Subject: Hematopoietic Stem Cell Transplantation for Aplastic Anemia and other Bone Marrow Failure Disorders

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<th>Policy Number: MCP-143</th>
<th>Original Effective Date: 6/26/13</th>
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<td>Revision Date(s): 6/2/15, 9/21/16, 12/10/19</td>
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**DISCLAIMER**

*This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina’s determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member’s benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member’s benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member’s plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS’s Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.¹*

**DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL**

**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 and can be acquired or congenital. The most common causes of acquired aplastic anemia include idiopathic (no known cause), hepatitis, drugs, chemical toxins, pregnancy, pure red cell anemia, paroxysmal nocturnal hemoglobinuria and parovirus B19. Congenital aplastic anemia usually is caused by genetic mutations in the hTR gene or a rare autosomal recessive inherited disease (Fanconi anemia). Affected patients generally present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and fatigue due to anemia. The diagnosis of AA is established following bone marrow aspiration and biopsy. Aplastic anemia is classified as non-severe (NSAA), severe (SAA) and very severe based on the degree of the peripheral blood cytopenias.

**Stem Cell Transplantation**
Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) from a donor into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCs are created in the bone marrow and are found in the bone marrow and peripheral blood. There is also a high concentration of HSCs in umbilical-cord blood. Hematopoietic stem-cell transplantation (HSCT) can be either autologous (using the person’s own stem cells) or allogeneic (using stem cells from a donor). 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 of more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase.

Allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor can provide curative therapy for individuals with SAA. It is considered a standard of care for individuals younger than 50 years of age, despite treatment-related morbidity and mortality. 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 a matched donor. For patients who lack an HLA-matched sibling, alternative sources of donor grafts include suitably HLA-matched unrelated donors, or HLA-haploidentical, related donors.

RECOMMENDATION 1 2 3-32 35 36-43

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, state regulations and/or MCP policies the Corporate Senior Medical Director’s designee can approve the requested transplant.

Members must meet UNOS/OPTN policies and guidelines for pretransplantation evaluation and listing criteria and the diagnosis must be made by a Specialist in the Disease and or Transplant Surgeon.

Pre-Transplant Evaluation:

Criteria for transplant evaluation include all of the following: 33-39

- History and physical examination
- Psychosocial evaluation and clearance:
  - No behavioral health disorder by history or psychosocial issues:
    - if history of behavioral health disorder, no severe psychosis or personality disorder
    - mood/anxiety disorder must be excluded or treated
    - member has understanding of surgical risk and post procedure compliance and follow-up required
  - Adequate family and social support
- EKG
- Chest x-ray
- Cardiac clearance in the presence of any of the following:
  - chronic smokers
  - > 50 years age
  - those with a clinical or family history of heart disease or diabetes
- Pulmonary clearance if evidence of pulmonary artery hypertension (PAH) or chronic pulmonary disease
- Performance Status 4: [ONE]
Karnofsky score 70-100%
Eastern Cooperative Oncology Group (ECOG) grade 0-2

- Neurological exam and clearance for transplant: [ONE]
  - Normal exam by H&P
  - Abnormal neurological exam with positive findings: [ONE]
    - Lumbar puncture normal cytology
    - Lumbar puncture with cytological exam abnormal: CNS disease treated prior to clearance

- Lab studies:
  - Complete blood count, Kidney profile (blood urea nitrogen, creatinine), electrolytes, calcium, phosphorous, albumin, liver function tests, Coagulation profile (prothrombin time, and partial thromboplastin time)
  - Serologic screening for HIV, Epstein Barr virus (EBV), Hepatitis virus B (HBV), and Hepatitis C(HCV), cytomegalovirus (CMV), RPR and/or FTA:
    - If HIV positive all of the following are met:
      - CD4 count >200 cells/mm-3 for >6 months
      - HIV-1 RNA undetectable
      - On stable anti-retroviral therapy >3 months
      - No other complications from AIDS (e.g., opportunistic infection, including aspergillus, tuberculosis, coccidioides mycosis, resistant fungal infections, Kaposi’s sarcoma, or other neoplasm)
    - If abnormal serology need physician plan to address and/or treatment as indicated
  - UDS (urine drug screen) if patient is current or gives a history of past drug abuse

- Colonoscopy (if indicated or if patient is 50 ≥ older should have had an initial screening colonoscopy, after initial negative screening requires follow up colonoscopy every ten years) with complete workup and treatment of abnormal results as indicated

- GYN examination with Pap smear for women ≥ 21 to ≤ 65 years of age or indicated (not indicated in women who have had a TAH or TVH) with in the last three year with complete workup and treatment of abnormal results as indicated

Within the last 12 months:

- Dental examination or oral exam showing good dentition and oral care or no abnormality on panorex or plan for treatment of problems pre or post-transplant
- Mammogram (if indicated or > age 40) with complete workup and treatment of abnormal results as indicated
- PSA if history of prostate cancer or previously elevated PSA with complete workup and treatment of abnormal results as indicated

*Participating Centers of Excellence may waive these criteria

Criteria for Transplantation:

1. **Hematopoietic Allogeneic stem-cell transplantation (HSCT)** is considered medically necessary and may be authorized in adults and children who have a **fully matched-HLA sibling donor** OR, haploidentical related donor when there are no matched sibling or unrelated donors (sharing a haplotype;
having the same alleles at a set of closely linked genes on one chromosome) for the treatment of bone marrow failure syndrome when ALL of the following criteria are met:

- All pre-transplant criteria are met; and
- Must be < 60 years of age;
- Must have a diagnosis of aplastic anemia (includes congenital and acquired) defined as:
  - Severe aplastic anemia (SAA) : [ONE]
    - A marrow biopsy showing less than 25 percent of normal cellularity; OR
    - A marrow showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: [TWO]
      - absolute reticulocyte count <40,000/microL;
      - absolute neutrophil count (ANC) <500/microL;
      - platelet count <20,000/microL
  - OR
    - Very severe aplastic anemia (vSAA) defined as:
      - the ANC is <200/microL
  - OR
    - Any of the following rare bone marrow failure disorders:
      - Diamond-Blackfan anemia (DBA)
      - Fanconi’s anemia (FA)
      - Schwachman-Diamond syndrome (SDS)
      - Pure red cell aplasia
      - Paroxysmal nocturnal hemoglobinuria
      - Congenital amegakaryocytic thrombocytopenia (CAMT)
      - Dyskeratosis congenital

And must meet age criteria for Aplastic Anemia Diagnosis:

- For age < 50 years: [ALL]
  - Stem cells are obtained from bone marrow

- For age >50 years : [ALL]
  - Failed at least one course of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporin;
  - Stem cells are obtained from bone marrow

2. **Hematopoietic Allogeneic stem-cell transplantation (HSCT)** is considered medically necessary and may be authorized in adults and children who have a matched unrelated donor (MUD) for the treatment of bone marrow failure syndrome when ALL of the following criteria are met: [ALL]
❑ All pre-transplant criteria are met; and
❑ Must be <60 years old;
❑ Failed at least one course of immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporin; and
❑ Stem cells are obtained from bone marrow; and
❑ Must have aplastic anemia (includes congenital and acquired) defined as:
  o Severe aplastic anemia: [ONE]
     ◦ A marrow biopsy showing less than 25 percent of normal cellularity; OR
     ◦ A marrow showing less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present:
       [TWO]
       ➢ absolute reticulocyte count <40,000/microL;
       ➢ absolute neutrophil count (ANC) <500/microL;
       ➢ platelet count <20,000/microL.

OR

  o Very severe aplastic anemia defined as:
     ◦ the ANC is <200/microL

AND

❑ The requesting transplant recipient should not have any of the following absolute contraindications:
  o Cardiac, pulmonary, and nervous system disease that cannot be corrected and is a prohibitive risk for surgery
  o Malignant neoplasm with a high risk for reoccurrence, non-curable malignancy (excluding localized skin cancer)
  o Systemic and/or uncontrolled infection
  o AIDS (CD4 count < 200 cells/mm3)
  o Unwilling or unable to follow post-transplant regimen
     ◦ Documented history of non-compliance
     ◦ Inability to follow through with medication adherence or office follow-up
  o Chronic illness with one year or less life expectancy
  o Limited, irreversible rehabilitation potential
  o Active untreated substance abuse issues, requires documentation supporting free from addiction for minimally 6 months if previous addiction was present
  o No adequate social/family support

❑ The requesting transplant recipient should be evaluated carefully and potentially treated if the following relative contraindications are present:
  o Irreversible lung disease patients require consultation and clearance by a Pulmonologist prior to consideration of transplantation, this includes the following:
  o Smoking, documentation supporting free from smoking for 6 months
  o Active peptic ulcer disease
  o Active gastroesophageal reflux disease
- CVA with long term impairment that is not amendable to rehabilitation or a patient with CVA/transient ischemic attack within past 6 months
- Obesity with body mass index of $>30 \text{ kg/m}^2$ may increase surgical risk
- Chronic liver disease such as Hepatitis B/C/D, or cirrhosis which increases the risk of death from sepsis and hepatic failure requires consultation by a gastroenterologist or hepatologist
- Gall bladder disease requires ultrasound of the gall bladder with treatment prior to transplantation

**CONTINUATION OF THERAPY**

When extension of a previously approved transplant authorization is requested, review using updated clinical information is appropriate.

- If Molina Healthcare has authorized prior requests for transplantation, the following information is required for medical review: [ALL]
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Kidney profile within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

- If authorized prior requests for transplantation were obtained from another insurer, the following information is required for medical review: [ALL]
  - Authorization letter/documentation from previous insurer;
  - Presence of no absolute contraindication as listed above;
  - History and physical within the last 12 months;
  - Cardiac update if history of cardiac disease within two years ($\geq 50$ years of age);
  - Psychosocial evaluation or update within the last 12 months;
  - Per initial and updated history and physical, any other clinically indicated tests and/or scans as determined by transplant center physician or Molina Medical Director.

**COVERAGE EXCLUSIONS**

1. Allogeneic (ablative or non-myeloablative) stem cell transplantation when the above criteria are not met.
2. Autologous stem cell transplant
3. Umbilical cord blood as a hematopoietic stem cell source is considered investigational due to the lack of sufficient evidence in the peer reviewed published literature.
4. Hematopoietic stem cell collection, storage and freezing for a future unplanned transplant.

**SUMMARY OF MEDICAL EVIDENCE**

The published medical evidence and outcomes for hematopoietic stem cell transplantation for aplastic anemia in children and adults in the United States consists of registry data obtained from transplant centers that perform adult and pediatric transplantation and is available from the United Network for Organ Sharing (UNOS) database. Registry data demonstrates graft survival rates and outcomes for stem cell transplantation based on demographic and clinical information. Additional relevant studies are outlined below.
A Cochrane review reported by Peinemann et al. (2013, 2014) evaluated 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. 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 and the 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, conclusions are not able to be made regarding the comparative effectiveness of first-line allogeneic HSCT with an HLA-matched sibling donor compared with first-line immunosuppressive therapy.

Buchbinder and colleagues (2012) conducted a descriptive analysis of 1718 patient’s post-HCT for acquired SAA between 1995 and 2006 that were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). This study describes the malignant and nonmalignant late effects in survivors with SAA after HCT and reported the prevalence and cumulative incidence estimates of late effects for 1-year HCT survivors with SAA. Of the HCT recipients, 1176 (68.5%) and 542 (31.5%) patients underwent a matched sibling donor (MSD) or unrelated donor (URD) HCT, respectively. The median age at the time of HCT was 20 years. The median interval from diagnosis to transplantation was 3 months for MSD HCT and 14 months for URD HCT. The median follow-up was 70 months and 67 months for MSD and URD HCT survivors, respectively. Overall survival at 1 year, 2 years, and 5 years for the entire cohort was 76% (95% confidence interval [CI]: 74-78), 73% (95% CI: 71-75), and 70% (95% CI: 68-72). Among 1-year survivors of MSD HCT, 6% had 1 late effect and 1% had multiple late effects. For 1-year survivors of URD HCT, 13% had 1 late effect and 2% had multiple late effects. Among survivors of MSD HCT, the cumulative incidence estimates of developing late effects were all <3% and did not increase over time. In contrast, for recipients of URD HCT, the cumulative incidence of developing several late effects exceeded 3% by 5 years: gonadal dysfunction 10.5% (95% CI: 7.3-14.3), growth disturbance 7.2% (95% CI: 4.4-10.7), avascular necrosis 6.3% (95% CI: 3.6-9.7), hypothyroidism 5.5% (95% CI: 2.8-9.0), and cataracts 5.1% (95% CI: 2.9-8.0). The authors concluded that the results indicated that all patients undergoing HCT for SAA remain at risk for late effects, must be counseled about, and should be monitored for late effects for the remainder of their lives.

Kim et al (2012) retrospectively analyzed the impact of older age on transplantation outcomes and survival in a total of 225 adult patients with AA who underwent allo-HSCT: 57 patients >40 years old (older patient group [OPG]) and 168 patient’s ≤40 years old (younger patient group [YPG]). Age at allo-HSCT ≤40 years, time from diagnosis to allo-HSCT ≤6 months, and matched related donor (MRD) were favorable prognostic factors in all study patients. Risk analysis of survival in the OPG showed that age >50 years was the only poor prognostic factor. Survival did not differ significantly between the YPG and patients <50 years old in the OPG.
conclusion, patients between the ages of 41 and 50 years with severe AA and MRDs should undergo allo-HSCT as early as possible to optimize survival. 23

In 2011 Peinmann and associates performed a meta-analysis to compare outcomes of first-line matched related donor hematopoietic stem cell transplantation to immunosuppressive therapy in patients with acquired severe aplastic anemia. 26 non-randomized controlled trials (7,955 patients enrolled from 1970 to 2001) were identified. No RCTs were identified. Risk of bias was high except in 4 studies. Young age and recent year of treatment were identified as factors for improved survival in the HSCT group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the IST group. In 19 studies (4,855 patients), summary statistics were sufficient to be included in meta-analysis. Considerable heterogeneity of non-randomized controlled studies did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies. The review concluded that young age and recent year of treatment were identified as factors for improved survival in the transplant group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the immunosuppressive group. Considerable heterogeneity across studies did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies. 18

Perez-Alburne et al. (2008) analyzed data from 195 children with acquired SAA who underwent unrelated donor transplantation between 1989 and 2003 to determine if unrelated donors provide a source of hematopoietic stem cells in children with severe aplastic anemia (SAA) who fail immunosuppressive therapy and lack a human leucocyte antigen (HLA)-matched sibling donor. Neutrophil recovery (86% at day-28) was higher with total body irradiation-containing conditioning regimen and in younger recipients (aged < or =16 years) receiving grafts from older donors (aged >40 years). Recovery was lower after mismatched transplants and transplantsations prior to 1997. Mortality rates were higher after mismatched transplants, in recipients with a poor performance score, and when the interval between diagnosis and transplantation was longer than 4 years. When restricted to donor-recipient pairs with allele-level HLA typing (8-loci; n = 118), mortality rates were also higher after mismatched transplants and older recipients receiving grafts from older donors; 5-year probabilities of overall survival after HLA-A, -B, -C, -DRB1 matched and mismatched transplants adjusted for donor and recipient age were 57% and 39%, respectively (P = 0.008). The authors concluded that unrelated donor transplantation is an acceptable alternative for children; early referral for transplantation and identification of an HLA-matched (allele-level) donor offers the best outcome. 14

Allogeneic hematopoietic stem cell transplantation may also be an option under specific circumstances for Diamond-Blackfan anemia (DBA), Fanconi’s anemia (FA) and paroxysmal nocturnal hemoglobinuria. In a report from the DBA registry, 20 of 354 registered individuals underwent hematopoietic stem cell transplantation, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts (Gluckman, 2008). Dufour and colleagues (2008) reported in a summary of allogeneic hematopoietic stem cell transplantation from matched related donors over 6 years in FA, totaling 103 individuals, that overall survival ranged from 83–88%, with transplant-related mortality ranging from 8%–18.5% and average chronic GVHD of 12%. Santarone and colleagues (2010) performed a retrospective study of 26 individuals with paroxysmal nocturnal hemoglobinuria and concluded that hematopoietic stem cell transplantation may lead to a long-term...
cure rate as high as 60% in a heterogeneous cohort of seriously ill individuals with paroxysmal nocturnal hemoglobinuria.  

Congenital amegakaryocytic thrombocytopenia (CAMT), dyskeratosis congenital, pure red cell aplasia and paroxysmal nocturnal hemoglobinuria are rare bone marrow failure disorders that respond to allogeneic hematopoietic stem cell transplantation. Small studies and case reports have shown favorable outcomes in these disorders.  

Professional Organizations: National Marrow Donor Program (NMDP): The NMDP lists severe aplastic anemia and other bone marrow failure (including Fanconi anemia, Diamond-Blackfan anemia and others) as indications for HSCT.  

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**Government Agency**


**Peer Reviewed Publications**


Professional Society Guidelines


38. Choosing Wisely Canada: Don't routinely use peripheral blood stem cells for patients with aplastic anemia when a suitable bone marrow donor is available due to a higher risk of graft-versus-host disease. Blood and Marrow Transplant. Five Things Physicians and Patients Should Question: American Society for Blood and Marrow Transplantation Canadian Blood and Marrow Transplant


Other Resources


➢ Negrin R. Hematopoietic cell transplantation in aplastic anemia in adults.
➢ Kahn S, Negrin R. Hematopoietic cell transplantation for idiopathic severe aplastic anemia and Fanconi anemia in children and adolescents.
➢ Schrier S, Bertuch A. Acquired aplastic anemia in children and young adults.
➢ Rogers Z. Shwachman-Diamond syndrome.
➢ Fuchs E, Luznik L. HLA-haploidentical hematopoietic cell transplantation.

44. Advanced Medical Review:

➢ Policy reviewed by practicing MD board certified in Internal Medicine, Oncology and Hematology, 2013.
➢ Policy reviewed by practicing MD board certified in Oncology, Hematology. 11/8/19.

Review/Revision History:

6/26/13: Policy created
6/2/15: This policy was updated with new pretransplant criteria.
9/21/16: The medical necessity criteria was reviewed and updated to include the following disorders: Diamond-Blackfan anemia (DBA) Fanconi’s anemia (FA) and Schwachman-Diamond syndrome (SDS). Professional guidelines are reference sections were updated.
9/19/17: Policy reviewed, no changes
7/10/18: Policy reviewed, no changes
12/10/19: The policy was reviewed and updated to include the following disorders: Pure red cell aplasia, Paroxysmal nocturnal hemoglobinuria, congenital amegakaryocytic thrombocytopenia (CAMT), Dyskeratosis congenital. Updated guidelines, coding and references sections. Clarified that haploidentical transplants may be considered medically necessary when there are no matched sibling or unrelated donors.