Stem-Cell Transplantation for Aplastic Anemia and Fanconi Anemia

**Coverage Policy**

Allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched human leukocyte antigen (HLA) donor is considered medically necessary for the treatment of EITHER of the following conditions:

- severe aplastic anemia (AA)
- Fanconi anemia

**Overview**

This Coverage Policy addresses hematopoietic stem-cell transplantation (HSCT) for the treatment of severe aplastic anemia and Fanconi anemia.

Aplastic anemia is a blood disorder in which the body's bone marrow doesn't make enough new red blood cells, white blood cells or platelets because the bone marrow is damaged. Severe aplastic anemia can be life-threatening. Fanconi anemia is a rare inherited blood disorder that leads to bone marrow failure. Fanconi anemia is a type of aplastic anemia.
Hematopoietic stem-cell transplantation (HSCT) involves taking hematopoietic stem cells that can regenerate all of the blood cells normally produced in the bone marrow from the bone marrow or blood of a donor, and infusing them into a person with aplastic anemia or Fanconi anemia.

**General Background**

Aplastic anemia, along with Diamond-Blackfan anemia, Fanconi anemia, and other anemias, is a bone marrow failure syndrome. These are rare disorders in which there is usually failure of the bone marrow to produce blood cells. Some of these conditions have typical changes in physical appearance or in laboratory findings which suggest a specific diagnosis. Failure of the bone marrow to produce blood cells predisposes an individual to the future development of other hematological disorders, including leukemia and myelodysplastic syndrome. Allogeneic hematopoietic stem-cell transplantation (HSCT) has been proposed for the treatment of these syndromes.

**Stem-Cell Transplantation**

Stem-cell transplantation refers to the transplantation of hematopoietic stem cells (HSCs) from a donor into a recipient. HSCs are immature cells that can develop into any of the three types of blood cells (i.e., red cells, white cells or platelets). Allogeneic HSCT uses stem cells from a donor other than the individual who has the disorder.

In allogeneic HSCT it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). Alternative donor sources are being evaluated for individuals with aplastic anemia and Fanconi anemia who do not have an HLA-identical donor. As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. Long-term survival after mismatched related donation is inferior to genotypically matched donor transplantation.

**Contraindications to Stem-Cell Transplantation**

The presence of any significant co-morbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplantation. Relative contraindications to HSCT include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

**Aplastic Anemia**

Aplastic anemia (AA), also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder that is characterized by pancytopenia and a hypocellular bone marrow (DeZern, 2012). This failure, which can be congenital or acquired, is related to either a defect in the stem-cell pool, or an injury to the microenvironment that supports the bone marrow. Immunosuppression improves marrow function in up to 80% of individuals with AA; however, it is not uncommon for those who respond to immunosuppressive therapy to experience disease relapse. Aplastic anemia is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of the peripheral blood cytopenias.

Severe AA is diagnosed according to the following criteria (Young, 2006):

- No other hematologic disease
- Bone marrow cellularity < 30%
- TWO of the following blood criteria:
Allogeneic hematopoietic stem-cell transplantation (HSCT) is a standard treatment option for individuals with severe AA. Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor provides curative therapy for individuals with severe AA. It is considered a standard of care for individuals younger than 45 to 50 years of age, despite treatment-related morbidity and mortality.

Hematopoietic recovery is often incomplete after immunosuppressive treatment, but tends to be complete and stable after HSCT. The probability of survival with sustained donor engraftment for individuals with severe AA undergoing allogeneic HSCT is >80%, with younger patients having even better outcomes (Velardi, 2007). In children, matched-sibling-donor allogeneic HSCT has a >90% five-year overall survival (OS) rate (Bakhshi S., 2011), with ten-year outcomes of 97% reported for some children (Davies, 2007).

Young adults have a reasonable opportunity for cure with bone marrow transplantation but also face more complications than children (Young, 2006). Older individuals and those without HLA-identical related donors generally receive first-line therapy with immunosuppressive drugs. Alternative donor transplantation may be an option in children who do not have an HLA-matched donor. Disadvantages to allogeneic HSCT are procedure-related morbidity and mortality, especially graft-versus-host disease (GVHD) in older patients, and an increased incidence of solid organ malignancies (Young, 2006; Ades, et al., 2004). Graft failure after HSCT remains a significant problem in patients with AA, especially in those patients who have been heavily transfused (Champlin, 2007).

**Literature Review**

Although data from randomized controlled trials (RCTs) are lacking, a large number of case series and retrospective analyses report improved outcomes with the use of allogeneic HSCT and it is considered a standard of care option for an individual with severe aplastic anemia.

Zhang et al. (2017) published a retrospective analysis comparing haploidentical allogeneic HSCT and immunosuppressive therapy (IST) for 28 children with acquired severe aplastic anemia. Eighteen children were treated with HSCT and 10 with immunotherapy. At a median follow-up of 23.5 months, there was no significant difference in overall survival rate between the groups (66.7% vs. 70%, HSCT and IST, respectively; p > 0.05), despite increased morbidity with HSCT. GVHD was reported in 83.3% of children who received HSCT.

Peinemann et al. (2013, 2014) reported results of a Cochrane systematic review with the primary outcome of evaluating the effectiveness and adverse events of first-line allogeneic hematopoietic stem cell transplantation of HLA-matched sibling donors compared to first-line immunosuppressive therapy in patients with acquired severe aplastic anemia. Three prospective trials involving 302 patients were included in the review. No trial was a randomized clinical trial. The authors reported that all studies had a high risk of bias due to the study design. The pooled hazard ratio for overall mortality for the transplant group versus the immunosuppressive therapy group was 0.95 (p = 0.90, low quality evidence). Overall mortality was not statistically significantly different between the groups. Treatment-related mortality ranged from 20% to 42% for the transplant group and was not reported for the immunosuppressive therapy group (very low quality evidence). Graft failure was 3%-16% for the transplant group and GVHD was from 26%-51%. Neither endpoint was applicable for the immunosuppressive therapy group. No data was reported by individual study authors regarding response and relapse for the transplant group. None of the included studies addressed health-related quality of life. The percentage of the evaluated patients with a Karnofsky performance status score in the range of 71% to 100% was 92% in the transplant group and 46% in the immunosuppressive therapy group. All studies were conducted more than 10 years ago; Cochrane authors note that these results may not be applicable to the standard of care of today. Due to limited, low quality data, with a high risk of bias, there is insufficient evidence to draw conclusions regarding the comparative effectiveness of first-line allogeneic HSCT with an HLA-matched sibling donor compared with first-line immunosuppressive therapy.
Pienemann et al. (2011) published a meta-analysis of 26 studies comparing results achieved by use of a matched related donor HSCT compared with immunosuppression (IST) as first-line therapy. No randomized clinical trial was identified. A systematic review was performed on overall survival. On multivariate analysis, younger age was identified as a statistically significant factor for improved survival in individuals who received HSCT. Overall mortality was reported in 23 studies (HSCT vs. IST: 3%–67% vs. 9%–58%, respectively).

In several studies OS rates are 51% to 100% for a range of time intervals (Perez-Albuerne, 2008; Inamoto, 2007; Unal, 2007). In a prospective study of individuals who were treated with allogeneic HSCT after failure with immunosuppressive therapy compared with those who received only immunosuppression, four-year failure-free survival, defined as survival with response, was 83.9% in the transplantation group compared with 9.1% in the group who received immunosuppressive therapy alone (Kosada, 2008).

The toxicity of myeloablative allogeneic HSCT has led to investigation of nonmyeloablative conditioning and allogeneic HSCT for selected individuals who have failed previous immunosuppressive therapy and/or who are transfusion dependent. Data from RCT are lacking; however, several small case series and retrospective analyses report durable engraftment and four-year OS of 93% and 89%, respectively, for individuals receiving sibling-matched and unrelated donor allografts, and five-year OS rates of 84% (Kennedy-Nasser, 2006; Resnick, 2006).

Fanconi Anemia
Fanconi anemia, also called Fanconi’s anemia, FA, and aplastic anemia with congenital anomalies, is a form of congenital aplastic anemia. It is a rare, genetic disorder of autosomal recessive inheritance, characterized by congenital abnormalities, progressive bone marrow failure, spontaneous and induced chromosome breakage and increased cancer susceptibility (Gluckman, 2007). At least thirteen genes have been implicated in the disease (Gluckman, 2007). Survival after diagnosis can range from two to 25 years. By age 40 to 48 years, the estimated cumulative incidence of bone marrow failure is 90%.

Allogeneic hematopoietic stem-cell transplantation (HSCT) can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders and is considered the treatment of choice for patients with severe hematological changes (Bonfim, 2007; Velardi, 2007; Bitan, 2006; Motwani, 2005). 

Literature Review
Although randomized control trial data are lacking, allogeneic HSCT is considered a standard of care treatment option for individuals with Fanconi anemia.

HSCT is currently the only curative therapy for the hematological abnormalities of FA. Although randomized controlled trials (RCT) data are lacking and evidence is not robust, FA is a universally accepted indication for allogeneic HSCT with a human leukocyte antigen (HLA)-identical sibling donor. FA is a rare disease, and, consequently, patient populations for many transplantation series have been relatively small. Data from case series, retrospective analyses and review of registry data suggest improved long-term outcomes with allogeneic HSCT with survival rates of 93% at 3.7 years (Bonfim, 2007) to 67% at eight years (Locatelli et al., 2007). Farzin et al. (2007) reported 10-year OS rates of 89% in a cohort of 35 patients with FA who underwent allogeneic HSCT. Pooled published data on HSCT using HLA-matched sibling donors show a survival of greater than 80% in FA patients less than 10 years of age, and greater than 65% for FA patients of all ages.

Alternative donors may be considered for individuals without other options; however, survival is generally less than with matched sibling donors (Guardiola, 2000). Graft-versus-host disease (GVHD) is more likely to be severe in patients with FA because of the underlying defect. However, outcomes were favorable compared with survival using matched related donors in a recent series of 12 consecutive children (Zecca, 2014). Participants had neither an HLA-identical sibling nor an HLA-matched unrelated donor and received haploidentical related donor reduced-intensity allogeneic HSCT. Cumulative incidences of grades II to IV acute and chronic graft-versus-host disease were 17% and 35%, respectively. The cumulative incidence of transplant-related mortality was 17%. The 5-year overall survival, event-free survival, and disease-free survival were 83%, 67%, and 83%, respectively.
Reduced-dose or nonmyeloablative conditioning regimens may result in acceptable toxicity, high engraftment rates, improved survival and comparable incidences of GVHD compared with standard dose regimens utilized for hematological malignancies (Balci, 2008; Bonfim, 2007; Bitan, 2006; Tan, 2006; Yabe, 2006; Janis-Netro, 2005). Data are not robust, and patient populations are small; nonetheless, this therapy may allow allogeneic transplantation in patients who are older, have co-morbid conditions, or have toxicities from previous treatment. Patients with minimal and chemotherapy-sensitive disease transplanted early in their disease course may have better outcomes.

Professional Societies/Organizations
National Marrow Donor Program ([NMDP], 1996-2017): The NMDP lists severe aplastic anemia and other bone marrow failure states including Fanconi anemia, as indications for HSCT. Referral for evaluation for HSCT is upon diagnosis.

American Society of Bone Marrow Transplantation ([ASBMT], 2015): On behalf of the ASBMT, Majhail et al. (2015) published a guideline document titled “Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation”. The ASBMT notes that for individuals with severe aplastic anemia with a new diagnosis or with relapsed or refractory disease allogeneic HSCT is considered standard of care. Although clinical trials and observational studies are not currently feasible for Fanconi anemia due to very low incidence, single- or-multi-center or registry studies in relatively small cohorts of patients have been shown allogeneic HSCT to be an effective treatment for individual patients. Autologous HST is generally not recommended for treatment of aplastic anemia or Fanconi anemia.

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside of the US
British Committee for Standards in Hematology ([BCSH], 2016): On behalf of the BCSH, Killick et al. published guidelines for the diagnosis and management of adult aplastic anemia. Regarding HSCT, the guideline notes that up-front matched unrelated donor HSCT for young and adult patients is the treatment of choice. Individuals between 35-50 years should be carefully assessed for comorbidities prior to consideration for transplantation. Unrelated donor HSCT in adults should be considered after lack of response to one course of immunosuppressive therapy. There have been recent improvements in outcomes after alternate donor HSCT for individuals who lack a suitably matched donor; however, these transplants are still experimental and specialist advice should be sought.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when used to report allogeneic bone marrow or blood-derived stem cell procedures:

<table>
<thead>
<tr>
<th>CPT** Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion</td>
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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, allogeneic

38240 Hematopoietic progenitor cell (HPC); allogeneic transplantation-per donor

38242 Allogeneic lymphocyte infusions

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<thead>
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<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
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<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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</td>
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References


