Molina Clinical Policy
Hematopoietic Stem Cell Transplantation for Hematologic Disorders: Policy No. 456

Initial Approval: 6/12/2024
Next Review Due By: June 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. 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 (e.g., 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 MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers hematopoietic stem cell transplantation for the following diseases:

Aplastic Anemia	Beta Thalassemia Major	Congenital Amegakaryocytic Thrombocytopenia
Diamond-Blackfan Anemia	Dyskeratosis Congenital	Fanconi's Anemia
Myelodysplastic Syndromes	Paroxysmal Nocturnal Hemoglobinuria	Pure Red Cell Aplasia
Schwachman-Diamond Syndrome	Sickle Cell Disease	

Hematopoietic stem cell transplantation (HSCT) refers to transplantation of hematopoietic stem cells from a donor into a patient. Hematopoietic stem cells are immature cells that can develop into any of the three types of blood cells (red cells, white cells, or platelets). Hematopoietic stem cells are created in the bone marrow and are found there, in peripheral blood, and in high concentrations in umbilical-cord blood. HSCT can be autologous (using the patient'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. As HLA variability increases, transplant-related morbidity and mortality (including graft rejection and graft-versus-host disease [GVHD]) also increases. HSCT can be utilized in the treatment of a variety of diseases from blood cancers to solid tumors (Chao 2024; Deeg & Sandmaier 2022; [1-2]Negrin 2022).

Haploidentical allogeneic HSCT is becoming a viable alternative for patients in need of a bone marrow transplant but lack a fully matched donor of stem cells. In general, allogeneic hematopoietic cell transplantation may cure a broad variety of malignant and non-malignant disorders. The hematopoietic stem cells required are obtained from a related or unrelated donor's bone marrow or peripheral blood. For best outcomes, the stem cell donor is a human leukocyte antigen (HLA)-matched sibling; however, there is only a 25% chance a sibling will be a full match for a patient in need of a stem cell transplant. When there is not an HLA-matched sibling, alternative sources of donor grafts may be used including suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical donors are options. Haploidentical related donors have a 50% match for important HLA markers. There are advantages and disadvantages of HLA-haploidentical HSCT. Advantages include the rapid availability of donor stem cell sources from family and graft versus leukemic effect which may improve overall survival. Haploidentical family members are available much faster than the many months it takes to conduct a nationwide search for unrelated donors, which means this alternative donor source may be especially relevant for minority ethnic groups for which well-matched unrelated donors are less common. The disadvantages of haploidentical allogeneic HSCT is alloreactivity leading to graft rejection and GVHD (Fuchs & Luznik 2021; [1]NCCN 2024).

Aplastic anemia, also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder that is characterized by pancytopenia and 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 parvovirus 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 present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and fatigue due to anemia. The diagnosis of aplastic anemia is established following bone marrow aspiration and biopsy. Aplastic anemia is classified as non-severe, severe, and very severe based on the degree of the peripheral blood cytopenias. Allogeneic HSCT from an HLA-matched sibling donor (MSD) can provide curative therapy for individuals with severe aplastic anemia. Allogeneic HSCT 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 (Khan & Myers 2024; Negrin 2024; Olson 2022; Olson & Dunbar 2023; Rogers & Myers 2022; Fuchs & Luznik 2021).

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by chronic hemolytic anemia and intermittent painful obstruction of blood vessels (vaso-occlusive crisis). The trademark feature of SCD is the presence of sickle-shaped red blood cells on peripheral blood smear. The disease can occur in individuals of any ethnicity, but is most common in individuals of African, Caribbean, Mediterranean, Middle Eastern, and Indian ancestry. Approximately 1 in 500 African American infants born in the United States are diagnosed with SCD which has led to screening panels in newborns. Approximately 60-70% of SCD cases in the United States are caused by a homozygous (e.g., present on both copies of the gene) variant known as hemoglobin S (HbS). Other forms of SCD have the variant known as hemoglobin C (HbC). Various types of **thalassemia** are also classified as an inherited hemoglobinopathy characterized by anemia that affects males and females. The disorders occur most often among people of Italian, Greek, Middle Eastern, Southern Asian, and African descent. It is estimated that 1000 individuals in the U.S. have **beta thalassemia major**, the most severe form of thalassemia and the only form for which transplant is indicated (Krishnamurti & Nur 2024; Field & Vichinsky 2023; Vichinsky 2023; NHLBI 2022; [1-2]DynaMed 2024; SCDAA 2021).

COVERAGE POLICY

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 reviewed 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.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Please see *MCP-459 Pre-Transplant and Transplant Evaluation* for pre-transplant criteria and transplant evaluation criteria that must be met prior to hematopoietic stem cell transplantation (HSCT).

I. Aplastic Anemia

Medically Necessary

1. *Allogeneic HSCT* may be **considered medically necessary** in adults and children who have a **fully matched human leukocyte antigen (HLA) sibling donor** for the treatment of bone marrow failure syndrome when **ALL** the following criteria are met:
    a. **ALL** Transplant Evaluation criteria are met
    b. Member is < 60 years of age
    c. Member has **ANY** of the following rare bone marrow failure disorders:
        i. Diamond-Blackfan anemia

ii. Fanconi's anemia
iii. Schwachman-Diamond syndrome
iv. Pure red cell aplasia
v. Paroxysmal nocturnal hemoglobinuria
vi. Congenital amegakaryocytic thrombocytopenia
vii. Dyskeratosis congenital

d. For Members with a diagnosis of aplastic anemia not caused by any of the bone marrow failures listed in criteria 1c **AND** > 50 years of age: Member must have failed at least one course of immunosuppressive therapy with antithymocyte globulin and cyclosporin

e. Member has a diagnosis of aplastic anemia (includes congenital and acquired) defined as **ONE** of the following:
   i. Severe aplastic anemia with **ONE** of the following:
      1. A marrow biopsy showing < 25% of normal cellularity
      2. A marrow biopsy showing < 50% normal cellularity in which fewer than 30% of the cells are hematopoietic and at least **TWO** of the following are present:
         a. Absolute reticulocyte count < 40,000/microL
         b. Absolute neutrophil count (ANC) < 500/microL
         c. Platelet count < 20,000/microL
   ii. Very severe aplastic anemia defined as an ANC of < 200/microL

f. Stem cells are obtained from bone marrow

2. *Haploidentical Allogeneic HSCT* may be **considered medically necessary** when there are no matched sibling or well matched unrelated donors, and **ALL** allogenic transplant criteria are met in addition to **ALL** the following:

   a. Member receiving transplant has met all disease specific criteria for HSCT transplantation

   b. Donor is medically, socially, and psychologically fit to donate

   c. Donor age <40 years preferred over donor age ≥40 years

   d. No major ABO incompatibility between donor and recipient; major ABO incompatibilities include:
      i. Recipient blood type O: Donor type A, B, or AB
      ii. Recipient blood type A: Donor blood type B or AB
      iii. Recipient blood type B: Donor blood type A or AB
      iv. Recipient blood type AB: No major ABO incompatibilities

   e. Matched cytomegalovirus (CMV) IgG serologic status between the donor and the recipient include:
      i. For a recipient who is CMV IgG negative, use a CMV IgG negative donor
      ii. For a recipient who is CMV IgG positive, use a CMV IgG positive donor

   f. Use an ABO compatible donor over a minor ABO incompatible donor (ABO compatible transplants are O→O, A→A, B→B, or AB→AB).

3. *Allogeneic HSCT* may be **considered medically necessary** in adults and children who have a matched unrelated donor for the treatment of bone marrow failure syndrome when **ALL** the following criteria are met:

a. **ALL** Transplant Evaluation criteria are met

b. Member is < 60 years of age

c. Member has **ANY** of the following rare bone marrow failure disorders:
   i. Diamond-Blackfan anemia
   ii. Fanconi's anemia
   iii. Schwachman-Diamond syndrome
   iv. Pure red cell aplasia
   v. Paroxysmal nocturnal hemoglobinuria
   vi. Congenital amegakaryocytic thrombocytopenia
   vii. Dyskeratosis congenital

d. For Members with a diagnosis of aplastic anemia not caused by any of the bone marrow failure disorders listed in criteria 3c: Member has failed at least one course of immunosuppressive therapy with antithymocyte globulin and cyclosporin

e. Member has a diagnosis of aplastic anemia (includes congenital and acquired) defined as **ONE** of the following:
   i. Severe aplastic anemia including **ONE** of the following:
      1. A marrow biopsy showing < 25% percent of normal cellularity
      2. A marrow biopsy showing < 50% percent normal cellularity in which < 30% of the cells are hematopoietic and at least **TWO** of the following are present:
         a. Absolute reticulocyte count < 40,000/microL
         b. ANC < 500/microL
         c. Platelet count < 20,000/microL
   ii. Very severe aplastic anemia defined as an ANC of < 200/microL

f. Stem cells are obtained from bone marrow

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat autologous or allogeneic (ablative or non-myeloablative) HSCT due to persistent, progressive, or early relapsed disease

2. Autologous HSCT

3. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant

4. Haploidentical HSCT is considered investigational when the following contraindications are present:

   a. Donor is medically or psychologically unfit

   b. Recipient has anti-donor HLA antibodies of sufficient strength to result in a positive crossmatch result by flow cytometry or by complement-dependent cytotoxicity assay

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

II. Sickle Cell Disease / Thalassemia Major

Medically Necessary

1. *Allogeneic HSCT*, ablative or non-myeloablative, from an HLA-matched donor (e.g., at least six out of eight match of the HLA-A, HLA-B, HLA-C and HLA-DRB1 markers) for the treatment of a child or adolescent at increased risk of complications of sickle cell disease or thalassemia major may be approved when **ALL** Transplant Evaluation criteria are met and **ANY** of the following criteria are met:

    a. In children and adolescents with **sickle cell disease** who are ≤ 16 years of age who have **ONE or more** of the following:
        i. Stroke or central nervous system event lasting longer than 24 hours
        ii. Progressive neurologic deterioration (e.g., abnormal cerebral MRI and arteriogram) and impaired neuropsychiatric testing
        iii. Recurrent acute chest syndrome or Stage I or II sickle lung disease
        iv. Recurrent vaso-occlusive painful episodes
        v. Sickle nephropathy glomerular filtration rate 30-50% of predicted normal
        vi. Osteonecrosis of multiple joints

    b. In children and adolescents with **thalassemia major** who are ≤ 16 years of age and have deterioration with conventional treatments including transfusions, splenectomy, and deferoxamine

2. *Repeat Allogeneic HSCT* may be **considered medically necessary** only one time in the case of primary graft failure **OR** failure to engraft*

*NOTE: Engraftment is defined as the first 3 consecutive days on which the ANC exceeds 0.5 x 10^9/L or ANC > 500 u/L at any time after transplantation.

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat autologous or allogeneic (ablative or non-myeloablative) HSCT due to persistent, progressive, or early relapsed disease

2. Autologous HSCT

3. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Aplastic Anemia

ElGohary et al. (2020) completed a meta-analysis and systematic review with the goal of assessing "the feasibility and safety of haploidentical HSCT in patients with severe and very severe [aplastic anemia]." The primary outcomes measured included the incidence of grades II-IV acute GVHD and chronic GVHD, transplant-related mortality (incidence of death without disease progression), and the rate of successful engraftment. Secondary outcomes measured included regimen-related toxicity, post-transplant lymphoproliferative disease, hemorrhagic cystitis, and the occurrence of cytomegalovirus and Epstein-Barr virus viremia ≤ 100 days post-transplant. A total of 15 studies with a total of 577 patients were included in the meta-analysis. Pooled results showed an overall engraftment rate of 97.3% with reduced intensity conditioning regimens having a greater proportion of engraftment success compared to non-

myeloablative conditioning regimens (97.7% vs 91.7%, p = 0.03). GVHD prophylaxis regimens did not appear to have a significant effect on engraftment success. The overall rate of acute GVHD (grade II-IV) was 26.6% with a lower rate noted in non-myeloablative conditioning regimens (18.7% vs 29.5%, p = 0.008). Conditioning regimens containing post-transplant cyclophosphamide were also associated with a lower rate of acute GVHD when compared to methotrexate and other regimens (18.7%, 28.6%, and 27.8% respectively, p = 0.02). The overall rate of chronic GVHD was 25% with no significant differences noted between conditioning regimens. The pooled rate of transplant-related mortality was 6.7% with no significant differences between reduced intensity conditioning and non-myeloablative conditioning regimens (5.3% vs 11.8%, p = 0.15). The use of post-transplant cyclophosphamide for GVHD prophylaxis led to "a relative, but nonsignificant, increase in the incidence of mortality per year (27.9%) as compared with [methotrexate] (6.5%) and other regimens (5.6%, p = 0.06)." The pooled rate of regimen-related toxicity was 6.2% and the pooled rate of hemorrhagic cystitis was 21.6% with no differences noted for conditioning or GVHD prophylaxis regimens in either outcome. The rate of cytomegalovirus infection was 44.3% with non-myeloablative conditioning regimens favoring lower rates of infection compared to reduced intensity conditioning (21.61% vs 53.3%, p = 0.04). Post-transplant cyclophosphamide was associated with a significantly lower incidence of cytomegalovirus infection compared to methotrexate and other regimens (10.4% vs 55.7% vs 38.6% respectively, p < 0.001). Researchers noted that conditioning regimens containing post-transplant cyclophosphamide or methotrexate "had a reduced incidence of [cytomegalovirus] infections in susceptible patients in comparison to other GVHD prophylactic regimens (0% and 2.1% vs 33.0% respectively, p < 0.001)." Epstein-Barr viral infections occurred in 23.8% of patients and post-transplant lymphoproliferative disease was reported in 1.5% of patients with no significant differences noted for conditioning or GVHD prophylaxis. Researchers noted that the engraftment outcomes for haploidentical HSCT appear favorable if a matched sibling or unrelated donor is not available for transplant. However, more research is needed to determine if there is a preferred conditioning regimen, GVHD prophylaxis regimen, or graft source to improve outcomes.

Zhang et al. (2019) completed a single-center, retrospective study to "explore the feasibility of upfront unrelated donor HSCT in the treatment of adult aplastic anemia." Inclusion criteria included: 1) a diagnosis of aplastic anemia based on the International AA Study Group criteria, 2) the patient received allogeneic HSCT as the first-line treatment, and 3) the patient did not receive horse antithymocyte globulin-based immunosuppressive therapy or cyclosporine A in the 6 months prior to enrollment. A total of 81 patients were enrolled in the study with 23 patients having an unrelated donor and 58 patients having an MSD. Seven of the 23 patients with an unrelated donor underwent mismatched unrelated donor HSCT, with 2 having a single mismatch at HLA-A, 2 having a single mismatch at HLA-C, and 3 having a single mismatch at HLA-DQB1. Both patient groups received conditioning therapy specific to the type of donor (unrelated vs. matched sibling). Engraftment was defined as "the first of an absolute neutrophil count ≥ 0.5x109/L for 3 consecutive days and a platelet count ≥ 20x109/L for the first day of 7 consecutive days without platelet transfusion." Patients were routinely monitored for acute and chronic GVHD, cytomegalovirus, and Epstein-Barr virus. Patients were treated preemptively in the event of cytomegaloviral or Epstein-Barr viral infections.

The primary outcome measured was failure-free survival with death, primary or secondary graft failure, and relapse being considered as treatment failure. The secondary outcome measured was overall survival. Rates of engraftment, GVHD, and complications were also reported. Propensity score matching was used "to reduce the influence of potential confounders." Results showed no differences between either group for neutrophil and platelet engraftment, though the time to engraftment was significantly longer in the unrelated donor group (median 101 days [range 21-230 days] vs 50.5 days [range 23-295 days]). The 5-year failure-free survival rates were 82.0 ± 10.2% for the unrelated donor group and 89.3 ± 4.6% for the MSD group (p = 0.404). The 5-year overall survival rates were 87.0 ± 9.1% for the unrelated donor group compared to 94.2 ± 3.3% for the MSD group (p = 0.501). Univariate and multivariate analyses showed a significant impact on failure-free survival and overall survival in patients with an ECOG score of 3 prior to transplantation. The incidence of grade II acute GVHD was higher in the unrelated donor group (21.7% vs 3.4%, p = 0.007). There were no incidences of grades III-IV acute GVHD in either group. The rates of chronic GVHD and extensive chronic GVHD were noted to be higher in the unrelated donor group but there was no statistical significance noted (18.2% vs 8.8%, p = 0.285). The incidence of cytomegalovirus infection was similar between groups (82.6% vs 70.7%, p = 0.270). No significant differences were noted between either group in rates of Epstein-Barr viral infections and Epstein-Barr post-transplantation lymphoproliferative disorder. Researchers noted that the results of this study suggest that HSCT from an unrelated donor is a feasible option when an MSD is not available in patients ages 14-55 years. Researchers noted additional studies comparing "upfront unmatched related donor HSCT with those undergoing first-line MSD HSCT or immunosuppressive therapy" are needed.

Sickle Cell Disease/Thalassemia Major

The published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of SCD and thalassemia major in selected individuals and consists of systematic reviews, retrospective and prospective multi-center clinical studies and case series. Several studies evaluated up to 485 SCD and thalassemia major symptomatic patients, the majority of whom received donor allografts from siblings who were HLA identical. The results from these series were similar, with overall survival rates ranging from 92–94% and event-free survival from 82–86% with a median follow-up ranging from 0.9–17.9 years (Arnold et al. 2017; Dedeken et al. 2014; Locatelli et al. 2013; Oringanje et al. 2013; Kavanagh et al. 2011).

Improved outcomes have not been demonstrated for autologous HSCT compared with allogeneic HSCT and conventional chemotherapy in individuals with sickle cell disease and thalassemia major therefore the role of autologous HSCT for this indication has not been established. Clinical trials are evaluating the role of unrelated donor HSCT in treating severe SCD and thalassemia major and enrolling children with a history of severe symptoms manifesting as strokes, frequent pain crises, or acute chest syndrome. Experience with myeloablative HSCT in older teenagers and adults with SCD and thalassemia major is insufficient and the role for this age group has not been established. A summary of the most relevant medical evidence is outlined below.

Locatelli et al. (2013) reported on the largest case series analyzed the outcomes of 485 patients with thalassemia major or SCD receiving HLA-identical sibling cord blood transplantation (CBT, n = 96) or bone marrow transplantation (BMT, n = 389). Compared with patients given BMT, CBT recipients were significantly younger (median age 6 vs 8 years, p = 0.02), and were treated more recently (median year 2001 vs 1999, p < 0.01). A higher proportion of patients with thalassemia major belonging to classes II-III of the Pesaro classification received BMT (44%) compared with CBT (39%, p < 0.01). In comparison with patients receiving BMT (n = 259, TM; n = 130, SCD), those given CBT (n = 66, TM; n = 30, SCD) had slower neutrophil recovery, less acute GVHD and none had extensive chronic GVHD. With a median follow-up of 70 months, the 6- year overall survival was 95% and 97% after BMT and CBT, respectively (p = 0.92). The 6-year disease-free survival was 86% and 80% in TM patients after BMT and CBT, respectively, whereas disease-free survival in SCD patients was 92% and 90%, respectively. The cell dose infused did not influence the outcome of patients given CBT. In multivariate analysis, Disease-free survival did not differ between CBT and BMT recipients. Patients with thalassemia major or SCD have excellent outcomes after both HLA identical sibling CBT and BMT.

Dedeken et al. (2014) reported on the outcomes of 50 consecutive children with severe SCD that received HSCT between November 1988 and April 2013 were reported. The stem cell source was bone marrow (n = 39), cord blood (n = 3), bone marrow and cord blood (n = 7) and peripheral blood stem cells (n = 1). All patients had > 1 severe manifestation: 37 presented with recurrent vaso-occlusive crises/acute chest syndrome, 27 cerebral vasculopathy and 1 nephropathy. The conditioning regimen consisted of busulfan +cyclophosphamide (BuCy) before November 1991 and BuCy + rabbit antithymocyte globulin after that date. Since 1995, all patients have been treated with hydroxycarbamide prior to transplantation for a median duration of 27 years. The median age at transplantation and median follow-up was 8.3 and 7.7 years, respectively. Acute GVHD and chronic GVHD were observed in 11 and 10 patients, respectively. An excellent outcome was achieved, with 8-year overall survival and event-free survival rates of 94.1% and 85.6%, respectively. Since hydroxycarbamide introduction, no graft failure occurred, and event-free survival reached 97.4%. Prior treatment with hydroxycarbamide may have contributed to successful engraftment.

Arnold et al. (2017) performed a retrospective study of children transplanted for SCD in the USA during 2000-2013 using two large databases. Univariate and Cox models were used to estimate associations of demographics, SCD severity, and transplant-related variables with mortality and chronic graft-versus-host disease. Among 161 patients with a 2-year overall survival rate of 90% (95% confidence interval [CI] 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (hazard ratio (HR) 21, 95% CI 2.8-160.8, P=0.003) and unrelated compared to MSD transplantation (HR 5.9, 95% CI 1.7-20.2, p = 0.005). Chronic GVHD was significantly more frequent among those transplanted late (HR 1.9, 95% CI 1.0-3.5, p = 0.034) and those who received an unrelated graft (HR 2.5, 95% CI 1.2-5.4; p = 0.017).

Haploidentical Transplantation for Sickle Cell Disease

Kassim et al. (2024) reported phase 2 results of a prospective, multicenter international trial of 70 individuals with sickle cell anemia treated with nonmyeloablative haploidentical bone marrow transplant (NCT01850108). Participants were aged 1-70 years and had an ECOG performance score of 0 or 1 or a Karnofsky score > 70. No adults were excluded

because of stroke or severe pre-existing heart, lung, or kidney disease. Participants lacked an HLA matched sibling donor but had a haploidentical donor available. Thiotepa was added to the conditioning regimen to improve engraftment and post-transplant cyclophosphamide was added to reduce GVHD.

Overall survival at one year was 96% and 94% at 2 years. This transplant protocol is a marked improvement over historical haploidentical transplants that had a 40% graft failure rate. The overall survival in this study approaches those seen in HLA matched allogeneic stem cell transplants. Graft failure occurred in 11.4% of participants, all of which were less than 18 years old. All participants with failed grafts received autologous reconstitution and were alive at follow-up. There were five deaths from infectious complications. Additional evaluations will be needed to understand why graft failure occurred more often in adolescents.

Leonard et al. (2023) reported data from another prospective, phase 2 trial (NCT03263559) of haploidentical HSCT in individuals with severe sickle cell anemia. This trial was a multi-center, single arm trial that also used reduced intensity myeloablative conditioning with thiotepa and post-transplant cyclophosphamide. The trial differed from the Kassim et al. (2024) haploidentical HSCT trial in that it included hydroxyurea and red blood cell transfusion preconditioning. There were 42 participants that proceeded to HSCT. The main indications for transplant were recurrent vaso-occlusive pain episodes, acute chest syndrome, or overt stroke. The primary outcome, event free survival at 2 years, was 88%, and the 2-year overall survival was 95%. There were 2 deaths related to organ failure and acute respiratory distress syndrome.

While there is an unmet need for disease modifying treatments in individuals with advanced sickle cell disease and end organ damage, a phase three trial has not yet been conducted. Until then, patients with advanced sickle cell disease with end organ damage are best treated and monitored within a clinical trial.

Haploidentical Transplantation

DeZern et al. (2023) reported results from a phase 2 trial (NCT02833805). The trial design was a single arm, single center, prospective, bone marrow transplantation for patients with severe aplastic anemia who do not have a fully matched HLA donor. This phase 2 trial used non-myeloablative conditioning and transplantation of partially HLA-Mismatched/Haploidentical related or matched unrelated donor bone marrow. The median patient age was 25 years and median follow-up time was 40.9 months. The protocol for the HLA-haploidentical HSCT included post transplantation cyclophosphamide based GVHD prophylaxis and reduced intensity conditioning. The haploidentical HSCT group that received 400cGy of total body irradiation had 100% overall survival with minimal GVHD in 20 consecutive patients.

Yang et al. (2019) published a systematic review and meta-analysis of haploidentical versus matched donor stem cell transplantation for patients with hematologic malignancies. Twenty-five studies enrolling 11,359 patients were included (haploidentical HSCT n = 2677; Matched HSCT n = 8682). Matched HSCT and haploidentical HSCT had similar risks for all primary endpoints including acute and chronic GVHD, nonrelapse mortality, and 1-year cumulative incidence of relapse. The authors concluded that haploidentical HSCT is a safe and effective transplant option for those that lack a matched donor, however a caveat was noted with regard to its suitability for patients who receive reduced intensity chemotherapy.

National and Specialty Organizations

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published guidelines for indications for HSCT and immune effector cell therapy (Kanate et al. 2020). The guidelines make recommendations for allogeneic and autologous HSCT based on the strength and availability of published evidence for each disease process. Recommendations are also made based on patient age (< 18 years and ≥ 18 years).

The **American Society of Hematology (ASH)** published *2021 Guidelines for Sickle Cell Disease: Stem Cell Transplantation* (Kanter et al. 2021). The guidelines make the following recommendations regarding HSCT for SCD:

- "The ASH guideline panel suggests HLA-matched related HSCT rather than standard of care (hydroxyurea/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (conditional recommendation, very low certainty in the evidence).
    - Consideration for transplantation should occur in all patients with neurologic injury who have a matched related sibling donor.

    - When considering transplantation for neurologic injury, children younger than age 16 years who receive MSD HSCT have better outcomes than those older than age 16 years.
- For patients with frequent pain, the ASH guideline panel *suggests* using related matched allogeneic transplantation…[for] patients who do not respond or have an inadequate response to standard of care, such as hydroxyurea, new targeted therapies, or chronic transfusion therapies (conditional recommendation, very low certainty in the evidence about effects).
- For patients with recurrent episodes of [acute coronary syndrome]…[despite optimal standard of care], the ASH guideline panel *suggests* using matched related allogeneic transplantation over standard of care (e.g., hydroxyurea, L-glutamine, crizanlizumab, and chronic transfusion therapy) (conditional recommendation, very low certainty in the evidence about effects).
- For patients with SCD with an indication for HSCT who lack a MSD, the ASH guideline panel *suggests* using transplants from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects).
- For allogeneic HSCT, the ASH guideline panel *suggests* using either total-body irradiation ≤ 400 cGy or chemotherapy-based conditioning regimens (conditional recommendation, very low certainty in the evidence about effects).
- For children with SCD who have an indication for allogeneic HSCT and a MSD, the ASH guideline panel *suggests* using myeloablative conditioning over reduced intensity conditioning that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects).
- For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over reduced intensity conditioning that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects).
- In patients with an indication eligible for HSCT, the ASH guideline panel *suggests* using allogeneic transplantation at an earlier age rather than an older age (conditional recommendation, low certainty in the evidence about effects).
    - Recommendations could not be made if an MSD was not available because of the paucity of available data.
    - The impact of age on HSCT outcome may also be affected by the conditioning regimen used.
- The ASH guideline panel *suggests* the use of HLA-identical sibling cord blood when available (and associated with an adequate cord blood cell dose and good viability) over bone marrow (conditional recommendation, very low certainty in the evidence about effects)."

The **Fanconi Anemia Research Fund**, part of the Fanconi Cancer Foundation, published the *Fanconi Anemia Clinical Care Guidelines 5th edition* with the following recommendations for HSCT for the treatment of Fanconi's anemia (Sroka et al. 2020):

- "For patients without a 10/10 or 9/10 matched related donor, 10/10 or 9/10 matched adult unrelated donor and 10-8/10 (or perhaps less) matched umbilical cord blood are associated with good outcomes.
- Transplant without radiation can be successful for patients with Fanconi's anemia.
- Radiation during transplant is clearly associated with increased risk of later cancer in larger series of persons without Fanconi's anemia. More studies are needed to determine if radiation or a radiation-free conditioning protocol increases the risk of cancer in patients with Fanconi's anemia.
- In transplanted Fanconi's anemia patients, development of chronic or acute GVHD increases the risk of later cancer."
- Haploidentical transplant can be a viable option if there are no other donor options available.
- Survival rates following alternate donor transplant continue to improve and outcomes from related and unrelated donors are similar.

The **National Heart, Lung, and Blood Institute (NHLBI) (2014)** published the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report. A section on hematopoietic cell transplantation is included, noting that HSCT is the only therapy for sickle cell disease that has curative potential. The NHLBI recommends that children with sickle cell disease who experience significant, noninfectious complications caused by vaso-occlusion should be considered for HSCT. If full siblings are available, HLA typing should be performed as results are best when performed in children with a sibling donor who is HLA-identical. HSCT is recommended for patients who have experienced significant complications caused by sickle cell disease (e.g., stroke, recurrent episodes of acute chest syndrome or pain). Further research is needed on the identification of clinical or genetic markers that reliably predict an adverse outcome thereby

allowing the application of HSCT before significant clinical complications occur. The need for additional research is reiterated for transplantation for those with sickle cell disease.

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant* ([1-6] NMDP date unknown).

CODING & BILLING INFORMATION

CPT(Current Procedural Terminology) Codes

Code	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38230	Bone marrow harvesting for transplantation; allogeneic
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor 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
	Cell Infusion Codes
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions
38243	Hematopoietic progenitor cell (HPC); HPC boost
	Histocompatibility and Biopsy Codes
38221	Diagnostic bone marrow; biopsy(ies)
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
86812	HLA typing; A, B, or C (e.g., A10, B7, B27), single antigen
86813	HLA typing; A, B, or C, multiple antigens
86816	HLA typing; DR/DQ, single antigen
86817	HLA typing; DR/DQ, multiple antigens

HCPCS (Healthcare Common Procedure Coding System) Codes

Code	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 or pre-and post-transplant care in the global definition

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper

billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

06/12/2024 New policy created by condensing MCPs 143 and 209 into a single policy. Changes to criteria include clarification that a failed course of immunosuppressive therapy is only for those with aplastic anemia. Haploidentical transplant criteria for aplastic anemia moved from MCP 362 to this policy. IRO Peer Review on June 3, 2024, by a practicing, board-certified physician with specialties in Hematology, Medical Oncology, and Internal Medicine.

REFERENCES

1. Arnold SD, Brazauskas R, He N, et al. Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases. Haematologica. 2017 Nov;102(11):1823-1832. Doi: 10.3324/haematol.2017.169581. Epub 2017 Aug 17. PMID: 28818869; PMCID: PMC5664386.
2. Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid. 2022 Jul;1(7):EVIDoa2200008. Doi: 10.1056/EVIDoa2200008. Epub 2022 Jun 12. PMID: 38319256.
3. Chao NJ. Selection of an umbilical cord blood graft for hematopoietic cell transplantation. Updated March 20, 2024. Accessed May 9, 2024.www.uptodate.com.
4. Dedeken L, Lê PQ, Azzi N, et al. Haematopoietic stem cell transplantation for severe sickle cell disease in childhood: a single centre experience of 50 patients. Br J Haematol. 2014 May;165(3):402-8. Doi: 10.1111/bjh.12737. Epub 2014 Jan 16. PMID: 24433465.
5. Deeg HJ, Sandmaier B. Determining eligibility for allogeneic hematopoietic cell transplantation. Updated February 21, 2022. Accessed May 7, 2024.www.uptodate.com.
6. DeZern AE, Zahurak M, Symons HJ, et al. Alternative donor BMT with posttransplant cyclophosphamide as initial therapy for acquired severe aplastic anemia. Blood. 2023 Jun 22;141(25):3031-3038. doi: 10.1182/blood.2023020435. PMID: 37084383.
7. [1]DynaMed. Sickle cell disease in adults and adolescents. EBSCO Information Services. Updated May 9, 2024. Accessed May 10, 2024. www.dynamed.com.
8. [2]DynaMed. Sickle cell disease in infants and children. EBSCO Information Services. Updated March 1, 2024. Accessed May 10, 2024. www.dynamed.com.
9. ElGohary G, El Fakih R, de Latour R, et al. Haploidentical hematopoietic stem cell transplantation in aplastic anemia: A systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT). Bone Marrow Transplant. 2020 Oct;55(10):1906-1917. Doi: 10.1038/s41409-020-0897-2. Epub 2020 Apr 28. PMID: 32346079.
10. Field JF, Vichinsky EP. Overview of the management and prognosis of sickle cell disease. Updated October 18, 2023. Accessed May 10, 2024. www.uptodate.com.
11. Fuchs EJ, Luznik L. HLA-haploidentical hematopoietic cell transplantation. Updated July 16, 2021. Accessed May 7, 2024. http://www.uptodate.com.
12. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020 Jul;26(7):1247-1256. doi: 10.1016/j.bbmt.2020.03.002. Epub 2020 Mar 9. PMID: 32165328.
13. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: Stem cell transplantation. Blood Adv. 2021 Sep 28;5(18):3668-3689. doi: 10.1182/bloodadvances.2021004394C. PMID: 34581773; PMCID: PMC8945587.
14. Kassim AA, de la Fuente J, Nur E, et al. An International Learning Collaborative phase 2 trial for haploidentical bone marrow transplant in sickle cell disease. Blood. 2024 Mar 17:blood.2023023301. doi: 10.1182/blood.2023023301. Epub ahead of print. PMID: 38493482.
15. Kavanagh PL, Sprinz PG, Vinci SR, et al. Management of children with sickle cell disease: a comprehensive review of the literature. Pediatrics. 2011 Dec;128(6):e1552-74. doi: 10.1542/peds.2010-3686. Epub 2011 Nov 28. PMID: 22123880.
16. Khan S, Myers KC. Hematopoietic cell transplantation (HCT) for inherited bone marrow failure syndromes (IBMFS). Updated April 12, 2024. Accessed May 7, 2024. http://www.uptodate.com.
17. Krishnamurti L, Nur E. Curative therapies in sickle cell disease including hematopoietic stem cell transplantation and gene therapy. Updated May 2, 2024. Accessed May 10, 2024. www.uptodate.com.
18. Locatelli F, Kabbara N, Ruggeri A, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood. 2013 Aug 8;122(6):1072-8. doi: 10.1182/blood-2013-03-489112. Epub 2013 May 21. PMID: 23692854.
19. Melaragno JI, Bowman LJ, Park JM, et al. The clinical conundrum of cannabis: Current practices and recommendations for transplant clinicians: An opinion of the immunology/transplantation PRN of the American College of Clinical Pharmacy. Transplantation. 2021 Feb 1;105(2):291-299. Doi: 10.1097/TP.0000000000003309. PMID: 32413017.
20. [1]National Comprehensive Cancer Network (NCCN). Hematopoietic cell transplantation (HCT) (v. 1.2024). Updated April 26, 2024. Accessed May 10, 2024. https://www.nccn.org/guidelines/category_3.
21. [2]National Comprehensive Cancer Network (NCCN). Myelodysplastic syndromes (v. 2.2024). Updated May 22, 2024. Accessed May 29, 2024. https://www.nccn.org/guidelines/category_1.
22. National Heart, Lung, and Blood Institute (NHLBI). What is thalassemia? Updated May 31, 2022. Accessed May 10, 2024. https://www.nhlbi.nih.gov/health/thalassemia.
23. National Heart, Lung, and Blood Institute (NHLBI). Evidence-based management of sickle cell disease: Expert panel report, 2014. Published 2014. Accessed May 13, 2024. https://www.nhlbi.nih.gov/guidelines.
24. [1] National Marrow Donor Program (NMDP). Disease-specific HCT indications and outcomes data. Accessed April 29, 2024. https://bethematchclinical.org
25. [2] National Marrow Donor Program (NMDP). Engraftment. Accessed April 29, 2024. https://bethematchclinical.org

26. [3] National Marrow Donor Program (NMDP). HLA matching. Accessed April 29, 2024. https://bethematchclinical.org
27. [4] National Marrow Donor Program (NMDP). Patient eligibility for HCT. Accessed April 29, 2024. https://bethematchclinical.org
28. [5] National Marrow Donor Program (NMDP). Transplant consultation timing guidelines. Accessed April 29, 2024. https://bethematchclinical.org
29. [6] National Marrow Donor Program (NMDP). Treatment before transplant. Accessed April 29, 2024. https://bethematchclinical.org
30. Negrin RS. Hematopoietic cell transplantation for aplastic anemia in adults. Updated April 10, 2024. Accessed May 7, 2024. www.uptodate.com.
31. [1]Negrin RS. Donor selection for hematopoietic cell transplantation. Updated November 21, 2022. Accessed May 7, 2024. www.uptodate.com.
32. [2]Negrin RS. Immunotherapy for the prevention and treatment of relapse following allogeneic hematopoietic cell transplantation. Updated August 24, 2022. Accessed May 10, 2024. www.uptodate.com.
33. Olson TS. Acquired aplastic anemia in children and adolescents. Updated March 29, 2022. Accessed April 30, 2024. http://www.uptodate.com.
34. Olson TS, Dunbar CE. Treatment of aplastic anemia in adults. Updated December 4, 2023. Accessed April 30, 2024. http://www.uptodate.com.
35. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev. 2013 May 31;(5):CD007001. doi: 10.1002/14651858.CD007001.pub3. Update in: Cochrane Database Syst Rev. 2016;(5):CD007001. PMID: 23728664.
36. Rogers ZR, Myers KC. Shwachman-Diamond syndrome. Updated August 12, 2022. Accessed May 2, 2024. http://www.uptodate.com.
37. Sickle Cell Disease Association of America (SCDAA). What is sickle cell disease (SCD)? Updated 2021. Accessed May 10, 2024. https://www.sicklecelldisease.org.
38. Sroka I, Frohnmayer L, Van Ravenhorst S, et al. Fanconi anemia clinical care guidelines (5th edition). Published 2020. Accessed May 14, 2024. https://www.fanconi.org.
39. Vichinsky EP. Overview of the clinical manifestations of sickle cell disease. Updated August 31, 2023. Accessed May 10, 2024. www.uptodate.com.
40. Yang B, Yu R, Cai L, et al. Haploidentical versus matched donor stem cell transplantation for patients with hematological malignancies: a systemic review and meta-analysis. Bone Marrow Transplant. 2019 Jan;54(1):99-122. doi: 10.1038/s41409-018-0239-9. Epub 2018 Jul 9. PMID: 29988061.
41. Zhang Y, Wu L, et al. Comparable outcomes of first-line hematopoietic stem cell transplantation from unrelated and matched sibling donors in adult patients with aplastic anemia: A retrospective single-center study. Biol Blood Marrow Transplant. 2019 Aug;25(8):1567-1575. doi: 10.1016/j.bbmt.2019.03.020. Epub 2019 Mar 26. PMID: 30926448.