



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplant for Primary Immunodeficiency Disorders

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Coverage Policy

CIGNA covers allogeneic hematopoietic stem-cell transplantation (HSCT) as medically necessary for the treatment of primary immunodeficiency disorders.

General Background

Immunodeficiency disorders, also known as primary, congenital, or inherited immunodeficiency disorders, are conditions where there is a failure of the immune system to fight invading microorganisms or tumors. The term primary denotes the genetic nature of the defects, differentiating them from secondary, or acquired, immunodeficiencies caused by malnutrition, infection, chemotherapy, or other external agents (Lindegren, 2004). The disorders vary in the severity and spectrum of symptoms, but without effective and early treatment, they can be fatal (Lindegren, 2004).

Primary immunodeficiency disorders are often classified according to the affected components of the immune system or immunologic phenotype (Lindegren, 2004; Notarangelo, 2006). The classifications include combined T cell and B cell (antibody) deficiencies, predominantly antibody deficiencies, other well-defined immunodeficiency syndromes, diseases of immune dysregulation, congenital defects of phagocyte number and function, or both, defects in innate immunity, autoinflammatory disorders, and complement deficiencies (Notarangelo, 2006). Although over 120 primary immunodeficiency syndromes have been identified, less than

20 disorders account for over 90% of the known cases (Lindegren, 2004). Examples of more commonly seen disorders are noted below:

Combined T-Cell and B-Cell Antibody Deficiencies

Including severe combined immunodeficiency (SCID) and partial combined immunodeficiency (CID), these disorders have B- and T-cells that are defective or nonexistent. The treatment of choice is allogeneic HSCT from a human leukocyte antigen (HLA)-identical donor. If an HLA-identical donor is not available, a haploidentical donor, often a parent, may be used. Results with unrelated donors have not been as successful as with related donors. Patients who do not receive an allogeneic HSCT have a life expectancy of 1–2 years (Buckley, 2002).

Predominantly Antibody Deficiencies

X-linked agammaglobulinemia and combined variable immunodeficiency (CVID) involve a profound defect in B lymphocyte development. Individuals with agammaglobulinemia have severe hypogammaglobulinemia and an absence of circulating B cells. Individuals with CVID, a heterogeneous group of disorders, have an increased incidence of malignant lymphomas and autoimmune disorders.

Other Well-Defined Immunodeficiency Syndromes

This classification includes Wiskott-Aldrich syndrome (WAS), ataxia-telangiectasia (AT), DiGeorge syndrome, chronic mucocutaneous candidiasis, and hyper-IgE syndrome. WAS is a rare, X-linked recessive disorder characterized by eczema, thrombocytopenia and recurrent infections due to partial defects in T-cells and B-cells. In the majority of patients, there is a high risk of developing life-threatening complications due to thrombocytopenia and infections early in life. An increased incidence in cancer, especially lymphoma and leukemia, is seen. AT results in impaired, but not absent immunity with a predisposition to cancer, especially lymphoma and leukemia. The majority of children with DiGeorge syndrome have some thymic tissue, and immune deficiencies are usually minimal. Complete DiGeorge syndrome is characterized by complete lack of thymus function. Other syndromes in this classification include chronic mucocutaneous candidiasis and hyper-IgE syndrome.

Diseases of Immune Dysregulation

These disorders include Chediak-Higashi syndrome and X-linked lymphoproliferative disease. Both disorders are extremely rare and usually fatal within months. Allogeneic HSCT is considered a definitive treatment (Nichols, 2002).

Congenital Defects of Phagocyte Number and Function, or Both

Chronic granulomatous disease and leukocyte adhesion defect are two disorders included in this classification and involve the inability of the phagocyte to adhere to target cells and/or destroy bacteria and fungi.

Defects in Innate Immunity

Anhidrotic ectodermal hyperplasia (NEMO Deficiency) and X-linked IgM syndrome are X-linked disorders, affecting only males. Clinical features include severe immunodeficiency. In addition, individuals with NEMO deficiency may have sweat gland abnormalities, osteopetrosis and lymphedema. X-linked IgM syndrome is characterized by recurrent respiratory infections, including pneumonia and autoimmune disorders such as arthritis, thrombocytopenia and kidney disease.

Autoinflammatory Disorders

Tumor necrosis factor (TNF) receptor-periodic fever is caused by a defect in the TNF gene coding receptor. Amyloidosis may also develop. Hyper-IgD syndrome is characterized by recurring chills and fever triggered by physiologic stress such as minor trauma or vaccination. Additional symptoms include cervical lymphadenopathy, hepatosplenomegaly, and arthritis.

Complement Deficiencies

Disorders in this classification include hereditary angioedema, caused by a low level or improper functioning of a C1 inhibitor protein. This disorder affects the blood vessels and rapid swelling may occur without warning; laryngeal swelling may be life-threatening.

Stem-Cell Transplantation: Stem-cell transplantation refers to transplantation of hematopoietic stem-cells (HSC) s into an individual. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets. HSC transplantation (HSCT) can be either autologous (using the individual's

own stem cells) or allogeneic (using stem cells from a donor). HSCT is provided to persons with bone marrow failure to replace their defective stem cells with those that are fully functioning.

Although there are a number of observational and descriptive studies involving the use of allogeneic HSCT for the treatment of primary immunodeficiency disorders there are no randomized controlled trials in the published, peer-reviewed scientific literature. Nonetheless, allogeneic HSCT is the only curative treatment for inherited immunodeficiency disorders is allogeneic hematopoietic stem-cell transplantation (HSCT) (National Marrow Donor Program [NMDP], 2008; Buckley, 2004; Lindegren, 2004). It is the treatment of choice for severe combined immunodeficiency (SCID) variants, as well as for several other inherited immunodeficiencies (Diaz de Heredia, 2008; NIH, 2007; Velardi, 2007). With an HLA-identical sibling, the probability of survival approaches 100%, with less favorable results for patients transplanted from an unrelated volunteer or an HLA-partially matched relative. Patients with the most severe immunodeficiencies must be transplanted as early as possible (Velardi, 2007).

Contraindications

Many factors affect the outcome of a tissue transplant. The selection process is designed to obtain the best result for each individual. Relative contraindications to HSCT include, but are not limited to:

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

Literature Review

Several retrospective review and case reports have demonstrated improved survival in patients with a variety of primary immunodeficiency disorders who underwent allogeneic HSCT (Diaz de Heredia, 2008, Cohen, 2007; Sato, 2007; Tsuji, 2006; Rao, 2005; Amrolia, 2000). In two small case reports where patients received reduced-intensity conditioning, median four-year overall survival was 100% with stable chimerism (Cohen, 2007; Sato, 2007).

Petrovic et al. (2009) performed a retrospective analysis of 31 patients with primary immunodeficiency who received an allogeneic HSCT. The disorders included severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, X-linked hyper IgM syndrome, and chronic granulomatous disease. Overall survival for all patients was 65%. Better survival was seen in patients transplanted at an earlier age and in those who were free of infections.

Diaz de Heredia et al., reported outcomes of 15 patients with primary immunodeficiency who underwent allogeneic umbilical cord blood transplantation. Diagnoses included severe combined immunodeficiency syndrome (SCID, n=11) and X-linked lymphoproliferative disease (n=2). Eight patients developed acute graft-versus-host disease (GVHD) and one patient developed chronic GVHD. With a median follow-up of 64 months, five-year overall survival was 73%. All surviving patients presented complete immunologic reconstitution.

Tsuji et al. (2006) retrospectively analyzed the results of 30 male pediatric patients with a variety of primary immune diseases who received allogeneic HSCT. Conditioning regimens varied by disease and patient status. Median age was 10 years. Twenty-seven of thirty patients had pre-existing infections with or without organ damage prior to transplantation. Median follow-up was 85.6 months. Overall survival rates were reported for time periods of 1984–1995 and 1996–2004 and were 25% and 80%, respectively.

Rao et al. (2005) reported on a series of 33 consecutive unrelated donor transplantations performed in children with primary immunodeficiency using a reduced-intensity conditioning regimen from 1998–2001. The results were compared to a retrospective control cohort of 19 patients who underwent transplantation with myeloablative conditioning from 1994–1998. The groups were similar in the rates of engraftment and GVHD.

Overall survival was significantly improved in the reduced-intensity conditioning group compared with the myeloablative conditioning group (94% versus 53%, respectively).

Amrolia et al. (2000) reported on a series of eight patients with immunodeficiency who were ineligible for conventional myeloablative conditioning because of comorbidity, and who could not receive HSCT without conditioning because of residual T or natural killer cell function that was likely to compromise engraftment. Patients received non-myeloablative conditioning. All patients engrafted to some extent, and GVHD was limited. One patient died of disease recurrence, and three had stable, mixed chimerism. At a median follow-up of one year, six of seven surviving patients had adequate T-cell function.

Severe Combined Immunodeficiency Disease (SCID): Grunebaum et al. (2006) performed a retrospective study of 91 patients with SCID who received an allogeneic hematopoietic stem cell transplantation (HSCT). Overall survival was 92.3%, 80.5%, and 52.5%, respectively, for patients receiving related human leukocyte antigen (HLA)-identical, HLA-matched unrelated, and HLA-mismatched related donor grafts.

Partial Combined Immunodeficiency (CID): Purine Nucleoside Phosphorylase (PNP) Deficiency: Myers et al. (2004) documented a case in which a three year-old boy with PNP deficiency received an allogeneic HSCT from an unrelated, female umbilical cord blood donor with one antigen mismatch. By day +33 after transplantation, the patient had normal PNP activity; by one year after transplantation, he had normal lymphocyte function.

Wiscott-Aldrich Syndrome (WAS): Friedrich et al. (2009) retrospectively analyzed 39 patients with WAS who underwent an allogeneic HSCT with a human leukocyte antigen (HLA)-identical sibling, HLA-mismatched parental, or HLA-compatible donor. With a mean follow-up of 11 years overall survival was 90% and 50%, respectively, for patients receiving an identical or non-identical donor graft. With the exception of one patient, all surviving patients are free of abnormalities of WAS, with stable and normal platelet numbers, lack of eczema, and regular immune functions as well as the absence of infectious complications.

Ozsahin et al. (2008) reported the results of a long-term, retrospective, multi-center study of 96 patients with WAS who received allogeneic HSCT and who were alive at least two years after transplant. Median patient age of patients in the study was two years. Forty-five patients received a matched sibling donor graft; 32 patients received a donor graft from an unrelated donor. Overall seven-year event-free survival was 75%. Event-free survival rates were 88% and 71%, respectively, for patients with matched sibling, and unrelated donors ($p=.03$). Twenty percent of patients had autoimmune manifestations (e.g. autoimmune thrombocytopenia, autoimmune hemolytic anemia) after transplantation. These appeared a median of 1.5 years after transplantation with a median duration of four years.

On behalf of the Spanish Working Party for Blood and Marrow Transplantation in Children (GETMON), Munoz et al. (2007) retrospectively analyzed the outcomes of allogeneic HSCT in 13 patients with WAS. One patient received two transplants due to late graft failure. Median age at transplant was 30 months. At a median of 101 months after transplantation nine patients were alive with complete clinical, immunologic, and hematologic recovery.

Kobayashi et al. (2006) retrospectively reviewed the outcomes of 57 patients with WAS who received an allogeneic HSCT. Overall survival rate at five years was 73.7%, with a five-year failure-free survival rate of 65.7%.

Pai et al. (2006) analyzed the results of 23 patients who received an allogeneic HSCT for WAS. Sixteen patients used a matched unrelated donor (MUD) source. Overall survival at a follow-up of three months to 132 months was 78.2% for the whole cohort. All recipients of matched sibling marrow and 81.2% (13/16) of unrelated were alive at the time of this report. Both recipients of mismatched related bone marrow died. No transplant-related deaths have occurred.

In a report from the International Bone Marrow Transplant Registry (Filipovich, et al., 2001), the cases of 170 patients with WAS who had undergone allogeneic transplantation were reviewed. The five-year probability of survival for all patients was 70%. The probability of survival was dependent upon the type of donor. Probability of survival was 87%, 52%, and 71% for patients receiving transplants from HLA-identical siblings, other related donors, and unrelated donors.

Chediak-Higashi Syndrome (CHS): Eapen et al. (2007) performed a retrospective analysis of 35 patients with CHS who underwent an allogeneic HSCT. Median age was five years. Patients had received variable therapies prior to transplantation. Eleven patients were in the accelerated phase of the disease at time of transplant; 22 patients had a history of life-threatening accelerated phase of the disease. Donor grafts were from an HLA-matched siblings (n=13), alternative related donors (n=10), and unrelated donors (n=12). With a median follow-up of 6.5 years, the five-year probability of overall survival was 62%. Nine of 13 deaths occurred within 100 days of transplant. Twenty-two patients were alive and 21 were in hematologic remission at the time of this study publication. Mortality was highest in patients who were in the accelerated phase of the disease at transplant, and after the use of an alternative related donor.

Leukocyte Adhesion Deficiency: Qasim et al. (2009) retrospectively analyzed the outcomes of 36 children with leukocyte adhesion deficiency that underwent allogeneic HSCT. At a median follow-up of 62 months, overall survival was 75%. Myeloablative conditioning was used in 28 patients and nonmyeloablative conditioning in eight patients. Survival rates after matched unrelated (86%) and matched related (79%) donor grafts were similar. Mortality rate was greatest with the use of haploidentical grafts with survival rate of 50% in that cohort.

Professional Societies/Organizations

The National Institute of Child Health and Human Development ([NICHD], 2008) notes that for several life-threatening immunodeficiencies, bone marrow transplantation offers the chance of a dramatic, complete, and permanent cure.

The National Marrow Donor Program notes that severe combined immunodeficiency (all types) and other inherited immune system disorders, including Wiskott-Aldich syndrome are treatable by allogeneic hematopoietic cell transplantation.

Summary

There is sufficient evidence in the published, peer-reviewed literature to support allogeneic hematopoietic stem cell transplantation (HSCT) as medically necessary for the treatment of primary immunodeficiency disorders (PID).

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT[®]* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic

38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions
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HCCPS Codes	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

†Note: Covered when medically necessary and when used to report allogeneic bone marrow or blood-derived stem cell procedures.

ICD-9-CM Diagnosis Codes	Description
279.06	Common variable immunodeficiency

***Current Procedural Terminology (CPT®) ©2008 American Medical Association: Chicago, IL.**

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	7/15/2008	0378	Stem-Cell Transplant for Primary Immunodeficiency Disorders

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