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

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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 the infusion of multipotent hematopoietic stem cells into a recipient, using cells from either a donor or the patient's own body, to restore hematopoietic function. Hematopoietic stem cells are immature cells that can differentiate into erythrocytes, leukocytes, or platelets, and are typically harvested from bone marrow, peripheral blood, or umbilical cord blood. HSCT can be autologous (using the patient's own stem cells) or allogeneic (using donor-derived stem cells). In allogeneic HSCT, optimal outcomes are achieved when the donor is human leukocyte antigen (HLA)-identical, usually a sibling. HLA mismatched or haploidentical transplants increase the risk of graft rejection and non-malignant hematological conditions. HSCT can be utilized in the treatment of a variety of diseases from blood cancers to solid tumors (Chao 2024; Deeg & Sandmaier 2025; Khaddour et al. 2023; [1-2]Negrin 2025).

Haploidentical allogeneic HSCT is an increasingly viable alternative for patients lacking a fully HLA-matched donor. The hematopoietic stem cells required are obtained from a related or unrelated donor's bone marrow or peripheral blood. For optimal outcomes, the preferred donor is a HLA-matched sibling, though there is only a 25% chance a sibling will be a full match. 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, partially HLA-mismatched, or HLA-haploidentical donors. Haploidentical related donors have a 50% match for important HLA markers. There are both benefits and challenges associated with HLA-haploidentical HSCT. Advantages include the greater and faster donor availability, particularly within families, and the potential for graft-versus-leukemic effect, which may improve long-term survival. Haploidentical donors are often accessible more quickly than the several months required to locate matched unrelated donors, a factor that is critical for patients of ethnic minor groups, for whom matched unrelated donors are less common. However, disadvantages include increased risk of graft rejection and graft-versus-host disease (GVHD) (Fuchs & Luznik 2024; NCCN 2026).

Aplastic anemia (AA), also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder marked by pancytopenia and hypocellular bone marrow. It can be acquired or congenital. The most common causes of acquired aplastic anemia include idiopathic etiology, hepatitis, certain medications, chemical exposures, autoimmune conditions, pregnancy, pure red cell anemia, paroxysmal nocturnal hemoglobinuria, and parvovirus B19 infection.

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Congenital AA is linked to genetic mutations in the hTR gene or to Fanconi anemia, a rare autosomal recessive inherited disorder. Affected individuals present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and fatigue from anemia. Diagnosis is confirmed through bone marrow aspiration and biopsy. AA is classified into moderate or non-severe, severe, and very severe categories, based on the degree of the cytopenia. Allogeneic HSCT from an HLA-matched sibling donor offers a curative option for individuals with severe AA. This approach is generally considered standard of care for individuals younger than 40 to 50 years of age, despite potential treatment-related morbidity and mortality. Older individuals or those without a rapidly available HLA-matched related donor often receive first-line immunosuppressive therapy; however, first-line HSCT with a matched unrelated or haploidentical donor is becoming an increasingly viable and sometimes preferred treatment option due to advances in care and prevention of GVHD (Fuchs & Luznik 2024; Khan & Myers 2024; Negrin 2024; Olson 2025; Olson & Dunbar 2025; Rogers & Myers 2025). Advances in HSCT and triple immunosuppressive therapy (anti-thymocyte globulin, cyclosporine, and eltrombopag) have significantly improved survival outcomes, with rates exceeding 80% (Nimmana & Penney 2025; Olson & Dunbar 2025).

Sickle cell disease (SCD) is an inherited hemoglobinopathy characterized by chronic hemolytic anemia and intermittent vaso-occlusive episodes. The hallmark of SCD is the presence of sickle-shaped red blood cells on peripheral blood smear. While the disease can occur in individuals of all ethnicities, it is most prevalent in populations of African, Caribbean, Mediterranean, Middle Eastern, and Indian ancestry. In the U.S., approximately 1 in 500 African American infants are born with SCD, prompting the implementation of newborn screening programs. Approximately 60-70% of SCD cases in the United States are caused by a homozygous inheritance of the hemoglobin S (HbS) gene. Other forms of SCD have the variant known as hemoglobin C (HbC). **Thalassemias** are also inherited hemoglobin disorders characterized by defective hemoglobin synthesis and chronic anemia. These disorders are most common in individuals of Italian, Greek, Middle Eastern, South Asian, and African backgrounds. It is estimated that fewer than 1000 individuals in the U.S. have **transfusion-dependent beta thalassemia,** also referred to as **thalassemia major**, the most severe form and the only form for which HSCT is considered a curative treatment (Field & Vichinsky 2026; Krishnamurti & Nur 2026; NHLBI 2022; SCDAA date unknown; Vichinsky & Field 2026).

RELATED POLICIES

MCP-459: Pre-Transplant and Transplant Evaluations
MCP-435: Omisirge (omidubicel-onlv)
MCP-449: Casgevy (exagamglogene autotemcel) for Beta Thalassemia
MCP-447: Casgevy (exagamglogene autotemcel) for Sickle Cell Disease
MCP-448: Lyfgenia (lovotibeglogene autoemcel)
MCP-420: Zyntenglo (betibeglogene autotemcel)

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 Evaluations* for pre-transplant criteria and transplant evaluation criteria that must be met prior to hematopoietic stem cell transplantation (HSCT)

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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 or an appropriate HLA well-matched donor for the treatment of aplastic anemia when ALL *MCP 459 Pre-Transplant and Transplant Evaluations* criteria are met, in addition to ALL the following criteria:
    a. Member has a diagnosis of ONE of the following:
        i. Severe aplastic anemia (congenital or acquired), defined as 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 (congenital or acquired), defined as meeting criteria for severe aplastic anemia above, with ANC < 200/microL
        iii. A rare bone marrow failure disorder, including ANY of the following:
            1) Diamond-Blackfan anemia
            2) Fanconi's anemia
            3) Schwachman-Diamond syndrome
            4) Pure red cell aplasia
            5) Paroxysmal nocturnal hemoglobinuria
            6) Congenital amegakaryocytic thrombocytopenia
            7) Dyskeratosis congenital
    b. Stem cell are obtained from bone marrow
    c. For Members above 50 years of age with acquired severe or very severe aplastic anemia: Member has failed at least one course of triple immunosuppressive therapy (i.e., antithymocyte globulin, cyclosporin and eltrombopag)
    For Members above 40 years of age with acquired severe or very severe aplastic anemia without a fully matched HLA sibling donor: Member has failed at least one course of triple immunosuppressive therapy (i.e., antithymocyte globulin, cyclosporin and eltrombopag)
    d. For Members under 40 years of age with or without a fully matched donor, failure of triple immunosuppressive therapy is not required

2. *Haploidentical Allogeneic HSCT* may be **considered medically necessary** when there are no HLA matched sibling or well-matched donors, and ALL allogenic transplant criteria above are met in addition to ALL the following:
    a. Donor is medically, socially, and psychologically fit to donate
    b. Recipient does not have anti-donor HLA antibodies of sufficient strength to result in a positive crossmatch result by flow cytometry or by complement-dependent cytotoxicity assay (i.e., a favorable immunological compatibility is established by the recipient lacking sufficient anti-donor antibodies that would result in donor cell death)
    c. Donor age < 40 years preferred over donor age ≥ 40 years
    d. Absence of 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 includes ONE of the following:
        i. For a recipient who is CMV IgG negative, use a CMV IgG negative donor

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

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat 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 Evaluations

Sickle Cell Disease / Thalassemia Major

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) from an appropriate HLA well-matched donor for the treatment of a Member* at increased risk of complications of sickle cell disease or thalassemia major may be **considered medically necessary** when ALL *MCP 459 Pre-Transplant and Transplant Evaluations* criteria are met, in addition to ANY of the following criteria are met:
   a. Members with sickle cell disease who have at least ONE 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. Members with thalassemia major who have deterioration with conventional treatments including transfusions, splenectomy, and deferoxamine

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

*NOTE: In adult Members (≥ 18 years old) with sickle cell disease or thalassemia major, HSCT should be considered with caution due to limited evidence and increased transplant-related risks (Kanter et al. 2021; Taher et al. 2025)

Investigational, Unproven, and/or Not Medically Necessary

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

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.

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SUMMARY OF MEDICAL EVIDENCE

Aplastic Anemia

Systematic Reviews and Meta-Analyses

ElGohary et al. (2020) completed a meta-analysis and systematic review with the goal of assessing to evaluate the feasibility and safety of haploidentical HSCT in patients with severe and very severe aplastic anemia (AA). The meta-analysis included 15 studies with a total of 577 patients. The primary outcomes measured included the incidence of grades II-IV acute graft-versus-host disease (GVHD), chronic GVHD, transplant-related mortality, and the engraftment success rate. Secondary outcomes measured included regimen-related toxicity, post-transplant lymphoproliferative disorder, hemorrhagic cystitis, and the occurrence of cytomegalovirus (CMV) and Epstein-Barr virus viremia within 100 days post-transplant. The pooled engraftment rate was 97.3%, with reduced intensity conditioning (RIC) regimens demonstrating superior outcomes compared to non-myeloablative conditioning (NMAC) regimens (97.7% vs 91.7%, p = 0.03). Engraftment success was not significantly affected by the choice of GVHD prophylaxis. The overall incidence of acute GVHD was 26.6%, with lower rates noted in NMAC regimens (18.7% vs 29.5%, p = 0.008). The use of post-transplant cyclophosphamide for GVHD prophylaxis was associated with a lower rate of acute GVHD compared to methotrexate and other prophylactic regimens (18.7% vs 28.6% vs 27.8% respectively; p = 0.02). Chronic GVHD occurred in 25% of patients, with no significant differences among conditioning regimens. The pooled transplant-related mortality rate was 6.7%, with no significant differences between RIC and NMAC regimens (5.3% vs 11.8%, p = 0.15). Post-transplant cyclophosphamide for GVHD prophylaxis was associated with a higher, though not statistically significant, annual mortality rate (27.9%) compared to 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 significant differences noted based on conditioning regimen or GVHD prophylaxis. The rate of CMV infection was 44.3% with significantly lower rates in the NMAC group compared to RIC (21.61% vs 53.3%, p = 0.04). Post-transplant cyclophosphamide was associated with significantly lower CMV infection rates compared to methotrexate and other regimens (10.4% vs 55.7% and 38.6%, p < 0.001). The study found that both post-transplant cyclophosphamide and methotrexate regimens had significantly reduced CMV infection rates in high-risk patients compared to other prophylactic strategies (0% and 2.1% vs 33.0%, p < 0.001). Epstein-Barr viral infections occurred in 23.8% of patients, while post-transplant lymphoproliferative disease was observed in 1.5%, with no notable differences across conditioning or prophylactic strategies. Overall, the study concluded that haploidentical HSCT is a promising option when a matched sibling or unrelated donor is unavailable. However, further research is needed to determine the optimal conditioning regimen, GVHD prophylaxis, and graft source to improve transplant outcomes.

Zhu et al. (2020) conducted a systematic review and meta-analysis comparing first-line allogeneic HSCT versus first-line immunosuppressive therapy (IST) for adults and children with acquired AA. The analysis included 15 retrospective studies published between 2000-2019, for a total of 5336 patients. Most studies involved severe aplastic anemia, though some also included very severe or non-severe types. Allogeneic donor types included matched related, matched unrelated, and haploidentical. The most common IST regimen was antilymphocyte globulin with or without cyclosporine. First-line allogeneic HSCT was associated with significantly longer overall survival rates compared with first-line IST, with a pooled hazard ratio (HR) of 0.4 (95% confidence interval [CI], 0.074-0.733, p = 0.016, I^2 = 58.8%). However, due to marked heterogeneity, a subsequent sensitivity analysis was performed. After the exclusion of 4 studies, the pooled HR for overall survival from the remaining 11 studies with 1875 patients was 0.955 (95% CI 0.443–1.468, P = 0.000, I^2 = 34.7%), which still supports statistically significant superiority of first-line HSCT versus IST for AA patients. Ten studies including 3339 patients reported on all-cause mortality, and no statistically significant difference was observed between treatment groups (relative risk [RR] 0.851, 95% CI 0.618–1.174, p = 0.327, I^2 = 57.1%). However, two studies, including 238 patients, reported on treatment-related mortality, which was significantly higher with first-line allogeneic HSCT than IST, with a pooled RR of 3.98, 95% CI 1.911–8.29, p = 0.000, I^2 = 0%). For study limitations, the authors noted selection bias, as younger patients with severe disease and available donors were more likely to receive transplantation while older patients, patients without donors, or patients with severe complications were more likely to receive IST. For example, the median age was 8-28 years in the allogeneic HSCT group and 6-55 years in the IST group. The authors concluded that overall survival is significantly longer in AA patients undergoing first-line allogeneic HSCT compared to first-line IST. However, initial treatment selection still requires a comprehensive evaluation of donor availability, age, expected quality of life, and risk of disease relapse.

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Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Zhang et al. (2019) conducted a single-center, retrospective study to evaluate the feasibility of upfront unrelated donor HSCT as a first-line treatment for adult patients with AA. Inclusion criteria were a diagnosis of AA based on the International AA Study Group criteria, receipt of allogeneic HSCT as initial therapy, and no prior treatment with horse antithymocyte globulin or cyclosporine A within the past 6 months. The study included 81 patients, with 23 receiving transplants from unrelated donors and 58 from matched sibling donors (MSD). Among those with unrelated donors, seven underwent mismatched HSCT, with single HLA mismatches at HLA-A (n=2), HLA-C (n=2), and HLA-DQB1 (n=3). Conditioning regimens were tailored based on donor type. Engraftment was defined as achieving an absolute neutrophil count ≥ $0.5x10^9$/L for three consecutive days and a platelet count ≥ $20x10^9$/L for seven consecutive days without platelet transfusion. The primary outcome was failure-free survival (FFS), with death, graft failure (primary or secondary), or relapse considered treatment failure. The secondary outcome was overall survival (OS). The study also reported on engraftment rates, GVHD incidence, and complications. Results showed no significant differences in neutrophil or platelet engraftment rates between groups, although the time to engraftment was significantly longer in the unrelated donor group (median 101 days vs 50.5 days; $p < 0.001$). The 5-year FFS was 82.0% ± 10.2% in the unrelated donor group and 89.3% ± 4.6% in the MSD group ($p = 0.404$), while the 5-year OS was 87.0% ± 9.1% versus 94.2% ± 3.3%, respectively ($p = 0.501$). The incidence of grade II acute GVHD was higher in the unrelated donor group (21.7% vs 3.4%, $p = 0.007$), though there were no cases of grades III-IV acute GVHD in either group. Chronic GVHD and extensive chronic GVHD were more frequent in the unrelated donor group but did not reach statistical significance (18.2% vs 8.8%, $p = 0.285$). CMV infection rates were comparable between groups (82.6% vs 70.7%, $p = 0.270$), and no significant differences were observed in the incidence of Epstein-Barr viral infection or post-transplantation lymphoproliferative disorder. Research suggests that unrelated donor HSCT is a viable alternative when a matched sibling donor is not available for patients aged 14-55 years. They highlighted the need for additional comparative studies evaluating upfront mismatched related donor HSCT versus first-line MSD HSCT or immunosuppressive therapy.

Rice et al. (2019) conducted a retrospective cohort study to evaluate the outcomes of allogeneic HSCT in patients aged ≥ 50 years old with severe AA. Data came from two international transplant registries, the EBMT and CIBMTR, and included 499 patients between 2005 and 2016 who underwent HSCT with an HLA-matched sibling donor or matched unrelated donor. The median age at transplant was 57.8 years, with 84% of patients age 50 to 64 and 16% age 65 to 77 years. Notably, most patients with available treatment history had received at least one prior course of immunosuppressive therapy. The primary endpoint was overall survival at 36 months. For the full cohort, the 3-year probability of overall survival was 56%, with a 59% survival for matched related donor HSCT and 52% for matched unrelated donor HSCT. Age at transplant was not significantly associated with overall survival, and mortality risk was not significantly different for patients aged 65-78 years compared with those age 50-64 years. However, grades II to IV acute GVHD risks were higher for patients aged 65 years or older, with a 20% incidence in patients 50-64 years old and 35% in those age 65 years or older. Baseline Karnofsky performance scores were evaluated as a prognostic factor associated with overall survival, with a score of 100% indicating the patient is fully active with no symptoms while lower scores indicated increasing functional impairment. Multivariable analysis confirmed higher mortality risks for patients with a performance score less than 90% (HR 1.41, 95% CI 1.03-1.92, $p = 0.03$). Infection was the leading cause of death, accounting for 40% of deaths, followed by GVHD, multi-organ failure, and then graft failure. The authors concluded that HSCT “deserves consideration” as an option in older patients with severe AA who have failed first-line IST.

Haploidentical Transplantation for Aplastic Anemia

Randomized Controlled Trials

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 AA 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.

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Systematic Reviews and Meta-Analyses

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 regarding its suitability for patients who receive reduced intensity chemotherapy.

Sickle Cell Disease/Thalassemia Major

Systematic Reviews and Meta-Analyses

Nair et al. (2025) conducted a systematic review to evaluate disease-specific outcomes after allogeneic HSCT in patients with SCD or thalassemia major. A meta-analysis was not performed due to heterogeneity in study populations, transplant approaches, follow-up durations, and outcome definitions. The review included 31 SCD and 78 thalassemia major unique publications from 1996 to 2023. The majority of SCD studies were non-interventional, and involved HLA-matched sibling donors, pediatric or adult and pediatric cohorts, and reported on vaso-occlusive crises (VOCs) complications, including acute pain, acute chest syndrome, priapism, or splenic sequestration. Disease improvement was measured primarily by post-transplant occurrence or absence of VOC complications. Twenty-nine SCD studies (n = 3181) assessed VOC outcomes after transplantation, and 6.9% of patients experienced at least one VOC event. Of the 25 SCD studies that reported on engraftment data (n = 2534), 85.6% (range 81.3-100.0%) of patients achieved neutrophil and/or platelet engraftment after HSCT. For thalassemia major, most studies were non-interventional, involved HLA-matched sibling donors, myeloablative conditioning, and included pediatric or adult and pediatric cohorts. All thalassemia major studies (n = 3848) assessed red blood cell transfusion requirements after transplantation. Of these, 98.3% of patients achieved neutrophil and/or platelet engraftment after HSCT. Among engrafted patients, 91.1% were alive and transfusion independent at follow-up (median follow-up duration of 6 to 288 months), while 8.8% resumed or continued regular blood cell transfusions, generally in the setting of graft failure or graft rejection. Twenty-one (0.6%) of patients died before engraftment. For both SCD and thalassemia major studies, the reported HSCT-related adverse outcomes included graft failure, graft rejection, and acute or chronic GVHD. In SCD studies that reported on these outcomes, graft failure was reported in 14.4% of patients, graft rejection in 5.5%, acute GVHD in 22.5%, and chronic GVHD in 20.4%. In thalassemia major studies that reported on these outcomes, graft failure was reported in 5.4% of patients, graft rejection in 7.5%, acute GVHD in 28.4%, and chronic GVHD in 15.2%. The authors concluded that allogeneic HSCT may not be consistently successful in all transplanted patients, and there is potential for residual disease burden in addition to significant transplant-related burden from complications like graft failure or rejection, GVHD, infection, organ damage, and mortality. Synthesis of available evidence on disease-related outcomes shows on average, 1 in 14 patients with SCD continue to experience VOCs or acute pain episodes following transplant, and 1 in 11 patients with thalassemia major continue to require red blood cell transfusions.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Liu et al. (2026) conducted a prospective, multicenter, non-randomized interventional phase 4 clinical trial to evaluate allogeneic HSCT for transfusion-dependent thalassemia. A total of 823 patients were transplanted with grafts from matched sibling donors (n = 331), matched unrelated donors (n = 352), or haploidentical related donors (n = 140). Patients were between 2 and 20 years of age and had no severe organ dysfunction, uncontrolled infection, HIV or hepatitis B/C positivity, prior transplant, and had adequate performance status. All patients received conditioning with busulfan, cyclophosphamide, fludarabine, and anti-thymocyte globulin, whereas GVHD prophylaxis varied by donor type. The primary endpoints were 2-year overall survival (OS) and event-free survival (EFS), with EFS defined as survival without death, graft failure, or recurrence of transfusion dependence. For all patients, 2-year OS was 95.2% and 2-year EFS was 94.9%. By donor type, 2-year OS and EFS was 97.2% for matched sibling donors, 93.1% and 92.9% for matched unrelated donors, and 95.4% and 94.7% for haploidentical donors, respectively. Two-year GVHD-free, relapse-free survival was 91.4% for matched sibling donors, 77.0% for matched unrelated, and 75.6% for haploidentical. Primary engraftment occurred in 819 patients and graft failure occurred in 4 patients, for an overall graft failure rate of 0.5%. Acute and chronic GVHD was significantly more common in alternative donors. Grades 2-4 acute GVHD occurred in 7.5% of matched sibling recipients, 27.6% for matched unrelated, and 32.3% for haploidentical, while grades 3-4 acute GVHD occurred in 1.9%, 14.6% and 14.7%, respectively. Two-year moderate-to-severe chronic GVHD occurred in 5.0% of matched sibling recipients, 11.2% for matched unrelated, and 15.1% for haploidentical. Overall, 2-year transplant related mortality was 2.5% for matched sibling, 6.3% for matched unrelated, and 4.6% for

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haploidentical. Thirty-eight deaths occurred, mainly due to infection, GVHD, or intracranial hemorrhage. The authors concluded that these findings may help expand the donor pool for patients with transfusion-dependent thalassemia lacking a matched sibling donor. The authors also stated that trial results confirm age > 15 years is an adverse factor, while 2-year OS, EFS, and transplant-related mortality were similar for all patients up to 15 years old (ClinicalTrials.gov NCT04009525).

Alzahrani et al. (2021) reported the outcomes of a multicenter cohort study on non-myeloablative HLA-matched related donor HSCT for SCD, including HbSS, HbSC, and HbS/beta-thalassemia subtypes. The study included 122 patients treated with alemtuzumab, 300 cGy total body irradiation, sirolimus, and unmanipulated filgrastim-mobilized peripheral blood hematopoietic progenitor cells. Median age at HSCT was 29 years old (range: 10-65 years old); 48% of patients were 30 years or older and 17% were 40 years or older. Most patients had severe SCD complications prior to HSCT, including VOC in 88% of patients, acute chest syndrome in 35%, sickle-related hepatopathy with or without iron overload in 34%, avascular necrosis in 31%, elevated tricuspid regurgitant jet velocity in 29%, stroke in 21%, and cerebrovasculopathy in 15%. The primary endpoint was engraftment at 1 year, which occurred in 87% of HSCT patients, and GVHD or relapse-free survival was also 87%. Overall survival was 98% at 1 year and 93% at 5 years. Sickle-free survival was 88% at 1 year and 85% at 5 years. Additionally, hemoglobin and hemolysis parameters improved following transplant, with mean hemoglobin increasing from 95 g/L to 135 g/L in males at 1 year, and from 88 g/L to 121 g/L at 1 year in females. Donor myeloid chimerism was sustained, with a mean value of 84% at 1 year and 88% at 5 years. Donor CD3 chimerism was 48% at year and 53% at 5 years. Median days of recipients taking immunosuppression was 489 days and donor chimerism remained stable after discontinuing immunosuppression. Graft failure occurred in 16 patients (13%). Adverse events included 2 cases of acute skin GVHD grades 1 and 2, with both cases resolving with topical steroids. There were 7 deaths, and 5 were among those with graft failure. Causes of death included relapsed SCD complications, sepsis after marrow aplasia, intracranial bleeding during retransplantation, and two sudden deaths among successfully engrafted patients. The authors concluded that this chemotherapy-free, non-myeloablative HSCT regimen was efficacious across three centers, was tolerated in a largely adult SCD population with compromised organ function, and was associated with no clinically significant GVHD.

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% CI 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (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).

Dedeken et al. (2014) reported on the outcomes of 50 consecutive children with severe SCD that received HSCT between November 1988 and April 2013. 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 VOC/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.

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 =

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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.

Haploidentical Transplantation for Sickle Cell Disease

Randomized Controlled Trials

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 Eastern Cooperative Oncology Group (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 VOCs, 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.

National and Specialty Organizations

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published *guidelines on 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 **ASTCT** published *2024 evidence-based guidelines on allogeneic HSCT for the treatment of severe aplastic anemia*. Prior to HSCT, the ASTCT recommends that all patients undergo thorough evaluation to confirm the diagnosis of severe AA and exclude any underlying inherited bone marrow failure syndrome or other alternate secondary etiologies, such as Fanconi Anemia or short telomere syndromes. The ASTCT states that age has historically been a key determinant for HSCT eligibility in severe AA patients. Traditionally, upfront HSCT was recommended for patients ≤ 40 years of age with an HLA-matched related donor, while immunosuppressive therapy was recommended for patients > 40 years of age without a related donor (Iftikhar et al. 2024). For example, Bejanyan et al. (2019) conducted a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of data from 142 transplant centers between 2000-2014 (n = 1364) and found that patients aged > 30 years had a higher risk of mortality compared to patients aged ≤ 30 years when undergoing marrow transplantation. Among HLA-matched sibling transplants, those aged > 30 had a 2.7 times higher mortality risk than those ≤ 30, while those among HLA-matched unrelated donor transplants had a 1.98 times higher risk of mortality. However, newer research suggests comparable overall survival rates in patients > 50 years of age when compared to patients ≤ 50 years of age, when using either an HLA-matched related or unrelated donor. Given the advancements in HSCT, the ASTCT recommends against using age 40 as a cutoff and suggests that upfront HSCT may be considered in patients up to age 50 or older in select cases. While

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GVHD remains an important risk factor for older adults, upfront HSCT should still be considered, especially for older adults with a low likelihood of response to immunosuppressive therapy, such as those with very severe AA, absence of paroxysmal nocturnal hemoglobinuria, or the presence of myeloid mutations (Iftikhar et al. 2024).

In children and adults up to 50 years of age or beyond, the ASTCT recommends HSCT using an HLA-matched related donor as the preferred first-line treatment for severe AA (strong recommendation based on moderate quality evidence). In adults who lack an HLA-matched related donor, the ASTCT recommends either an HLA-matched unrelated donor or haploidentical HSCT over immunosuppressive therapy, with no preference between the two (conditional recommendation based on low quality evidence). For children and young adults who lack an HLA-matched related donor, the ASTCT similarly recommends either an HLA-matched unrelated donor or haploidentical HSCT (conditional recommendation based on very low-quality evidence). In any patient for whom haploidentical HSCT is being considered, testing for the presence of donor specific antibodies should be performed, as their presence is strongly associated with graft failure and would require either desensitization or a search for an alternative donor. For patients treated with first-line immunosuppressive therapy and failed, the ASTCT recommends HSCT over a second course of immunosuppressive therapy (Iftikhar et al. 2024).

The **American Society of Hematology (ASH)** published 2026 *Guidelines for the Diagnosis and Management of Severe Acquired Aplastic Anemia*. The panel developed the evidence-based guidelines by conducting systematic reviews and using the GRADE approach. Under good practice statements, the ASH states that clinicians should perform a bone marrow aspirate and biopsy for patients with unexplained pancytopenia, and that for patients with a diagnosis of severe or very severe AA who are eligible for HSCT, clinicians should perform HLA testing as soon as possible. For frontline therapy, the ASH makes the following conditional recommendations based on low or very low certainty in the evidence of the effects (Scheinberg et al. 2026):

- For patients ≤ 40 years old with severe or very severe AA who have a matched sibling donor available, the ASH recommends HSCT over IST.
- For patients > 40 years old with severe or very severe AA who have a matched sibling donor available, the ASH recommends IST over HSCT.
- For patients ≤ 40 years old with severe or very severe AA who do not have a matched sibling donor available, the ASH recommends either matched unrelated HSCT or IST.
- For patients > 40 years old with severe or very severe AA who do not have a matched sibling donor available, the ASH recommends IST.
- For patients of any age with severe or very severe AA, the ASH recommends IST over haploidentical HSCT.
- For patients of any age with severe or very severe AA undergoing IST, the ASH recommends the addition of eltrombopag.

For second line therapy and for relapse, the ASH makes the following conditional recommendations based on very low certainty in the evidence of the effects (Scheinberg et al. 2026):

- For patients ≤ 60 with severe or very severe AA with no response to initial IST, the ASH recommends HSCT over a second anti-thymocyte globulin-based IST.
- For patients > 60 with severe or very severe AA with no response to initial IST, the ASH recommends either HSCT or a second anti-thymocyte globulin-based IST.
- For patients ≤ 60 with severe or very severe AA who respond to initial IST but subsequently relapse, the ASH recommends HSCT or a second anti-thymocyte globulin-based IST.
- For patients > 60 with severe or very severe AA who respond to initial IST but subsequently relapse, the ASH recommends a second anti-thymocyte globulin-based IST over HSCT.

The **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 chest 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)."
- For adults with SCD, the ASH recommends undergoing HSCT with an MSD and nonmyeloablative conditioning over reduced intensity conditioning that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects). While HSCT has curative potential for SCD, outcomes in children younger than 16 years old are better compared to adults. Adults with SCD are more likely to have accumulated disease-related morbidities, which may limit eligibility.
- The ASH recommends that HSCT with a MSD be considered for all SCD patients at risk of neurologic injury, recurrent VOCs, or history of recurrent acute chest syndrome. The panel also expressed "strong views" that all patients with severe complications of SCD should receive information about HSCT as an option, even without an MSD.

The **Center for International Blood and Marrow Transplant Research (CIBMTR)** (2024), in the Forms Instruction Manual, states the following:

- Comprehensive Baseline & Follow-up Manuals: 2100: Post-Infusion Follow-Up (Q10-16):
    - Engraftment is defined as an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L (or ≥ 500/mm^3) for three consecutive days or three consecutive laboratory values obtained on different days
    - ANC recovery is defined as an ANC of ≥ 500/mm3 (or ≥ 0.5 × 109/L) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 500/mm3. If the laboratory report displays an automated ANC value of exactly 500/mm3, the actual ANC value should be calculated from the manual differential if available. The calculated value from the manual differential will determine ANC recovery.

The **CIBMTR** is a research collaboration between the Medical College of Wisconsin and the **National Marrow Donor Program** (NMDP). In an NMDP IND Annual Report (BB-IND #7555-0136) for A Centralized Cord Blood Registry to Facilitate Allogeneic, Unrelated Donor Umbilical Cord Blood Transplantation, neutrophil engraftment is defined as

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achievement of an ANC of ≥ 500 neutrophils/mm3 sustained for three consecutive laboratory measurements on different days (NMDP 2022).

The **European Society for Blood and Marrow Transplantation (EBMT)** published *Indications for haematopoietic cell transplantation and CAR-T for haematological diseases, solid tumours and immune disorders: 2025 EBMT practice recommendations* (Greco et al. 2025) outlining current indications for HSCT. The guidelines indicate that allogenic HSCT is a standard of care in newly diagnosed or relapsed/refractory disease in acquired severe AA. Allogenic HSCT is a standard of care in severe clinical sickle cell disease in the absence of severe organ/tissue damage.

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, non-infectious 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, as "substantial risks" are involved with the procedure, and it's not yet feasible in the majority of people with SCD.

As of 2024, the **NHLBI** recognizes HSCT as a potential curative treatment option for some people with SCD. However, they state that to be successful, transplants require a well-matched donor, usually being a close blood relative. Currently, most transplants are done in children who've had severe complications such as strokes, acute chest crises, and repeated pain crises, and are successful in about 90% of children when the donor is an HLA-matched blood relative. The NHLBI notes that HSCT is riskier in adults, and that current research is exploring ways to expand access for children and adults without a matched family donor or for patients who are older than most recipients (NHLBI 2024).

The **National Marrow Donor Program (NMDP)** provides evidence-based pre- and post-HSCT guidelines to patients and providers, including: *Hematopoietic cell transplant (HCT) consultation guidelines & outcomes*, *Understanding engraftment*, *Post-transplant care and early HCT complications* ([1-3]NMDP date unknown).

The **NMDP** published a *summary of ASTCT guidelines for HSCT in severe aplastic anemia*, emphasizing the expansion of eligibility and donor options. The NMDP notes that due to recent advances in allogeneic HSCT, the evidenced-based guidelines have moved away from the historical age 40 cutoff, expanding eligibility for older adults. The NMDP also emphasizes the suggested prioritization of matched unrelated donors or haploidentical donors over non-transplant immunosuppressive therapies for patients without a matched related donor. The NMDP states that the updates to evidence-based guidelines, which include relaxing age restrictions and expanding the definition of suitable donor types, reflect the significant advancement in transplant eligibility and strategies for severe AA (NMDP 2024).

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The **Thalassaemia International Federation (TIF)** published *Guidelines for the Management of Transfusion-Dependent Beta Thalassaemia (5th edition - 2025).* The TIF notes that HSCT in adults has so far been limited, with only a few hundred patients undergoing transplant since the year 2000. In an EBMT survey of 1061 cases of matched sibling donor transplants performed between 2000 and 2010 across 132 centers in 28 countries, the median patient age was 7 years. A statistically significant difference in OS was reported in children between 10-13 years of age versus children between 14-17 years of age (96% versus 82%). In the adult group of 82 patients (median age of 22 years, range 18-45), OS was 80% and transplant-free survival was 77%. The prevention of organ toxicity from toxic iron species, which is a key predictor of clinical outcomes, has not been conclusively demonstrated in clinical trials. The clinical situation for adult thalassemia patients has greatly improved, and age alone is not as important as a factor as is the extension of tissue damage developed from years of exposure to tissue reactive iron species. However, a controlled trial in well-chelated adult patients is needed. The TIF recommends that HSCT be offered to transfusion-dependent beta thalassemia patients and their parents at an early age if an HLA-identical donor is available (Grade B recommendation, Class I evidence). A matched unrelated donor can be used, provided that high compatibility criteria for both HLA class I and II loci are met (Grade B recommendation, Class I evidence). While haploidentical HSCT shows promising results, it should only be considered at experienced centers in the context of well-designed clinical trials (Grade B recommendation, Class IIb evidence) (Taher et al. 2025, pp. 384-390).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

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)

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

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APPROVAL HISTORY

06/10/2026 Policy revised. Under aplastic anemia, removed 60 years of age cutoff, revised diagnostic criteria structure so that only one hematologic condition is required, revised definition of very severe aplastic anemia, added eltrombopag to immunosuppressive therapy (IST) criteria, removed IST failure requirement for Members ≤ 40 without a matched sibling donor, and added criteria to highlight the potential medical necessity of repeat HSCT in the case of graft failure. Under sickle cell disease and thalassemia major, expanded coverage to select adult Members, with a cautionary note due to limited evidence and increased risk. IRO peer reviewed on May 28, 2026 by a practicing physician board certified in hematology, internal medicine, and medical oncology.

06/11/2025 Policy reviewed. Removed numerical HLA matching criteria. Changed definition of engraftment and ANC criteria in coverage policy to align with current guidelines. Removed age stipulation under Sickle Cell/Thalassemia section.

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.

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