

## ***Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias***

**Effective:** July 1, 2024

**Next Review:** January 2025

**Last Review:** May 2024

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

Hematopoietic cell transplantation is performed to restore normal function following chemotherapy treatment.

### **MEDICAL POLICY CRITERIA**

Allogeneic hematopoietic cell transplantation, using myeloablative or reduced-intensity conditioning, may be considered **medically necessary** for selected patients with the following disorders:

- A. Hemoglobinopathies
  1. Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage. Factors associated with a high risk of stroke or end-organ damage include: recurrent chest syndrome, recurrent vaso-occlusive crises, red blood cell alloimmunization on chronic transfusion therapy.
  2. Homozygous beta-thalassemia (i.e., thalassemia major)
- B. Bone marrow failure syndromes

1. Hereditary
  - a. Inherited aplastic anemia
  - b. Fanconi anemia
  - c. Dyskeratosis congenita
  - d. Shwachman-Diamond
  - e. Diamond-Blackfan
2. Acquired
  - a. Bone marrow failure syndromes secondary to drug or toxin exposure
  - b. Acquired aplastic anemia (i.e., pancytopenia with hypocellular bone marrow)
- C. Primary immunodeficiencies (See Policy Guideline #1)
  1. Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
  2. Absent or defective natural killer function (e.g. Chediak-Higashi syndrome)
  3. Absent or defective neutrophil function (e.g. Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)
- D. Inherited metabolic disorders (See Policy Guideline # 2): Lysosomal and peroxisomal storage disorders, except Hunter, Sanfilippo, and Morquio syndromes
- E. Genetic disorders affecting skeletal tissue: Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease)

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

### DEFINITIONS

- **Consolidation therapy:** Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body. It may include radiation therapy, a stem cell transplant, or treatment with drugs that kill cancer cells. Also called intensification therapy and postremission therapy.
- **Relapse:** The return of a disease or the signs and symptoms of a disease after a period of improvement.
- **Salvage therapy:** Treatment that is given after the cancer has not responded to other treatments.
- **Tandem transplant:** Refers to a planned second course of high-dose therapy and HCT within six months of the first course.

### 1. IMMUNODEFICIENCIES

The following lists the immunodeficiencies that have been successfully treated by

allogeneic hematopoietic cell transplantation (HCT)<sup>[1]</sup>

### **Lymphocyte immunodeficiencies**

Adenosine deaminase deficiency  
Artemis deficiency  
Calcium channel deficiency  
CD 40 ligand deficiency  
Cernunnos/X-linked lymphoproliferative disease deficiency  
CHARGE syndrome with immune deficiency  
Common gamma chain deficiency  
Deficiencies in CD 45, CD3, CD8  
DiGeorge syndrome  
DNA ligase IV  
Interleukin-7 receptor alpha deficiency  
Janus-associated kinase 3 (JAK3) deficiency  
Major histocompatibility class II deficiency  
Omenn syndrome  
Purine nucleoside phosphorylase deficiency  
Recombinase-activating gene (RAG) 1/2 deficiency  
Reticular dysgenesis  
Winged helix deficiency  
Wiskott-Aldrich syndrome  
X-linked lymphoproliferative disease  
Zeta-chain-associated protein-70 (ZAP-70) deficiency

### **Phagocytic deficiencies**

Chediak-Higashi syndrome  
Chronic granulomatous disease  
Hemophagocytic lymphohistiocytosis  
Griscelli syndrome, type 2  
Interferon-gamma receptor deficiencies  
Leukocyte adhesion deficiency  
Severe congenital neutropenias  
Shwachman-Diamond syndrome

### **Other immunodeficiencies**

Autoimmune lymphoproliferative syndrome  
Cartilage hair hypoplasia  
CD25 deficiency  
Hyper IgD and IgE syndromes  
ICF syndrome  
IPEX syndrome  
NEMO deficiency  
NF-KB inhibitor, alpha (IKB-alpha) deficiency  
Nijmegen breakage syndrome

## 2. INHERITED METABOLIC DISORDERS

### **Allogeneic HCT has been proven effective in some cases of:**

Alpha-mannosidosis  
Aspartylglucosaminuria  
Childhood onset cerebral X-linked adrenoleukodystrophy  
Globoid-cell leukodystrophy  
Hurler Syndrome  
Maroteaux-Lamy Syndrome  
Metachromatic leukodystrophy  
Sly Syndromes,

### **Allogeneic HCT is possibly effective for:**

Farber lipogranulomatosis  
Fucosidosis  
Galactosialidosis  
Gangliosidosis  
Gaucher types 1 and 3  
GM1  
Mucopolipidosis II (I-cell disease)  
Multiple sulfatase deficiency  
Niemann-Pick disease  
Neuronal ceroid lipofuscinosis  
Sialidosis  
Wolman disease.

### **Allogeneic HCT has not been effective in:**

Hunter syndrome  
Morquio syndrome  
Sanfilippo syndrome<sup>[2]</sup>

## LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Diagnosis and Indication for transplant

## CROSS REFERENCES

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
2. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16

## BACKGROUND

### HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) (HCT, previously referred to in this policy as a hematopoietic stem cell transplant [HSCT]) refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in patients who receive myeloablative doses of cytotoxic drugs with or without whole body radiation therapy. Although broadly speaking there are two types of HSCTs, autologous and allogeneic, only allogeneic HSCT is relevant to this discussion. Allogeneic HCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic cells and the recipient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

### PREPARATIVE CONDITIONING FOR ALLOGENEIC HEMATOPOIETIC HCT

The conventional practice of allogeneic HCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allotransplantation. They represent a continuum in their intensity, from nearly totally myeloablative, to minimally myeloablative with lymphoablation.

### GENETIC DISEASES AND ACQUIRED ANEMIAS

#### Hemoglobinopathies

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, reducing oxygen delivery. The supportive treatment of beta-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function.<sup>[3]</sup> The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HCT.

Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin, and, unlike thalassemia major, has a variable course of clinical severity.<sup>[3]</sup> Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for males and 48 for females. Three major therapeutic options

are available: chronic blood transfusions, hydroxyurea, and HCT, the latter being the only possibility for cure.<sup>[3]</sup>

### **Bone marrow failure syndromes**

Aplastic anemia in children is rare and is most often idiopathic and less commonly due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease, characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently this disease terminates in a myelodysplastic syndrome or acute myelogenous leukemia. Most patients with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age.<sup>[4]</sup> In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

Dyskeratosis congenita is characterized by marked telomere dysregulation with clinical features of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia.<sup>[5]</sup> Early mortality is associated with bone marrow failure, infections, pulmonary complications, or malignancy.<sup>[5]</sup>

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.<sup>[5]</sup> Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially acute myelogenous leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow with 30% of patients also having a variety of physical anomalies.<sup>[5]</sup>

### **Primary immunodeficiencies**

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes.<sup>[1]</sup> The most severe defects (collectively known as severe combined immunodeficiency or SCID) cause an absence or dysfunction of T lymphocytes, and sometimes B lymphocytes and natural killer cells.<sup>[1]</sup> Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the life span of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood.<sup>[1]</sup> Bone marrow transplant is the only definitive cure and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function.<sup>[6]</sup>

### **Inherited metabolic diseases**

Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait.<sup>[7]</sup> Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal

storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic substrate and a deficiency of the product of the enzyme reaction.<sup>[7]</sup> Hurler syndrome usually leads to premature death by five years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don't cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem-cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier.<sup>[7]</sup> The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells, for example microglial cells in the brain and Kupffer cells in the liver.<sup>[7]</sup>

Allogeneic HCT has been used primarily to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1.<sup>[7]</sup> The first stem-cell transplant for an inherited metabolic disease was in 1980 in a patient with Hurler syndrome. Since that time, more than 1,000 transplants have been performed worldwide.<sup>[7]</sup>

**Table 1. Lysosomal and Peroxisomal Storage Disorders**

Category	Diagnosis	Other Names
<b>Mucopolysaccharidosis (MPS)</b>	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler, Scheie, H-S Hunter Sanfilippo A-D Morquio A-B Maroteaux-Lamy Sly
<b>Sphingolipidosis</b>	Fabry's Farber's Gaucher's I-III GM1 gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff's disease Globoid leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis       Krabbe disease MLD
<b>Glycoproteinosis</b>	Aspartylglucosaminuria Fucosidosis alpha-Mannosidosis beta-Mannosidosis Mucopolysaccharidosis III and IV	Sialidosis
<b>Other lipidoses</b>	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis	Type III-Batten disease
<b>Glycogen storage</b>	GSD type II	Pompe
<b>Multiple enzyme deficiency</b>	Galactosialidosis	

	Mucopolipidosis type II	I-cell disease
<b>Lysosomal transport defects</b>	Cystinosis Sialic acid storage disease Salla disease	
<b>Peroxisomal storage disorders</b>	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

### Infantile malignant osteopetrosis

Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow.<sup>[8]</sup> Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis. Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately six months of age, and severe hematologic malfunction with bone marrow failure. Seventy percent of these patients die before the age of six, often of recurrent infections.<sup>[8]</sup> HCT is the only curative therapy for this fatal disease.

## EVIDENCE SUMMARY

### HEMOGLOBINOPATHIES

#### Sickle Cell Disease (SCD)

The use of HCT in patients with sickle cell disease has been well studied over the past decade. Therefore, this section will only summarize the available systematic reviews.

#### Systematic Reviews

Rotin (2023) conducted a systematic review to compare the safety and efficacy of allogeneic hematopoietic stem cell transplant (HSCT) and gene therapy (GT) for sickle cell disease (SCD).<sup>[9]</sup> Phase I to III clinical trials and case reports/series were included. In total, 56 studies (HSCT, n=53; GT, n=3) representing 1,198 patients met inclusion criteria (HSCT, n=1,158; GT, n=40). Two-year overall survival for HSCT was 91%; mortality was 2.5% for GT. Acute chest syndrome and vaso-occlusive episodes were reduced post-HSCT and GT. The authors concluded that a standardized reporting is needed to better compare outcomes within and between treatment groups.

In Iqbal (2021) published a systematic review on the efficacy of allogeneic hematopoietic cell transplantation in sickle cell disease on behalf of the Pediatric Diseases Working Party of European Society for Blood and Marrow Transplantation and the Sickle Cell Transplantation International Consortium.<sup>[10]</sup> A total of 33 studies including 2,853 patients met inclusion criteria. Analyses were completed for individual age groups and the whole population. For all ages, pooled rates of overall survival (OS), disease-free survival (DFS), acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD), non-relapse mortality (NRM), and graft failure (GF) were 96%, 90%, 20%, 10%, 4%, and 5%, respectively. In children, these outcomes were 97%, 91%, 26%, 11%, 5%, and 3%, respectively, and in adults they were 98%, 90%, 7%, 1%, 0%, and 14%, respectively.



In a 2020 update of a Cochrane systematic review, authors determined whether stem cell transplantation improves survival and prevents symptoms and complications associated with sickle cell disease.<sup>[11]</sup> In addition, authors examined the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease. Selection criteria was limited to randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, , and setting. Though 12 trials were identified, 11 trials did not meet the inclusion criteria for review and the remaining trial was ongoing at the time of publication. Authors conclude that studies on the use of hematopoietic stem cell for treatment of sickle cell disease are limited to observational and other less robust studies. Authors did not identify any completed randomized controlled trials assessing the benefit or risk of hematopoietic stem cell transplantations. This systematic review identified the need for a multicenter randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.

### Clinical Trials

Parsons (2022) conducted a clinical trial to evaluate the health-related quality of life (HRQoL) impact in the two years following familial haploidentical stem cell transplant (SCT) among children with high-risk SCD. The authors reported a significant improvement in EF ( $p=0.03$ ) at two years versus baseline.<sup>[12]</sup> A similar pattern of scores over time was seen for parent ratings of child's global HRQoL. Despite treatment intensity in the initial months following AlloSCT, patient scores recovered or exceeded baseline scores at two years.

### **Beta-Thalassemia**

More than 3,000 patients worldwide have been treated for beta-thalassemia with allogeneic HCT.<sup>[3]</sup> Overall survival rates have ranged from 65% to 100% and thalassemia-free survival up to 73%.<sup>[3]</sup> The Pesaro risk stratification system classifies patients with thalassemia who are to undergo allogeneic HCT into risk groups I through III on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with two risk factors, and III with all three).<sup>[13]</sup> The outcome of allogeneic HCT in over 800 patients with thalassemia according to risk stratification has shown overall and event-free survival of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III.<sup>[13]</sup> The use of HCT in patients with beta-thalassemia has been well studied over the past decade. Therefore, this section will only summarize the available systematic reviews.

### Systematic Reviews

A 2014 Cochrane systematic review evaluated the safety and effectiveness of different types of allogeneic HCT in subjects with transfusion-dependent beta-thalassemia major (homozygous beta-thalassemia), beta-thalassemia intermedia, or beta0/+ -thalassemia variants requiring chronic blood transfusion.<sup>[14]</sup> Selection criteria were limited to randomized controlled and quasi-randomized studies that compared allogeneic HCT with each other or with standard therapy (i.e., regular transfusion and chelation regimen). No studies were identified that met these inclusion criteria. Some limited data have become available the last few years in nonrandomized trials comparing conditioning regimens, different risk groups, outcomes with different donor sources, various myeloablative treatments, and outcomes with HLA matched or

related and unrelated donors. However, the authors concluded that questions related to the safety and efficacy of different types of stem cell transplantation remain unanswered.

### **Reduced-intensity Conditioning (RIC)**

Experience with reduced-intensity preparative regimens and allogeneic HCT for the hemoglobinopathies is limited to a small number of patients. In adult patients, severe GVHD has been observed with the use of RIC regimens.<sup>[15]</sup> Challenges with high rates of graft rejection (10% to 30%) may be due to hemoglobinopathy patients possibly being allosensitized due to repeated blood transfusions and, as opposed to cancer patients who may undergo RIC allogeneic transplants, patients with hemoglobinopathies have received no prior immunosuppressive therapies and may even have significant bone marrow hyperplasia.<sup>[13]</sup>

## **BONE MARROW FAILURE SYNDROMES**

### **Fanconi Anemia (FA)**

In Fanconi anemia (FA), bone marrow transplant is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HCT, with cure of the marrow failure and amelioration of the risk of leukemia.<sup>[4]</sup>

#### Nonrandomized Studies

Yabe (2021) published a retrospective review of 163 FA patients, include 118 with aplastic anemia, 30 with myelodysplastic syndrome, and 15 with acute leukemia.<sup>[16]</sup> A non-T-cell-depleted graft was used in 98% of patients and an alternative donor was used in 73%. Median follow-up was 8.7 years. Five-year OS was 81% overall, and 89%, 71%, and 44% in aplastic anemia, myelodysplastic syndrome, and acute leukemia patients, respectively. The OS in the aplastic anemia group was significantly higher than in the other two groups. Of the 137 patients surviving to one year, 15 developed subsequent malignancies.

AlDawsari (2020) reported on 45 patients who received matched related donor HCT for FA in a retrospective multicenter analysis from the Eastern Mediterranean Blood and Marrow Transplantation Group.<sup>[17]</sup> Median age at transplant was 18. Fludarabine-base conditioning was used in 64.5% of patients, while irradiation-based conditioning was used in 11.1%, and other combinations were used in the remaining patients. The indications for treatment were bone marrow failure (86.7%) and myelodysplastic syndrome (13.3%). Twenty-seven (60%) patients had successful engraftment and five (11.1%) had primary engraftment failure. Median time to neutrophil engraftment and platelet engraftment was 14 days (range 10 to 21 days) and 17 days (10 to 33 days), respectively. Grade II to IV acute and chronic GVHD occurred in 7.0% and 36.6% of patients, respectively. No new malignancies were reported. The OS probability was 53.6% (95% CI, 38.3 to 68.9%) at a median follow-up of 13 months (95% CI, 1 to 240).

Also in 2020, Murillo-Sanjuán reported a retrospective multicenter report of HCT for pediatric patients with FA from the Spanish Working Group for Bone Marrow Transplantation in Children.<sup>[18]</sup> Pediatric patients with FA with bone marrow failure (n=30) or myelodysplastic syndrome (n=4) were treated with Fludarabine conditioning followed by HCT. Matched sibling donors were used in 18 cases, matched unrelated donors in 15, and unrelated haploidentical donor in one. Of the 34 total patients, 33 engrafted. Acute and chronic grade II to IV GVHD occurred in 29% and 11% of patients, respectively. At five years post-transplant OS was 73%

overall, 80% for bone marrow failure patients, and 25% for myelodysplastic syndrome patients. No differences between sibling and unrelated donor transplants were reported for OS.

In 2015, Kuşkonmaz reported on the outcomes of 26 patients with FA who underwent HCT using fludarabine (Flu) based conditioning regimen at a single center from 2004 to 2014.<sup>[19]</sup> The median age of the patients at the time of transplantation was 9.6 years (range 5.6 to 17.0 years). Donors were (HLA)-identical siblings in 18 patients, HLA-identical other relatives in six patients, and HLA 1-antigen mismatched sibling in two patients. Twenty-five patients had successful engraftment, and one developed poor graft function and underwent a second HCT. Acute GVHD ( $\geq$  grade 2) occurred in two patients (7.6%) and chronic GVHD in one patient (3.9%). Three patients developed venoocclusive disease (11.5%). Survival rate was 96.2% (25/26) at a median follow-up of 54 months (10 to 131 months). Although none of the patients developed secondary malignancy during the follow-up period, the follow-up period was too short to estimate this risk.

In 2015, Ristano published on an Italian FA registry, including over 180 patients, more than half which (102 out of 180, 57%) had received a HCT from either a non-affected sibling or matched unrelated donor.<sup>[20]</sup> The incidence of all solid cancers and of head and neck tumors was not statistically different between patients who had received a HCT and those who had not ( $p=0.43$  and  $p=0.50$ , respectively), however the analysis is limited by the small number of events. In HCT patients the majority of deaths were related to treatment complications such as infections ( $n=11$ , 25.5% of total deaths in HCT patients), GVHD ( $n=11$ , 25.5%) and other transplant related mortality (TRM) ( $n=13$ , 30%). Solid tumors accounted for 9% of deaths ( $n=4$ ).

In a 2008 study of allogeneic HCT from matched related donors over six years in Fanconi anemia, totaling 103 patients, overall survival ranged from 83% to 88% with transplant-related mortality ranging from 8% to 18.5% and average chronic graft-versus-host disease (GVHD) of 12%.<sup>[21]</sup>

In an attempt to improve outcomes for alternative donor HCT for FA patients, MacMillan added fludarabine (FLU), to the conditioning regimen for 130 FA patients that were treated between 1995 and 2012, with median follow-up times between 4 to 18 years. The addition of FLU enhanced engraftment three-fold, and in regression analysis, recipients of FLU-containing regimens had a lower risk of mortality at five years. The European Group for Blood and Marrow Transplantation (EBMT) working party has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median two-year survival was 28 + 8%.<sup>[5]</sup> Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year overall survival rates were 13% and 52% in patients who received non-fludarabine versus fludarabine-based regimens.<sup>[5]</sup>

Zanis-Neto (2005) reported the results of 30 patients with Fanconi anemia treated with reduced-intensity conditioning (RIC) regimens, consisting of low-dose cyclophosphamide.<sup>[22]</sup> Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade 2-3 acute GVHD rates were 57% and 14% for patients who received the higher and lower doses, respectively ( $p=0.001$ ). Four of the seven patients who received the higher dose were alive at a median of 47 months (range: 44 to 58), and 22 of 23 given the lower dose were alive

at a median of 16 months (range: 3 to 52). The authors concluded that a lower dose of cyclophosphamide conditioning had lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the CIBMTR, Wagner reported that fludarabine-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved three-year overall survival (OS) (52% vs. 13%, respectively;  $p < 0.001$ ) compared with nonfludarabine regimens.<sup>[23]</sup>

## **Acquired Severe Aplastic Anemia (SAA)**

### Systematic Reviews

ElGohary 2020 performed a systematic review and meta-analysis on 15 prospective or retrospective studies ( $n=577$ ) evaluating outcomes after HCT in patients with idiopathic aplastic anemia.<sup>[24]</sup> Seven studies were retrospective in nature, deriving data from registries and records, while eight studies had a prospective design. Across the studies, the pooled incidence of successful engraftment was 97.3% (95% CI 95.9 to 98.7). Grade II to IV GVHD was reported in 26.6% of patients. The pooled incidence of transplant-related mortality was 6.7% per year (95% CI 4.0 to 9.4). Patients who received reduced intensity conditioning regimens had lower rates of GVHD (18.7% vs 29.5%) and engraftment (91.7% vs 97.7%) compared to nonmyeloablative regimens.

Zhu (2020) reported a systematic review and meta-analysis of allogeneic HCT versus immunosuppressive therapy for acquired aplastic anemia.<sup>[25]</sup> A total of 15 studies met inclusion criteria. All included studies were rated as high quality using the Newcastle-Ottawa scale. The pooled hazard ratios for OS and failure-free survival were 0.4 (95% CI 0.074 to 0.733,  $p=0.016$ ,  $I^2=58.8\%$ ) and 1.962 (95% CI 1.43 to 2.493,  $p=0.000$ ,  $I^2=0\%$ ), indicating superior outcomes for HCT versus immunosuppressive therapy. In the two studies reporting comparable treatment related mortality, there was significantly higher treatment related mortality among patients undergoing first-line allogeneic HCT versus immunosuppressive therapy (pooled RR 3.98, 95% CI 1.911 to 8.29,  $p=0.000$ ,  $I^2=0\%$ ). Acute GVHD occurred in 42.5% of patients, with 25% of patients experiencing grad II to IV. Chronic GVHD occurred in 30%, with 7% of patients dying from GVHD.

A 2014 Cochrane systematic review evaluated the effectiveness and adverse events of first-line allogeneic HCT of human leucocyte antigen (HLA)-matched sibling donors (MSD) compared with first-line immunosuppressive therapy (IST) for acquired severe aplastic anemia (SAA).<sup>[26]</sup> Selection criteria included participants with newly diagnosed severe SAA in RCTs or prospective non-RCTs. Three studies met inclusion criteria; the studies were conducted between 1976 and 1997.<sup>[27-29]</sup> Thus, these data were collected more than 15 years ago. All three studies were rated as high risk for bias due to the study design. The meta-analysis showed no statistically significant difference in overall mortality between MSD-HCT ( $n=121$ ) and IST ( $n=181$ ), with overall survival (OS) ranging from 45% to 84% and 45% to 87%, respectively. However, treatment-related mortality in the MSC-HCT group ranged from 20% to 42%. Graft failure rates were variable and caused death in 3% to 16% of transplanted patients. GVHD affected 25-50% of transplanted patients.

One of these studies included in the review, by Bayever (1984),<sup>[27]</sup> reported 92% of patients in the MSD-HCT group had a Karnofsky Performance Status higher than 70% compared to less than 50% of the IST group participants. Secondary clonal disease or malignancies were rare in

both groups. The authors noted that a 2008 article<sup>[30]</sup> reported improved outcomes since 1996 for HCT but not for IST, possibly attributable to detailed HLA-matching and less irradiation-based conditioning. Limitations of this systematic review included the data being 15 or more years old and therefore not applicable to current standard care. The use of Mendelian randomization requiring HLA-matched sibling donor did not necessarily minimize bias since patients with large families had a greater chance of finding a donor and thus being assigned to the HCT group than patients with fewer siblings. In addition, the testing of multiple siblings as potential donors may delay assignment and treatment compared with patients with no siblings who could be assigned immediately and thus were at earlier risk for adverse events. The authors concluded that insufficient and biased data did not permit conclusions about the comparative effectiveness of MSD-HCT and IST.

### Nonrandomized Studies

Small case series have been published that focus on children with SAA that do not have a matched sibling donor, thereby requiring either an unrelated or unmatched donor. The goal of these case series is to optimize the conditioning regimes and therapeutic strategies for these children in order to improve transplantation success (engraftment) and improved health outcomes like overall survival.

Nqwube (2015) performed a small prospective multi-center HCT trial in 17 children with SAA using a novel reduced-intensity conditioning (RIC) regimen with alemtuzumab, fludarabine and melphalan, and the best available donor. Eight transplants were from related donors, and nine were from unrelated donors, matched at 7 to 8/8 loci, with follow-up times ranging from 6 to 128 months.<sup>[31]</sup> Unrelated donors and related donors were assessed separately for overall survival and event free survival, with OS being 78% and 100% when donors were unrelated and related, respectively. For all other transplant outcomes, these two groups were analyzed together. Overall, treatment related mortality was 12% and the incidence of acute graft-versus-host disease was between 18 and 29%. At two years, 92% of patients had discontinued immunosuppression successfully.

Esteves (2015) recently followed 16 SAA patients who underwent haploidentical transplantation using a RIC regimen with post-transplant treatment with cyclophosphamide (Cy).<sup>[32]</sup> The rate of neutrophil engraftment was 94% and of platelet engraftment was 75%. Two patients had secondary graft failure and were successfully salvaged with another transplant. Three patients developed acute GVHD and the one-year OS was 67.1%.

In 2015, the European Group for Blood and Marrow Transplantation (EBMT) working party analyzed the outcomes of 563 children with SAA (up to 12 years old), comparing those treated with matched family donor (MFD) (HCT (n=396) or immunosuppressive treatment (IST)(n=167).<sup>[33]</sup> There was no significant difference between HCT and IST in terms of OS (91% and 87%, respectively), but event-free survival (EFS) was significantly higher in the HCT group (87% vs. 33% (p=0.001). Of the 167 initially treated with IST, 91/167 (55%) failed front-line IST and were successfully rescued after HCT, with an OS of 83%. The OS and EFS rates reported in this age group of children with SAA are superior to those reported for adolescents (12 to 18 years old) with SAA who have undergone HCT versus IST.<sup>[34]</sup> In adolescents, OS was 86% in the HCT group and 90% in patients given front-line IST alone and EFS was 83% and 64%. Both of these studies indicated that HCT, using a matched family donor is the first-choice treatment.

In 2012, a randomized Phase III trial compared two different conditioning regimens in high-risk aplastic anemia patients (n=79) who underwent allogeneic HCT.<sup>[35]</sup> Patients in the cyclophosphamide (Cy) plus anti-thymocyte globulin (ATG) arm (n=39) received Cy at 200 mg/kg; those in the Cy-fludarabine (Flu)-ATG group (n=40) received Cy at 100 mg/kg and Flu at 150 mg/m<sup>2</sup> (NCT01145976). No difference in engraftment rates was reported between arms. Infection with an identified causative organism and sinusoidal obstruction syndrome, hematuria, febrile episodes, and death from any cause tended to be more frequent in the Cy-ATG arm but did not differ significantly between arms. Overall survival at four years did not differ between the Cy-ATG and Cy-Flu-ATG arms (78% vs. 86%, respectively, p=0.41). Although this study was reported to be underpowered by authors to detect real differences between the conditioning regimens, the results suggest an RIC regimen with Cy-Flu-ATG appears to be as safe as a more traditional myeloablative regimen comprising Cy-ATG in allogeneic HCT.

### **Dyskeratosis Congenita**

Results with allogeneic HCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis.<sup>[5]</sup> Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results are available at this time.<sup>[5]</sup>

#### Nonrandomized Studies

In 2013, outcomes after allogeneic HCT were reported in 34 patients with dyskeratosis congenita who underwent transplantation between 1981 and 2009.<sup>[36]</sup> The median age at transplantation was 13 years (range, 2 to 35). Approximately 50% of transplantations were from related donors. The day-28 probability of neutrophil recovery was 73% and the day-100 platelet recovery was 72%. The day-100 probability of grade II to IV acute GVHD and the three-year probability of chronic GVHD were 24% and 37%, respectively. The 10-year probability of survival was 30%; 14 patients were alive at last follow-up. Ten deaths occurred within four months from transplantation because of graft failure (n=6) or other transplantation-related complications; nine of these patients had undergone transplantation from mismatched related or from unrelated donors. Another 10 deaths occurred after four months; six of them occurred more than five years after transplantation, and four of these were attributed to pulmonary failure. Transplantation regimen intensity and transplantations from mismatched related or unrelated donors were associated with early mortality. Transplantation of grafts from HLA-matched siblings with Cy-containing nonradiation regimens was associated with early low toxicity. Late mortality was attributed mainly to pulmonary complications and likely related to the underlying disease.

### **Shwachman-Diamond Syndrome**

Experience with allogeneic HCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease.<sup>[5]</sup>

#### Nonrandomized Studies

In 2020, Myers reported a retrospective reported of 52 patients who underwent HCT for Schachman-Diamond syndrome.<sup>[37]</sup> The indication for transplant was bone marrow failure (cytopenia or aplastic anemia) in 39 patients and myelodysplasia (MDS)/acute myelogenous leukemia (AML) in 13 patients. HLA-matched sibling donors were used for 18 patients, an

HLA-matched or mismatched relative for six patients, and an HLA-matched or mismatched unrelated donor for 28 patients. Myeloablative conditioning was used in 13 patients and reduced intensity was used in 26. Five-year OS for bone marrow failure patients was 72% (95% CI 57 to 86%). For MDS/AMS patients, five-year OS was 15%, with relapse as the predominant cause of death.

Also in 2020, Cesaro reported a retrospective analysis of long-term outcomes following allogeneic HCT for Shwachman-Diamond syndrome by the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation.<sup>[38]</sup> Of the 74 included patients, six had acute myeloid leukemia, seven had myelodysplastic syndrome, and 61 had bone marrow failure. Identical sibling donor cells were used in 18 patients, unrelated donor cells in 50, and other family member cells in six. Conditioning was reduced intensity in 31 patients and myeloablative in 36. Successful engraftment was achieved in 84% of cases. Acute and chronic grade I to IV GVHD were reported in 55% and 20% of patients, respectively. Five-year OS was 63% (95% CI 50.8 to 73.4) and at a median of 7.3 years, 28 patients had died from progression/relapse or toxicity.

Cesaro (2005) reported 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Bone Marrow Transplantation registry given HCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (MDS-AML) (n=9); or another diagnosis (n=1).<sup>[39]</sup> Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n=6), mismatched related (n=1), or unrelated graft (n=19). Graft failure occurred in five (19%) patients, and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, OS was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total body irradiation-based conditioning regimens were factors associated with a poorer outcome.

## **Diamond-Blackfan Anemia**

### Nonrandomized Studies

In Diamond-Blackfan anemia, allogeneic HCT is an option in corticosteroid-resistant disease.<sup>[5]</sup> In a report from the Diamond-Blackfan anemia registry, 20 of 354 registered patients underwent allogeneic HCT, and the five-year survival rates were 87.5% if recipients received HLA-identical sibling grafts, but poor in recipients of alternative donors.<sup>[5]</sup> The CIBMTR reported the results in 61 patients who underwent HCT between 1984 and 2000.<sup>[40]</sup> Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of overall survival after transplantation for patients transplanted from an HLA-identical sibling donor (versus an alternative donor) was 78% versus 45% (p=0.01) at one year and 76% versus 39% (p=0.01) at three years, respectively.

## **Severe Congenital Neutropenia**

Allogeneic HCT is the only curative treatment of severe congenital neutropenia (SCN).

### Nonrandomized Studies

Fioredda (2015) recently published a report on the outcome of 136 SCN patients who underwent HCT between 1990 and 2012 in European and the Middle East.<sup>[41]</sup> The three-year overall survival (OS) was 82%, and transplant-related mortality (TRM) was 17% in this

population. In multivariate analysis, transplants performed at a young age (<10 years), in recent years (after 2000), and from HLA-matched donors were associated with a significantly better OS. Whether the donors were related or unrelated made no difference on overall survival. Frequency of graft failure was 10%. Incidence of acute graft-versus-host disease (GVHD) grade 2 to 4 was 21% and chronic GVHD was 20%. In multivariate analysis, HLA-matched related donor and prophylaxis with cyclosporine A and methotrexate were associated with lower occurrence of acute GVHD. No secondary malignancies were observed after a median follow-up of 4.6 years.

## **PRIMARY IMMUNODEFICIENCIES**

### Nonrandomized Studies

Chiesa (2020) conducted a retrospective, multicenter evaluation of 712 patients with chronic granulomatous disease who received a HCT between 1993 and 2018.<sup>[42]</sup> The majority of patients in the cohort were children (n=635) and the median age at transplantation was seven years (range, 0.1 to 48.6). Additionally, 87% of patients underwent transplantation after 2006. The three-year OS probability was 85.7% (95% CI 82.8 to 88.5) and the three-year EFS probability was 75.8% (95% CI 72.3 to 79.3). Donor engraftment was achieved in 88% of evaluable patients. The cumulative incidence of grades II to IV and grades III to IV acute GVHD was 20.1% and 9%, respectively. The cumulative incidence of chronic GVHD at three years was 17.8%.

Burroughs (2020) reported outcomes in patients with Wiskott-Aldrich syndrome who received a HCT at a Primary Immune Deficiency Treatment Consortium center between 2005 through 2015.<sup>[43]</sup> The most common conditioning regimens were a myeloablative busulfan-based regimen (n=84) and a busulfan-based reduced intensity conditioning regimen (n=25). After a median follow-up of 4.5 years, the five-year OS probability was 91% (95% CI, 85 to 95). Patients who received the HCT prior to age five years had superior five-year OS outcomes compared to older patients (94% vs 66%). The cumulative incidence of grades II to IV and grades III to IV acute GVHD were 27% and 15%, respectively.

In 2017, Ngwube reported a case series of HCT for Wiskott-Aldrich syndrome.<sup>[44]</sup> The authors performed a retrospective chart review of twelve patients with a median age of 10.5 months. All patients received allogeneic HCT. Median time to neutrophil and platelet engraftment was 19 and 18.5 months, respectively. At a median follow-up of 67 months, OS was 92%. Grade IV acute graft-versus-host disease occurred in two patients. At day +180, five patients (42%) had mixed donor chimerism. Of those patients, two had full donor chimerism after receiving a second transplant with the same donor, two patients had normalization of the platelet count despite the mixed chimerism, and at the time of publication, one patient remained transfusion dependent awaiting a second transplant.

Norman published a single center case series of HCT for primary immunodeficiency syndrome in 2017.<sup>[45]</sup> Twenty-two patients received HCT over five years for a variety of primary immunodeficiency syndromes, including severe combined immunodeficiency, chronic granulomatous disease and familial haemophagocytic lymphohistiocytosis. Of these cases, reduced intensity or reduced toxicity conditioning was used in 91%. Donors were unrelated in 75% of cases. Transplant related mortality was 9.5% (calculated at day +100) and there were three total mortalities. Cumulative OS was 86%.



Fox (2017) reported a case series of 29 adult patients receiving allogeneic HCT for primary immunodeficiencies.<sup>[46]</sup> All patients received reduced intensity conditioning. There were 18 unrelated donors and 11 related donors. Transplant related mortality occurred in four cases over a median follow-up of 3.5 years. No early or late rejection was observed. OS at three years was 85.2%. Stable mixed chimerism or full donor chimerism was observed in all patients.

In 2016, Patirolgu reported on a retrospective study describing the outcomes of HCTs performed at a single center for primary immunodeficiency diseases in 20 patients at a single center from 2010 to 2015.<sup>[47]</sup> There was a mixed patient population addressed in this study, with one of nine different conditions, including severe combined immunodeficiency, hemophagocytic lymphohistiocytosis, chronic granulomatous disease, type 2 Griscelli syndrome, B-cell deficiency plus bone marrow failure, severe congenital neutropenia, X-linked lymphoproliferative disease, T-cell deficiency plus relapsed non-Hodgkin lymphoma, and type 1 leukocyte adhesion deficiency. Of the 20 patients, 11 received related HLA-matched, six received haploidentical, two received unrelated HLA-matched, and one received HLA-mismatched transplant. The median age at transplant was 21 months, and median follow-up was five months. Overall survival rate was 65%. Mean engraftment times for neutrophils and platelets were  $14.25 \pm 3.08$  and  $24.7 \pm 11.4$  days. GVHD was observed in 30% of patients.

In 2015, Umeda reported on the clinical outcomes of allogeneic HCT in a retrospective analysis of eight patients with Chediak-Higashi syndrome (CHS), with analysis performed on the remaining six patients still alive.<sup>[48]</sup> Four of five patients transplanted with myeloablative conditioning had successful engraftment but only three survived, while all three patients transplanted with RIC had successful engraftment and survive long term. Despite the engraftment success in both groups, the authors report that it is too early to tell if the post-transplant neurological deficits reported by other groups on patients with CHS will develop.

In 2015, Allewelt conducted a retrospective analysis of seven patients who underwent allogeneic HCT at a single center for HIGM syndrome with CD40 ligand deficiency.<sup>[49]</sup> Median age at transplant was 5.2 years (range 0.7 to 19.3). Five patients received myeloablative conditioning, and two patients received reduced intensity conditioning. Post-transplantation complications included veno-occlusive disease, hemorrhagic cystitis, adenoviremia, and cryptosporidium recurrence in one patient each. Two patients developed acute GVHD grades II-IV that resolved promptly with treatment and none developed extensive chronic GVHD. All patients were alive at a median follow-up of 9.7 (range 9.7 to 16.1) years post-transplantation with predominantly donor chimerism and no recurrent infections. HCT results in excellent survival and sustained immune reconstitution in patients with CD40 ligand deficiency using both myeloablative and reduced intensity conditioning approaches and various graft sources, including bone marrow, peripheral blood, and umbilical cord blood.

A prospective study in 16 centers in 10 countries worldwide enrolled patients aged 0 to 40 years with chronic granulomatous disease (CGD) treated with RIC HCT consisting of high-dose Flu, serotherapy or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration.<sup>[50]</sup> Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related-donors or HLA-9/10 or HLA-10/10 matched unrelated-donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at two years, incidence of acute and chronic GVHD, achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least six months of follow-up. A total 56 patients (median age 12.7 years) with chronic granulomatous disease were enrolled; 42

patients (75%) had high-risk features (i.e., intractable infections and autoinflammation), 25 (45%) were adolescents and young adults (age 14 to 39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At median follow-up of 21 months, OS was 93% (52/56) and EFS was 89% (50/56). The two-year probability of OS was 96% (95% CI, 86.46 to 99.09) and of EFS was 91% (79.78 to 96.17). Graft-failure occurred in 5% (3/56) of patients. The cumulative incidence of acute GVHD of grade III to IV was 4% (2/56) and of chronic GVHD was 7% (4/56). Stable ( $\geq 90\%$ ) myeloid donor chimerism was documented in 52 (93%) surviving patients.

Outcomes of HCT in patients with chronic granulomatous disease (CGD) were compared with those in patients with CGD who were given conventional treatment.<sup>[51]</sup> Forty-one patients in Sweden were diagnosed with CGD between 1990 and 2012. From 1997 to 2012, 14 patients with CGD, aged 1 to 35 years, underwent HCT and received grafts either from an HLA-matched sibling donor or a matched unrelated donor. Thirteen of the 14 (93%) transplanted patients were reported alive and well at publication. The mean age at transplantation was 10.4 years, and the mean survival time was 7.7 years. In contrast, 7 of 13 men or boys with X-linked CGD who were treated conventionally died from complications of CGD at a mean age of 19 years, while the remaining patients suffered life-threatening infections.

Hassan (2012) reported a multicenter retrospective study, which analyzed the outcome of HCT in 106 patients with adenosine deaminase deficient-SCID who received a total of 119 transplants.<sup>[52]</sup> HCT from matched sibling and family donors had significantly better OS (86% and 81%) in comparison to HCT from matched unrelated (66%;  $p < 0.05$ ) and haploidentical donors (43%;  $p < 0.0001$ ). Superior OS was also seen in patients who received unconditioned transplants in comparison to myeloablative procedures (81% vs. 54%;  $p < 0.003$ ) although in unconditioned haploidentical donor HCT, non-engraftment was a major problem. Long term immune recovery showed that regardless of transplant type, overall T cell numbers were similar although a faster rate of T cell recovery was observed following matched sibling and family donor HCT. Humoral immunity and donor B cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HCT.

HCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies such as severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies in approximately 90% of cases.<sup>[1, 53]</sup> According to a European series of 475 patients collected between 1968 and 1999, survival rates for SCID were approximately 80% with a matched sibling donor, 50% with a haploidentical donor, and 70% with a transplant from an unrelated donor.<sup>[53]</sup> Since 2000, overall survival for patients with SCID who have undergone HCT is 71%.<sup>[1]</sup>

Moratto retrospectively reported the long-term outcome and donor cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HCT in the period 1980-2009.<sup>[54]</sup> Overall survival was 84.0% and was even higher (89.1% five-year survival) for those who received HCT since the year 2000, reflecting recent improvement in outcomes after transplantation from mismatched family donors and for patients who received HCT from an unrelated donor at older than five years. Patients who went to transplantation in better clinical condition had a lower rate of post-HCT complications. Retrospective analysis of lineage-specific donor cell engraftment showed that stable full donor chimerism was attained by 72.3% of the patients who survived for at least one year after HCT. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte counts and post-HCT autoimmunity, and myeloid donor cell chimerism  $< 50\%$  was associated with persistent thrombocytopenia.

For Wiskott-Aldrich syndrome, an analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes.<sup>[55]</sup> Fifty-five transplants were from HLA-identical sibling donors, with a five-year probability of survival of 87% (95% (CI) 74 to 93%); 48 were from other relatives, with a five-year probability of survival of 52% (37 to 65%); and 67 were from unrelated donors with a five-year probability of survival of 71% (58% to 80%; p=0.0006).

For patients with genetic immune/inflammatory disorders such as hemophagocytic lymphohistiocytosis, the current results with allogeneic HCT are 60% to 70% five-year disease-free survival. For patients with other immunodeficiencies, overall survival rates are 74%, with even better results (90%) with well-matched donors for defined conditions such as chronic granulomatous disease.<sup>[11]</sup>

X-linked lymphoproliferative disease type 1 (XLP1) is a rare, deadly immune deficiency caused by mutations in *SH2D1A*.<sup>[56]</sup> Allogeneic HCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. A recent study reported an eight-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allogeneic HCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, Flu, and melphalan. Fourteen of 16 patients received 8/8 HLA-matched unrelated or related bone marrow grafts, whereas two patients received mismatched unrelated grafts. All patients had hematopoietic recovery. No cases of hepatic veno-occlusive disease or pulmonary hemorrhage were reported. One patient (6%) developed acute GVHD and later also developed chronic GVHD (6%). Five patients (31%) developed mixed chimerism. One-year survival estimated by Kaplan-Meier analysis was 80%, with long-term survival estimated at 71%. There were no occurrences of lymphoma after HCT.

### **Reduced-intensity Conditioning**

Studies so far indicate that RIC regimens may have an important role in treating patients with primary immunodeficiency.<sup>[57]</sup> In the absence of prospective or larger registry studies, it is not possible to prove superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae, e.g., infertility and growth retardation, may be avoided or reduced. Currently, RIC HCT using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (older than five years of age), and chronic granulomatous disease with ongoing inflammatory or infective complications. Minimal intensity conditioning HCT may be particularly suited to unrelated donor HCT in young SCID patients with significant comorbidities.

### **INHERITED METABOLIC DISORDERS**

In the past 25 years, HCT has been performed in about 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders.<sup>[7]</sup> The majority (>80%) have been in patients with mucopolysaccharidosis I (MPS I; Hurler syndrome), other MPS syndromes (MPS II, MPS III A and B, MPS VI), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid leukodystrophy.<sup>[7]</sup> With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up.<sup>[58]</sup> The benefit of allogeneic HCT appears limited to select subsets of patients with few types of lysosomal storage diseases, and is not effective in patients who have developed overt neurological symptoms or in those with aggressive infantile forms.<sup>[58]</sup>

## Mucopolysaccharidosis Syndromes

### Hurler Syndrome (MPS I)

Impressive results have been observed with allogeneic HCT in Hurler syndrome, which has been performed in these patients for more than 30 years. The benefits that have been observed include improvement of neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others.<sup>[7]</sup>

#### *Nonrandomized Studies*

In 2016, Ghosh reported on 10 years of experience using enzyme replacement therapy pre-HCT in two pediatric metabolic and transplant centers.<sup>[59]</sup> Of the 81 patients who underwent a first transplant procedure for Hurler, 88% (71/81) survived and 81% (66/81) were alive and engrafted at a median follow-up of 46 months (range 3 to 124 months). Overall survival and EFS in our cohort were 86% and 80% respectively. The incidence of grade II-IV acute and any chronic GVHD was 17% and 11% respectively. Urinary glycosaminoglycans were significantly reduced after a period of enzyme replacement therapy, and further reductions were seen at 13 to 24 months and >24 months post-transplantation. In several individuals with decreased cardiac contractility, an improvement of their condition during enzyme replacement therapy enabled them to undergo transplantation. Combined ERT and HCT appears to be the standard of care for patients with Hurler syndrome at many centers.

In 2015, an evaluation of survival and graft outcomes of 62 patients with mucopolysaccharidosis I–IV that have received HCT since 2005, indicate that these patients have high OS (95.2%) and EFS (90.3%) with only low percentages of 13.3% acute graft-versus-host disease (GVHD) and 14.8% chronic GVHD.<sup>[60]</sup>

A retrospective analysis of 217 Hurler syndrome patients from a large international multi-center study that successfully underwent HCT were assessed at a median of 9.2 years post-transplantation for predictors of long-term outcome.<sup>[61]</sup> The primary endpoints assessed were neurodevelopmental outcomes and growth. The investigators reported considerable residual disease burden in the majority of the transplanted patients, with high variability between patients. The major predictors of neurodevelopment were the preservation of cognitive function at the time of transplant, and a younger age at transplantation. Normal  $\alpha$ -L-iduronidase enzyme level obtained posttransplantation was another highly significant predictor for superior long-term outcome in most organ systems. Other factors that improved long-term outcomes included using exclusively noncarrier donors and achieving complete donor chimerism.

Experience with allogeneic HCT and a reduced-intensity preparative regimen has been reported in seven patients with Hurler syndrome.<sup>[62]</sup> Six of the patients received transplants from unrelated donors and one received the transplant from a sibling. All patients had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the seven children were alive at a median of 1,014 days (range: 726 to 2,222 days) post-transplant.

Survival of engrafted Hurler syndrome patients has been radically changed from that of untransplanted patients, with long-term survival data indicating that life span will be extended many decades.<sup>[2]</sup> An analysis of nearly 150 transplanted patients with Hurler syndrome showed an overall survival rate of more than 80%.<sup>[63]</sup>

### **Hunter Syndrome (MPS II)**

Hunter syndrome (MPS II) is composed of two distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged life span, minimal to no central nervous system involvement, and a slow progression.<sup>[2]</sup> Experience with allogeneic HCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly.<sup>[2]</sup> Some authors suggest that HCT would not be justifiable in the attenuated form, because the risks outweigh the possible benefits.<sup>[2]</sup>

### Nonrandomized Studies

Eight patients with Hunter syndrome received an allogeneic HCT between the ages of 3 and 16 years.<sup>[64]</sup> In six cases, the donor was a sibling with identical HLA status, in one case, the donor was unrelated HLA-compatible, and in one case, the donor was a mismatched unrelated donor. The severity of disease prior to transplant was rated by assessing the age at diagnosis, behavior, and intelligence quotient (IQ) at the time of graft and genotype. Five patients were considered to have severe CNS involvement (i.e., diagnosis before the age of four years and an IQ less than 80), two were considered to have the attenuated form (i.e., diagnosis at five years and normal IQ), and one as intermediate (i.e., diagnosis after the age of four and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive with the exception of one patient who died of unrelated causes. Successful engraftment was achieved in all patients and cardiovascular abnormalities stabilized in all patients, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. Neuropsychological outcome was variable: the two patients with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four patients with the severe form of the syndrome deteriorated after the graft, and their IQ/developmental quotient had declined below 50 at the time of the last evaluation. Of the patients with the severe form, three lost the ability to walk in their early teens, two lost language at 9 and 11 years, and two developed epilepsy. The remaining two patients with the severe form required special schooling and had poor social and language skills.

## **Other Mucopolysaccharidosis Syndromes**

### Nonrandomized Studies

Experience with allogeneic HCT in patients with MPS III (Sanfilippo syndrome) has also been disappointing, with no alteration in the course of neuropsychologic deterioration seen in these patients.<sup>[2]</sup> The literature addressing the use of HCT in Sanfilippo disease consists of two case reports.<sup>[65, 66]</sup> Vellodi (1992) reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HCT and were followed up for nine years.<sup>[65]</sup> At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next eight years, both girls had a steady decline in cognitive development and both functioned in the area of significant developmental delay. The authors postulated that a possible reason for continued deterioration in the twins, despite the demonstration of full chimerism, was a very low level of enzyme throughout the years after transplant. One other patient with MPS III who had received a transplant was 5.3 years old at the time of the transplant, and continued to regress post-transplant.<sup>[66]</sup>

The few patients with Maroteaux-Lamy and Sly syndrome that have received transplants have shown promising results, with clinical improvement post-transplant.<sup>[2]</sup>

## **Other Inherited Metabolic Disorders**

Outcomes with the leukodystrophies and allogeneic HCT have been variable but somewhat promising. In boys and men with X-linked adrenoleukodystrophy; outcomes have depended on disease status at transplant and transplant-related complications<sup>[2]</sup>, but reports of preservation of neuropsychologic and neurologic function have been made.

### Nonrandomized Studies

Miller (2011) reported the results of 60 boys who underwent allogeneic HCT for cerebral adrenoleukodystrophy between 2000 and 2009.<sup>[67]</sup> The median age at HCT was 8.7 years; conditioning regimens and allograft sources varied. At HCT, 50% demonstrated a Loes radiographic severity score of 10 or more, and 62% showed clinical evidence of neurologic dysfunction. A total of 78% (n=47) are alive at a median 3.7 years after HCT. The estimate of five-year survival for boys with Loes score less than 10 at HCT was 89%, whereas that for boys with Loes score of 10 or more was 60% (p=0.03). The five-year survival estimate for boys absent of clinical cerebral disease at HCT was 91%, whereas that for boys with neurologic dysfunction was 66% (p=0.08). The cumulative incidence of transplantation-related mortality at day 100 was 8%. Posttransplantation progression of neurologic dysfunction depended significantly on the pre-HCT Loes score and clinical neurologic status.

Fewer than 40 patients with globoid-cell leukodystrophy have undergone allogeneic HCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.<sup>[2]</sup>

Many patients with metachromatic leukodystrophy who have undergone allogeneic HCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival.<sup>[2]</sup>

Mynarek (2011) reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HCT.<sup>[68]</sup> Patients were diagnosed with the disease at a median age of 2.5 years (range 1.1 to 23 years) and underwent HCT at a median age of 3.6 years (1.3 to 23.1 years). After a median follow-up of 5.5 years (2.1 to 12.6 years), OS was 88%. One patient died 76 days after HCT from sepsis, GVHD and pulmonary hemorrhage and another patient died on day 135 due to viral infections and multi-organ failure. Before HCT, the extent of developmental delay in the 17 patients varied over a wide range. After HCT, patients made developmental progress, however normal development was not achieved. Hearing ability improved in some but not all of the patients.

## **INFANTILE MALIGNANT OSTEOPETROSIS**

The success of allogeneic HCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a five-year disease-free survival of 73% to 79% versus transplantation with an unrelated or mismatched donor of 13% to 45%.<sup>[8]</sup>

### **Nonrandomized Studies**

A retrospective analysis of 194 patients with infantile osteopetrosis transplanted between 1990 and 2011 reported five-year disease-free survival of 62% for recipients of HLA-matched sibling transplants, and 42% for recipients of a graft from a matched unrelated donor.<sup>[69]</sup> Mortality risks were higher after alternative donor compared with HLA-matched sibling donor transplantation (HR 1.65; 95% CI 1.04 to 2.62; p=0.03). The most common cause of death was graft failure,

accounting for 50% of deaths after HLA-matched sibling and 43% of deaths after alternative donor transplantation.

A retrospective analysis of 122 children who received an allogeneic HCT for autosomal recessive osteopetrosis between 1980 and 2001 reported five-year disease-free survival of 73% for recipients of a genotype HLA-identical HCT (n=40), 43% for those of a phenotype HLA-identical or one HLA-antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20), and 24% for patients who received an HLA-haplotype-mismatch graft from a related donor (n=41).<sup>[70]</sup>

## PRACTICE GUIDELINE SUMMARY

### AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020 the American Society for Transplantation and Cellular Therapy (ASTCT) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings.<sup>[71]</sup> Table 2 provides the allogeneic guidelines for specific indications. Each indication is given a rating, which include:

- (1) Standard of care, where indication for HCT is well defined and supported by evidence,
- (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy,
- (3) Standard of care, rare indication, for rare diseases where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible,
- (4) Developmental, for diseases where pre-clinical and/or early phase clinical studies show HCT to be a promising treatment option, and
- (5) Not generally recommended, where available evidence does not support the routine use of HCT.

**Table 2. Recommendations for Use of Allogeneic HCT to Treat Genetic Diseases and Acquired Anemias**

Indications	Allogeneic HCT <18 Years
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S
Fanconi anemia	R
Dyskeratosis congenita	R
Sickle cell disease	C
Thalassemia	S
Congenital amegakaryocytic thrombocytopenia	R
Severe combined immunodeficiency	R
T-cell immunodeficiency, severe combined immunodeficiency variants	R
Wiskott-Aldrich syndrome	R
Hemophagocytic disorders	S
Severe congenital neutropenia	R
Chronic granulomatous disease	R

<b>Indications</b>	<b>Allogeneic HCT &lt;18 Years</b>
Other phagocytic cell disorders	R
Immunodysregulation polyendocrinopathy entropathy X-linked syndrome (IPEX)	R
Juvenile rheumatoid arthritis	D
Systemic sclerosis	D
Other autoimmune and immune dysregulation disorders	R
Mucopolysaccharidosis I	R
Other mucopolysaccharidoses (II, IV, VI)	D
Other lysosomal metabolic diseases	D
Osteopetrosis (severe, recessive)	R
Osteopetrosis (intermediate)	D
Globoid cell leukodystrophy (Krabbe)	R
Metachromatic leukodystrophy	R
Cerebral X-linked adrenoleukodystrophy	R
<b>Indication</b>	<b>Allogeneic HCT &gt;18 Years</b>
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S
Fanconi anemia	R
Dyskeratosis congenita	R
Sickle cell disease	C
Thalassemia	D
Hemophagocytic syndromes, refractory	S
Mast cell diseases	R
Common variable immunodeficiency	R
Wiskott-Aldrich syndrome	C
Chronic granulomatous disease	R
Multiple sclerosis	N
Systemic sclerosis	N
Rheumatoid arthritis	N
Systemic lupus erythematosus	N
Crohn's disease	N
Polymyositis-dematomyositis	N

C: clinical evidence available; D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication; S: standard of care.



## SUMMARY

There is enough research to show that allogeneic hematopoietic cell transplantation using myeloablative or reduced-intensity conditioning in select individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome or a genetic disorder affecting skeletal tissue leads to improvement in survival and other disease-specific outcomes. Therefore, allogeneic hematopoietic cell transplantation using myeloablative or reduced-intensity conditioning may be considered medically necessary in select individuals when the policy criteria are met.

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## CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	;thawing of previously frozen harvest, without washing, per donor
	38209	;thawing of previously frozen harvest with washing, per donor
	38210	;specific cell depletion with harvest, T cell depletion
	38211	;tumor cell depletion
	38212	;red blood cell removal
	38213	;platelet depletion
	38214	;plasma (volume) depletion
	38215	;cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	;autologous transplantation	
38242	Allogeneic lymphocyte infusions	
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

**Date of Origin:** December 2018