Clinical Policy Title: Hematopoietic stem cell transplant for thalassemia major and sickle cell disease

Clinical Policy Number: 05.03.04

Effective Date: February 1, 2017
Initial Review Date: January 18, 2017
Most Recent Review Date: January 18, 2017
Next Review Date: January 2018

Policy contains:
- Hematopoietic cell transplant (HSCT).
- Human leukocyte antigen (HLA).
- Sickle cell disease.
- Thalassemia major.

Related policies:

- CP# 05.03.02 Stem cell transplant for breast cancer
- CP# 14.02.06 Bone marrow transplant
- CP# 18.03.02 Stem cell transplant for autoimmune disease

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of hematopoietic stem cell transplant (HSCT) for thalassemia major or sickle cell disease to be clinically proven, and therefore medically necessary, given the following conditions:

For children or young adults with sickle cell disease, the patient must be symptomatic with a human leukocyte antigen (HLA)-matched donor, and the procedure performed at an early age as possible.

For children with thalassemia major, the patient must have an HLA-matched donor and the procedure is performed prior to iron overload/iron-related tissue damage. For young adults with the disease, the
patient must have been well chelated since infancy and have a history of/are at risk for conditions such as stroke, vaso-occlusive crises, and recurrent chest syndrome.

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

Only allogenic procedures are covered, not autologous procedures.

Alternative covered services:

- Blood transfusion
- Folic acid
- High fluid intake
- Hydroxycarbamide
- Infection prevention (vaccination, antibiotics)
- Pain medication

Background

Sickle cell disease constitutes a group of red blood cell disorders, marked by abnormal hemoglobin. Persons with the disease inherit two defective genes, one each from their father and mother. In affected persons, red blood cells (which normally are round), become sticky and hard, and assume the shape of a sickle. These cells often die prematurely, and can become stuck and obstruct blood flow, limiting the ability of the cells to move through vessels to deliver oxygen.

Reduced oxygen in tissues can cause painful episodes in the patient with sickle cell disease. Damage to and malfunctions of various organs, including the patient’s brain, eyes, lung, liver, heart, kidneys, penis, joints, bone, and skin, are common among this population. The most common forms of the disease are sickle cell anemia (about 60 to 70 percent of cases) and hemoglobin thalassemia (NHLBI, 2016).

Adverse effects of sickle cell disease include infections, acute and chronic pain, severe anemia, stroke, acute chest syndrome, cognitive problems, jaundice, enlarged heart, pulmonary hypertension, blood in the liver, gall stones, leg ulcers, delayed growth and puberty, delaydactylitis, and priapism. Those affected women with the disorder who become pregnant are at elevated risk for complications in delivery and adverse outcomes, even if needed blood transfusions are given (Ngo, 2010). Patients are at elevated risk for a variety of bacterial infections, as their spleen is compromised and cannot protect adequately against certain microbes. Infections can occur in the blood, lung, brain and spinal cord, and bone.
Treatments vary, but one often used is blood transfusions, especially in sickle cell patients who have suffered a stroke, to prevent a recurrence of stroke. Another treatment is hydroxyurea, an oral medicine that can prevent or reduce complications of sickle cell disease, including pain, acute chest syndrome, dactylitis, and vaso-occlusive crises.

All U.S. newborns are screened for sickle cell disease, and screening can be performed in utero by testing amniotic fluid or tissue from the placenta. About 1 in every 365 African American children is born with the condition, a rate much greater than any ethnic group; the large majority of the 100,000 Americans with the condition are African Americans. About 1 of 13 African American babies is born with sickle cell trait, meaning the baby does not have the disease but can transfer it to future generations.

Historically, most sufferers of sickle cell disease died before reaching adulthood. Due to improvements in treatment and preventing episodes of the disease, the current life expectancy is now 40 to 60 years. The average age at death rose from less than 20 in 1979, to 40 in 2005 (38 for males and 42 for females). Mortality rates are declining among children, but rising among adults (Lanzkron, 2013). Most children with sickle cell anemia (93.9 percent) and those with milder forms of the disease (98.4 percent) now live to adulthood (Quinn, 2010).

Parents of babies diagnosed with sickle cell disease are encouraged to consult a physician at least once per year. Preventive measures like daily administration of penicillin to children under five years old can help reduce the chance of infections. Complying with recommended immunizations, e.g., pneumococcus, influenza, and meningococcus, can also prevent infections.

The only known cure for sickle cell disease is a successful hematopoietic stem cell transplantation (HSCT), also used for a variety of cancers, and introduced for sickle cell and thalassemia major patients in 1981 by teams from Seattle WA and Italy (La Nasa, 2013). This procedure is only performed on a minority of sickle cell patients, as many are too old to qualify for a transplant, and there is often a shortage of potential donors who would likely result in a cure. As of mid-2015, a total of 1,200 such procedures had been performed, far below the prevalence of 100,000 Americans and millions of persons worldwide with the disease (Bhatia, 2015a).

The process of HSCT begins by first identifying a suitable stem cell donor. An identical twin represents the most ideal match, with a sibling the next best opportunity for successful transplant. An unrelated donor can be a match, but can only be identified after months of testing blood. Hematopoietic stem cells are found in bone marrow, the peripheral blood, and the umbilical blood. Prior to surgery, the patient must undergo a series of treatments that suppress the immune system and prevent rejection of the transplanted cells. Radiation and/or chemotherapy may also be used in this pre-operative process. The procedure is done in transplant centers using an intravenous infusion of the stem cells, and the patient is monitored before he/she can be discharged.
Despite the risks posed by transplants, the large majority of parents of, or adolescents with, sickle cell disease or thalassemia major are supportive of HSCT for their child. Of 89 parents/adolescents surveyed in one study, 72 percent were willing to accept a mortality risk of 5 percent or greater, while 57 percent were willing to accept a risk of 10 percent or greater (Meier, 2015).

Thalassemia major is a disorder similar to sickle cell disease. The condition is inherited at birth by mutated genes from each parent, and is marked by severe anemia and expansion of the bone marrow beginning in infancy, due to the inability to produce normal hemoglobin. Untreated thalassemia major is usually fatal in the first decade of life, and the most commonly used treatments are blood transfusions and iron chelation therapy. Like patients with sickle cell disease, those with thalassemia major can be candidates for HSCT.

Prior to 2015, a total of 174 “closed” and “interventional” clinical trials governing sickle cell disease were listed on the clinicaltrials.gov web site. Various types of outcomes in trials focused on pain (23%), bone marrow transplant (13%), hydroxyurea (8%), iron overload (8%), and pulmonary hypertension (8%). Only 35% of sickle cell trials completed before 2014 resulted in a journal manuscript (Lebensburger, 2015).

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on October 27, 2016. Search terms were: “sickle cell” and “cell transplant.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**
Some guidelines exist that address all hematopoietic cell transplants. Only those specific to sickle cell disease and thalassemia major were reviewed for this clinical policy.

There are several guidelines available that address methods of diagnosis and treatment of sickle cell disease, but none address HSCT (Benjamin, 1999, Brawley, 2008, USPSTF, 2007). A 2002 guideline from the National Heart, Lung, and Blood Institute (NHLBI) focuses on managing complications of sickle cell disease, including hydroxyurea therapy and blood transfusion. It does recommend that children with sickle cell disease with significant complications should be considered for HCST, if full siblings that are matched donors are available. It adds that no comparative studies are available to compare outcomes of one treatment vs. another (NHLBI, 2002). A 2014 NHLBI guideline on sickle cell disease does not address cell transplants (NHLBI, 2014).

A 20 member panel known as the European Blood and Marrow Transplantation Inborn Error Working Party and the Paediatric Disease Working Party issued guidelines for HSCT for thalassemia major and sickle cell disease, divided by the two conditions and adults vs. children (Angelucci, 2014). These recommendations include:

For children with sickle cell disease:
1. Young patients with symptomatic sickle cell disease with a matched sibling donor should be transplanted as early as possible, preferably before school age.
2. Unmanipulated bone marrow or unrelated cord blood transplantation from matched sibling donors are the recommended stem cell source.

For children with thalassemia major:
1. Young thalassemia major patients with an available identical sibling should be offered transplantation as soon as possible before development of iron overload and iron-related tissue damage.
2. Transplant-related risk factors should be evaluated according to the Pesaro risk score
3. Human leukocyte antigen genocidal cord blood and bone marrow are equally effective stem cell sources.
4. Peripheral blood stem cell transplantation should be avoided because of increased risk of chronic graft-versus-host disease.

For adults with thalassemia major:
1. Transplant in adults who have been well chelated since infancy should be offered within controlled trials.
2. Assessment of clinical condition according to the Pesaro risk score and adequate transfusions/chelation regimen are the major issues to be evaluated before deciding to perform a transplant.

In general, the literature shows that allogenic HSCT for persons with sickle cell disease and thalassemia major using stem cells from bone marrow of well-matched donors generally are associated with higher
rates of overall and disease free survival. However, studies that compare HSCT effectiveness with standard treatments for the disorder with adequate control groups and statistical comparisons are limited. The efficacy of stem cells other than from bone marrow and donors not HLA-matched still needs to be studied more thoroughly (Hayes, 2016).

Even the earliest experience with HSCT showed highly positive long-term results in a population that previously had a high mortality rate early in life. One study of 108 thalassemia major patients who underwent HSCT from 1985 to 2007 documented a 15-year survival rate of 86.8 percent, and a thalassemia-free survival rate of 69.4 percent (Galambrun, 2013). A nine-year follow up of children with sickle cell disease given transplants from an HLA-matched related donor found an overall survival of 93 percent and a recurrence rate of zero (Dallas, 2013). Another study of 87 patients receiving transplants from a matched sibling from 1988 to 2004, and followed up for an average of six (6) years had an overall survival of 93.1 percent and an event-free survival of 86.1 percent (Bernardin, 2007).

Not surprisingly, those patients at greatest risk, using the Pesaro scale, had lower survival rates after transplants. A review of 179 thalassemia major children who underwent a bone marrow transplant from an HLA-matched sibling showed a 5-year probability of survival of 91 percent for Pesaro class II patients, compared to a 64 percent survival for class III (highest risk) patients (Sabloff, 2011).

Improved outcomes over time for transplant patients can be attributed, at least in part, to more effective pre-transplant medical regimens. The traditional busulfan was compared with the newer treosulfan in 189 patients with (high risk) Pesaro Class III thalassemia major. The treosulfan group showed significantly lower rates of sinusoidal obstruction syndrome and early treatment related mortality (Mathews, 2013). Another group of 75 stem cell transplants for thalassemia major patients treated with anti-thymocyte globulin conditioning regimens found an overall survival rate of 96 percent after (an average of) nine years post-operative (Goussetis, 2012). A review comparing a modified preconditioning cytoreduction with hydroxurea and azathioprine starting 45 days from transplant raised the thalassemia-free survival rate from 73 to 92 percent (Gaziev J, 2016).

Some pre-transplant practices have no evidence-based guidelines, and thus are varied among practitioners. One survey showed a variation in transfusion practices among pediatric HSCT patients, including baseline transfusion threshold and what prompts an increase in the threshold (Bercovitz, 2013).

Although HLA-matched donors are encouraged, positive outcomes from other donors have been identified. One review found 5-year survival after mismatched related-donor transplantation and unrelated-donor umbilical cord blood transplantation to be 62 percent and 57 percent, respectively. The authors conclude that these donors are an option if an HLA-identical donor is not available (Fernandes, 2012).

An evaluation of quality of life for 124 persons from Sardinia with thalassemia major who underwent HSCT in the 1980s and 1990s and survived a median of 22.8 years was recently conducted. The group,
who underwent surgery as children, showed that the long-term health-related quality of life was similar to that of the general population; mental health, education level, employment status, marital status, living arrangements, and birth rate were all similar. The same study showed that survivors of the disorder who underwent conventional treatment had poorer outcomes compared to those undergoing HSCT (LaNasa, 2013).

Annual costs of treating sickle cell disease in U.S. children in 2005 were an average of $9,369 (Medicaid) and $13,469 (private insurance) greater than those children without the disease, or 6 and 11 times greater. The total yearly cost of treating these children was $335 million (Amendah, 2010).

Barriers to HSCT among African Americans have been identified, as they have low participation rates in clinical trials and reduced access to the most current medical therapies. The authors postulate that these barriers occur due to gaps in knowledge of sickle cell disease, limited access to trial information, and mistrust of medical professionals. Providers can reach out to sickle cell camps to improve access to these needed services (Omondi, 2013).

Policy updates:

None.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tr>
<td>Hayes (2016)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Assessment of evidence of efficacy of HSCT</td>
<td>• Allogenic HSCT for persons with sickle cell disease using stem cells from bone marrow of well-matched donors generally results in higher overall survival, disease free survival.</td>
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<td>• Effectiveness and safety of HSCT vs. standard treatments for sickle cell disease is hampered by limited studies with adequate control groups and statistical comparisons.</td>
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<td>• Questions remain on whether stem cells from other than bone marrow and donors other than HLA-matched are effective.</td>
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<td>Dallas (2013)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>Survival of pediatric sickle cell patients undergoing HSCT with HLA-matched related donors</td>
<td>• 22 pediatric sickle cell patients with HSCT at St. Jude Children’s Research Hospital.</td>
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<td>• Donors include myeloablative sibling (14), and reduced intensity parental haploidentical donor (8).</td>
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<td>• Mean follow up was 11 years in the myeloablative group, 9 years in haploidentical group.</td>
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<td>• Overall survival was 93 percent (20 of 22), recurrence was 0.</td>
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<tr>
<td>Galambrun (2013)</td>
<td><strong>Key points:</strong></td>
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Citation | Content, Methods, Recommendations
---|---
thalassemia patients after HSCT | • 96 of 108 patients had matched donor, median follow up was 12 years.  
• 15 year overall survival was 86.8 percent, thalassemia-free survival was 69.4 percent.

Sabloff (2011) | **Key points:**
Survival of thalassemia major patients undergoing HSCT, by risk factor | • 179 patients with HSCT from matched sibling.  
• Median age at transplant = 7 years, median follow up was 6 years.  
• Overall 5-year survival for Pesaro risk class II and III (sickest) was 64 and 91 percent.  
• Disease-free 5-year survival for Pesaro risk class II and III was 62 and 88 percent.

Amendah (2010) | **Key points:**
Costs of treating sickle cell disease for children | • Claims data bases for 2005 used to estimate medical expenses for children with and without sickle cell disease.  
• Children with disease vs. other children average cost = $9,369 more for Medicaid (6x).  
• Children with disease vs. other children average cost = $13,469 more for private insurance (11x).

References

Professional society guidelines/other:


Peer-reviewed references:


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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