusion in sickle cell patients at high-risk of ischemic stroke: a decision analysis. *Blood*. 2000 May 15;95(10):3057-64.
38. Panepinto JA, Walters MC, Carreras J, Marsh J, Bredeson CN, Gayle RP, et al. Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research. *Br J Haematol*. 2007 Jun;137(5):479-85. Epub 2007 Apr 24.
39. Preboth M. Practice guidelines: management of pain in sickle cell disease. *Am Fam Physician*. 2000 Mar 1;61(5):1544, 1549-50.
40. Quinn CT, Miller ST. Risk factors and prediction of outcome in children and adolescents who have sickle cell anemia. *Hematol/Oncol Clin*. 2004 Dec;18(6).
41. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. *Blood*. 2004 Jun 1;103(11):4023-7. Epub 2004 Feb 5.
42. Quirolo K, Vichinsky E. Hemoglobin disorders. In: Behrman RE, Kleigman RM, Jenson HB, editors. *Nelson textbook of pediatrics*, 17th ed. Philadelphia: Saunders; 2004. p. 1623-8.
43. Resnick IB, Aker M, Tsirigotis P, Shapira MY, Abdul-Hai A, Bitan M, et al. Allogeneic stem cell transplantation from matched related and unrelated donors in thalassemia major patients using a reduced toxicity fludarabine-based regimen. *Bone Marrow Transplant*. 2007 Nov;40(10):957-64. Epub 2007 Sep 10.
44. Robertson KA. Hematopoietic stem cell transplantation: clinical indications. In: Behrman RE, Kleigman RM, Jenson HB, editors. *Nelson textbook of pediatrics*, 17th ed. Philadelphia: Saunders; 2004. p. 732-7.
45. Rund D, Rachmilewitz E. Beta-thalassemia. *N Engl J Med*. 2005 Sep 15;353(11):1135-46.
46. Sarnaik SA. Thalassemia and related hemoglobinopathies. *Indian J Pediatr*. 2005 Apr;72(4):319-24.
47. Sauntharajah Y, Vichinsky EP, Embury SH. Sickle cell disease. In: Hoffman R, Benz, Jr. EJ, Shattil SJ, Furie B, Cohen HJ, Silberstein LE, editors. *Hematology: basic principles and practice*, 4th ed. Orlando: Churchill Livingstone; 2005. p. 591-634.
48. Sevilla J, Fernandez-Plaza S, Diaz MA, Madero L, Paediatric Working Party of the EBMT. Hematopoietic transplantation for bone marrow failure syndromes and thalassemia. *Bone Marrow Transplant*. 2005 Mar;35 Suppl 1:S17-21.
49. Sickle Cell Disease Association of America (SCDAA). About sickle cell disease. Updated 2005. Accessed 2008 May 27. Available at URL address: http://www.sicklecelldisease.org/about_scd/index.phtml
50. Thompson AA. Advances in the management of sickle cell disease. *Pediatr Blood cancer*. 2006 May 1;46(5):533-9.

51. van Besien K, Bartholomew A, Stock W, Peace D, Devine S, Sher D, et al. fludarabine-based conditioning for allogeneic transplantation in adults with sickle cell disease. *Bone Marrow transplant.* 2000 Aug;26(4):445-9.
52. Walters MC. Stem cell therapy for sickle cell disease: transplantation and gene therapy. *Hematology Am Soc Hematol Educ Program.* 2005;66-73.
53. Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Menzer WC, et al. Bone marrow transplantation for sickle cell disease. *N Engl J Med.* 1996 Aug 8;335(6):369-76.
54. Walters MC, Storb R, Patience M, Leisenring W, Taylor T, Sanders JE, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood.* 2000 Mar 15;95(6):1918-24.
55. Walters MC, Quirolo L, Trachtenberg ET, Edwards S, Hale L, Lee J, et al. Sibling donor cord blood transplantation for thalassemia major: Experience of the Sibling Donor Cord Blood Program. *Ann N Y Acad Sci.* 2005;1054:206-13.
56. Wang WC. Sickle Cell Anemia and Other Sickling Syndromes. In: Greer JP, Foester J, Lukens JN, Rodgers GM, Paraskevas F, Glader B, editors. *Wintrobe's Clinical Hematology*, 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2004.
57. Wethers DL. Sickle cell disease in childhood: part I. Laboratory diagnosis, pathophysiology and health maintenance. *Am Fam Physician.* 2000 Sep 1;62(5):1027-8.
58. Wethers DL. Sickle cell disease in childhood: part II. Diagnosis and treatment of major complications and recent advances in treatment. *Am Fam Physician.* 2000 Sep 15;62(6):1309-4.
59. Yesilipek MA. Stem cell transplantation in hemoglobinopathies. *Hemoglobin.* 2007;31(2):251-6.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	0464	Stem-Cell Transplant for Sickle Cell Disease and Thalassemia Major

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.