Clinical Policy: Allogeneic Hematopoietic Cell Transplants for Sickle Cell Anemia and β-Thalassemia

Reference Number: LA.CP.MP.108 Coding Implications
Date of Last Revision: 2/22 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
This policy describes the medical necessity requirements for allogeneic hematopoietic cell transplants for sickle cell anemia and β–thalassemia. Sickle cell anemia and β–thalassemia are two hemoglobinopathies caused by deleterious genetic alterations in hemoglobin. These monogenic diseases present a range of heterogeneous symptoms that stem from damaged red blood cell function. Despite their limitations, allogeneic hematopoietic cell transplants are the only curative therapies possible for these hemoglobinopathies.

Policy/Criteria

I. It is the policy of Louisiana Healthcare Connections that allogeneic hematopoietic cell transplants for sickle cell anemia and homozygous β-thalassemia are **medically necessary** when all the following criteria are met:

A. *Sickle Cell Anemia,* meets all:
   1. Age ≤ 45 years (children and young adults);
   2. HLA-matched, first-degree relative donor is available;
   3. History of stroke or is at risk of stroke or end-organ damage, as shown by at least one of the following: prior stroke, recurrent acute chest syndrome, recurrent vaso-occlusive crises, or red blood cell alloimmunization on chronic transfusion therapy.

B. *Homozygous β-Thalassemia,* meets all:
   1. Age ≤ 45 years (children and young adults);
   2. HLA-matched donor is available, one of the following:
      a. Cord blood is the source of stem cells, and the donor is a first-degree relative;
      b. Bone marrow is the source of stem cells;
      c. Peripheral blood is the source, and the donor is either unable to, or refuses to donate bone marrow;
   3. Transfusion-dependent due to thalassemia;
   4. A standard, myeloablative conditioning regimen will be used;
   5. Request is made by, or in consultation with, a provider specializing in treating thalassemia.

II. It is the policy of Louisiana Healthcare Connections that there is insufficient evidence regarding the safety and efficacy of the following:

A. Autologous hematopoietic cell transplant for sickle cell anemia;
B. Autologous hematopoietic cell transplant for β-thalassemia;
C. Allogeneic hematopoietic cell transplants for the treatment of sickle cell anemia or homozygous *β*- Thalassemia for any other indications than those specified above.

Background
Hemoglobinopathies are a group of over 1,000 hematological disorders that result from deleterious molecular alterations to hemoglobin and are broadly classified into two categories

based on the phenotypic characteristics of these variations.[1] The first of these categories includes disorders, such as sickle cell anemia, in which there is a structural defect in one of the globin subunits.[1] Thalassemia belongs to the second category of hemoglobinopathies in which there is a quantitative defect in the production of one or more of the globin subunits.[1]

In adults, hemoglobin is a heterotetramer that is comprised of the α-and β-globin subunits.[2] Each globin subunit forms a stable linkage with heme so that oxygen in the cytosol of an erythrocyte can bind reversibly to heme's iron atoms.[2] The hemoglobin tetramer $\alpha_2\beta_2$ binds and unloads oxygen in a cooperative manner, which maximizes the transport of oxygen to cells.[2] Additional gas transport functions of hemoglobin include the transport of carbon dioxide and nitric oxide.[3] Each of these physiological aspects of hemoglobin are deleteriously affected in the hemoglobinopathy disorders.

Sickle Cell Anemia and β-Thalassemia
Sickle cell disease results from a synonymous mutation that exchanges glutamic acid with valine at position 6 in the β-globin subunit.[4] Homozygous inheritance of this mutation results in the disease phenotype, whereas heterozygous carriers do not exhibit clinical disease symptoms; heterozygous carriers are also referred to as having sickle cell trait. [4] This amino acid substitution causes deoxygenated hemoglobin to rigid polymers in red blood cells, which ultimately forms the classic sickle-shaped morphology.[2] The sickle red blood cells occlude the microvasculature which leads to tissue hypoxia, infarction, and chronic hemolytic anemia.[4] Thus, sickle cell anemia presents a heterogeneous range of clinical manifestations, including pain, strokes, vaso-occlusive episodes, multi-organ injury, reduced quality of life, and shortened lifespan.[2,4]

Autosomal mutations in the gene encoding the β-globin subunit cause β-thalassemia (also known as thalassemia major or Cooley's anemia).[5] These mutations inhibit the synthesis of β-globin in erythropoietic cells.[2,5] The extent of the molecular basis for these mutations is very heterogeneous because over 200 mutations within the β-globin subunit, ranging from synonymous mutations to deletions.[1] Consequently, α-globin molecules form toxic aggregates which destroy erythroid precursors through a process called ineffective erythropoiesis.[2,5] Also, individuals with β-thalassemia suffer from anemia due to shortened red blood cell survival, hemolytic anemia.[5]

Hematopoietic Cell Transplantation
Hematopoietic cell transplantation (HCT) is recognized as the only cure for sickle cell disease, and the success rate for specific pediatric groups has been shown to be 85 – 90%.[4] In the United States, it is estimated that the number of children with homozygous sickle cell anemia is 70,000 – 100,000, of which 5,000 – 7,000 could be eligible for transplantation.[6] A survey of the European Blood and Marrow Transplant and CIBMTR data files that approximately 1,200 patients in total have received HCT for sickle cell disease, and the 3 year survival rate is approximately 90% regardless of the source of hematopoietic stem cells.[6] Furthermore, Lucarelli *et al*. and Angelucci *et al.* both have documented the literature for recent reports on outcomes of HCT from HLA-matched donors in cases of β-thalassemia.[8,9] Although stem cell sources and the risk categories of the patients vary, overall survival and thalassemia-free survival range from approximately 65% - 90 % among the numerous reports.[8,9]

The establishment of complete donor-derived erythropoiesis can stabilize function in affected organs, such as the central nervous system and lungs.[7] However, HCT related organ toxicities, graft vs. host disease, graft rejection, and donor availability are major limitations of this procedure.[7] Infertility and gonadal failure are two specific morbidities with which HCT is associated.[4] Also, use of fully matched sibling donors as potentially eligible donors is one of the limitations for HCT implementation.[4] However, siblings are preferable HCT donors due to the lowered risk of graft vs host disease.[6]

Other differences between the considerations for HCT for β-thalassemia and sickle cell anemia include key issues for risk factors for transplant-related complications, transplant outcome, and conditioning regimen.[9] The major risk factors when considering HCT for β-thalassemia include age and organ dysfunction due to iron overload, whereas the major risk factors for HCT due to sickle cell anemia are age and history of cerebral events.[9] Control of iron overload and related tissue damage is a significant consideration for HCT for β-thalassemia, while obtaining a cure from chronic inflammation and prevention of sickle cell related organ damage must be considered for sickle cell anemia.[9] Lastly, β-thalassemia patients require an ablative conditioning regimen, whereas a reduced intensity regimen seems to induce stable chimerism and full donor erythropoiesis in sickle cell anemia patients.[9]

Coding Implications

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CPT®* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

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HCPCS Codes	Description
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

ICD-10-CM Code	Description
D56.1	Beta thalassemia
D57.00-D57.819	Sickle-cell disorders

Reviews, Revisions, and Approvals	Date	Approval Date
Converted corporate to local policy.	11/2020	
Annual review. References reviewed, updated, and reformatted. Changed "review date" in the header to "date of last revision" and "date" in the revision log header to "revision date." "Experimental/investigational" verbiage replaced in policy statement with, "there is insufficient evidence regarding the safety and efficacy." Added "and may not support medical necessity" to coding implications. Reviewed by specialist.	2/22	2/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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