

# Bone marrow transplant for children with hyper IgM disorder

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Policy contains: Bone marrow transplant; CD40 mutation, CD40 ligand mutation; hematopoietic stem cell transplantation; hyper IgM; pneumocystis jirovecii pneumonia.

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## Coverage policy

Bone marrow transplantation is clinically proven and, therefore, may be medically necessary for children with hyper Immunoglobulin M (IgM) disorder (Bonilla, 2015; National Organization for Rare Diseases, 2018).

### Limitations

All other uses of bone marrow transplantation for children with hyper IgM disorder are not medically necessary.

### Alternative covered services

No alternative covered services were identified during the writing of this policy.

## Background

The hyper IgM syndrome is a rare, inherited immune deficiency disorder resulting from defects in the CD40 ligand (CD40L)/CD40-signaling pathway that affect T cell communication with B lymphocytes (Dunn, 2020). This results in an inability to switch from the production of antibodies of the IgM type to antibodies of the immunoglobulin G (IgG), immunoglobulin E (IgE), and immunoglobulin A (IgA) types. It manifests clinically as a severe life-threatening infection due to defects in humoral and cell-mediated immunity (e.g., fungal infections, opportunistic infections, or bacterial infections).

The diagnosis of hyper IgM syndrome is suggested by flow cytometry showing normal T-cell numbers in the presence of serum IgM that is elevated (or even normal) with reductions in serum IgG, IgE, and IgA (Dunn, 2020). Diagnosis is confirmed with genetic studies, which show mutation in either CD40 or CD40L. A marked reduction in class-switched memory B cells is also present, as are antigen-specific responses (de la Morena, 2017; Dunn, 2020).

About 70% of persons with X-linked hyper IgM disorder inherit the condition in an X-linked recessive pattern, and most cases affect approximately one in one of 1,000,000 newborn males (Dunn, 2020). Autosomal recessive forms of hyper IgM syndrome, known as hyper IgM syndromes type 2, 3, 4, and 5, are extremely rare and appear to affect males and females equally.

Most patients present initially with an elevated susceptibility to infection. A total of 145 patients, 131 of whom were males (median 12 years) with hyper IgM syndrome who were in the U.S. Immunodeficiency Network patient registry showed 91% with infections, with pulmonary, ear, and sinus infections being the most common; 42% had pneumocystis jirovecii pneumonia (Leven, 2016). Overall survival is 20% by age 25 (de la Morena, 2017).

The long-term outcome of X-linked hyper-IgM syndrome caused by mutations in CD40L is poor. Various treatments have been tried, with varying degrees of success, including (Dunn, 2020; Meng, 2018):

- Administration of therapeutic immunoglobulin, antibiotics for infections, and steroids for neutropenia or severe autoimmune manifestations.
- Gene therapy, which remains in the animal testing stage.
- Activation of CD40 receptor regulated by CD40 agonists, which remains incomplete.
- Hematopoietic stem cell transplantation.

## Findings

A study of 176 patients diagnosed with X-linked hyper IgM syndrome from 1964 to 2013 were randomized into those receiving hematopoietic stem cell transplantation ( $n = 67$ ) and those who did not ( $n = 109$ ). After follow-up for an average 8.5 years, the two groups had an insignificant difference in overall survival ( $P = .671$ ), which was more than 80%. However, risk associated with transplantation decreased for diagnosis years 1987 to 1995, and the hazard ratio was significantly less than 1.0 for those diagnosed from 1995 to 1999 (de la Morena, 2017).

An international collaborative study ( $n = 130$ ) of patients with CD40L deficiency tracked patients for five years after hematopoietic stem cell transplantation, and determined overall survival, event-free survival, and disease-free survival to be 78.2%, 58.1%, and 72.3%, respectively. Patients who underwent transplantation beginning in 2000 had better outcomes as did children less than 10 years old at the time of the procedure (Ferrua, 2019).

A Japanese study (Mitsui-Sekinaka, 2015) retrospectively analyzed data from 56 patients with hyper IgM disorder, including 29 patients who received hematopoietic stem cell transplantation. The long-term survival rate was poor in those not undergoing transplantation (survival rate at 40 years of age, 28.2%). The overall survival rate of patients undergoing transplantation was significantly higher ( $P = .0231$ ). Moreover, event-free and disease-free survival rates were significantly greater in patients five years old or younger at the time of transplantation ( $n = 14$ ) than in older patients ( $n = 15$ ). The authors note that persistent infections and severe organ damage were frequently observed in patients older than six years.

Wang (2014) retrospectively analyzed the clinical and molecular features of 20 Chinese patients diagnosed with hyper IgM disorder and followed up in hospitals affiliated to Shanghai Jiao Tong University School of Medicine from 1999 to 2013. The median onset age of these patients was 8.5 months (range: 20 days – 21 months). Half of them had positive family histories, which helped identify them as sufferers from the disease. The most common symptoms were recurrent sinopulmonary infections (90%), neutropenia (70%), oral ulcer (65%), and protracted

diarrhea (65%). Six patients received hematopoietic stem cell transplants and four had immune reconstructions and clinical remissions. Eighteen unique mutations in CD40L gene were identified, with 12 novel mutations.

Petrovic (2009) retrospectively analyzed the transplantation outcomes of 31 patients with primary immunodeficiency diseases treated at All Children's Hospital in Tampa, Florida. The primary immune diseases included severe combined immunodeficiency, Wiscott-Aldrich syndrome, X-linked hyper IgM syndrome, and chronic granulomatous disease. The age of the patients at the time of transplantation ranged from 1 month to 19 years, and conditioning regimens varied based on the patient's underlying disease. In 23 patients, the graft source was bone marrow, four patients received umbilical cord blood grafts, and four patients received peripheral blood stem cell grafts. Better survival rates were observed in patients transplanted at a younger age and with a history free of infections. The authors concluded that transplantation at an early age before significant infections, autoimmune manifestation, and malignant transformation have occurred is beneficial to survival.

In 2022, we added a statement from the National Organization for Rare Diseases (2018) and a joint guideline from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology (Bonilla, 2015). Both organizations recommend hematopoietic stem cell transplantation as the only curative treatment for hyper IgM disorder, although they admit experience is limited. In addition, the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology, and Joint Council of Allergy, Asthma & Immunology guideline issued a moderate-strength recommendation for hematopoietic stem cell transplantation as prophylaxis for *Pneumocystis jirovecii* pneumonia for all patients with known or suspected CD40 or CD40L deficiency, as this infection occurs in 30% to 40% of patients with defects of CD40 or CD40L (Bonilla, 2015). No policy changes are warranted.

In 2023, we updated the references and found no newly published relevant information to add to the policy. No policy changes are warranted.

In 2024, we added a literature review of 258 cases from 24 journals (all in English) of hyper IgM disorder due to CD40 ligand gene mutation treated with hematopoietic stem cell transplant. Donor types were mostly matched siblings (30.6%) and unrelated persons (40.3%). Bone marrow was the source of grafts for just over half (50.8%) of the patients. Survival after transplantation was 70.9%, lung injury and liver complications before transplant adversely affected prognosis (Wang, 2021).

No policy changes are warranted.

## References

On December 19, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were : "CD40 (MeSH)," "CD40 ligand (MeSH)," and "hyper IgM syndrome." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

4/2016: initial review date and clinical policy effective date: 7/2016

1/2018: Policy references updated.

1/2019: Policy references updated. The policy ID changed from 17.02.01 to CCP.1226.

12/2019: Policy references updated.

3/2021: Policy references updated.

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