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 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

The body of evidence on hematopoietic stem cell transplantation as a treatment for hyper-immunoglobulin M syndrome reflects a rare disease for which no randomized controlled trials exist, and the literature is composed primarily of retrospective cohort studies, case series, narrative reviews, and case reports. Across the reviewed evidence, scientists broadly agree that hyper-immunoglobulin M syndrome, particularly the X-linked form caused by mutations in the CD40 ligand gene, carries a poor long-term prognosis when managed with supportive care alone, with median survival from diagnosis estimated at approximately 25 years and only 20% to 50% of patients surviving to the third decade of life. There is also broad consensus that hematopoietic stem cell transplantation represents the only potentially curative intervention for this condition. However, important areas of disagreement persist: the evidence is divided on whether transplantation confers a clear overall survival advantage compared with conservative management, the optimal timing and conditioning regimen for transplantation remain debated, and the quality of available evidence is limited by the retrospective nature of nearly all published studies. The clinical utility of transplantation is most strongly supported when it is performed early in life, before the onset of organ damage, and when a well-matched donor is available. What follows is a thematic analysis of the evidence organized by study type.

Guidelines

The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology jointly published a practice parameter for the diagnosis and management of primary immunodeficiency (Bonilla, 2015). This guideline classifies hyper-immunoglobulin M syndromes, including those caused by defects in the CD40 ligand and CD40 genes, among the combined immunodeficiency diseases, recognizing that the molecular defect impairs both humoral and cellular immunity. This classification is clinically significant for the question of transplantation because it positions the disorder alongside severe combined immunodeficiency and other conditions for which transplantation is a first-line definitive therapy.

Transplantation as a Recommended Therapeutic Option

The Bonilla (2015) guideline identifies hematopoietic stem cell transplantation as an indicated therapy for CD40 ligand deficiency and CD40 deficiency, listing both conditions in a summary table of immunodeficiency diseases for which transplantation is appropriate. The guideline affirms that transplantation is the only intervention with potential to correct the underlying immune defect, because the disorder involves T-cell dysfunction that immunoglobulin replacement alone cannot address. However, the guideline does not assign a strong recommendation grade to transplantation for hyper-immunoglobulin M syndrome specifically, reflecting the limited quality of available evidence, which the authors characterize as consisting largely of case series and expert opinion (Category III and IV evidence). The guideline notes that the great majority of recommendations within the practice parameter are based on evidence from published case series or the opinions of experts in the field, given the absence of randomized trials in primary immunodeficiency management.

Supportive Care Recommendations

In addition to identifying transplantation as a curative option, the Bonilla (2015) guideline recommends a comprehensive supportive care regimen for patients with CD40 ligand and CD40 deficiency. This includes immunoglobulin replacement therapy, prophylaxis against Pneumocystis jirovecii pneumonia, and the use of granulocyte colony-stimulating factor for neutropenia. The guideline also emphasizes the importance of avoiding exposure to Cryptosporidium species, given the established association between this organism and sclerosing cholangitis, a complication that significantly worsens prognosis. The guideline does not provide detailed recommendations regarding the timing of transplantation relative to disease progression, the choice of conditioning regimen, or donor selection, reflecting the limited evidence available at the time of publication.

Retrospective Cohort Studies

The largest and most directly relevant studies in the evidence base are retrospective cohort analyses that compare outcomes of patients who underwent transplantation with those who received supportive care alone or that analyze transplantation outcomes in detail.

The evidence on whether transplantation improves overall survival is notably divided. De la Morena and colleagues (2017) conducted the largest study to date, a multinational retrospective analysis of 176 patients with X-linked hyper-immunoglobulin M syndrome (n = 176) from 28 clinical sites, with diagnoses spanning 1964 to 2013 and an average follow-up of 8.5 years. Of these patients, 67 (38%) received transplantation. The central finding was that no statistically significant difference in overall survival was observed between patients treated with or without transplantation (P-value [the probability that the observed result occurred by chance] = .671). The median survival from diagnosis was 25 years for the entire cohort, and median survival was similar between the two groups (25 years without transplantation versus 20 years with transplantation).

In contrast, Mitsui-Sekinaka and colleagues (2015) analyzed 56 patients with X-linked hyper-immunoglobulin M syndrome (n = 56), of whom 29 received transplantation. This study found that overall survival was significantly higher in transplanted patients compared with those who did not undergo transplantation (P = .0231). The overall survival at 10 years was 100% for transplanted patients versus 62.5% for non-transplanted patients, and at 30 years, 65.9% versus 35%. The median survival for the entire cohort was 23 years, consistent with the findings of De la Morena and colleagues (2017).

These two studies reach opposing conclusions on the central question of whether transplantation improves survival, which has direct implications for clinical utility. De la Morena and colleagues (2017) noted that this discrepancy may be partly explained by methodological differences: in the Mitsui-Sekinaka and colleagues (2015) analysis, there were no early deaths in the transplant group, raising the possibility that patients who did not survive long enough to receive transplantation were counted among non-transplant deaths, potentially confounding the comparison. Despite the lack of an overall survival difference across all years, De la Morena and colleagues (2017) found that the hazard associated with transplantation decreased over time. For patients diagnosed between 1995 and 1999, the hazard ratio was significantly less than 1, meaning transplantation was associated with a survival benefit during that era. This finding suggests that as transplantation techniques have improved, the procedure has become safer and potentially more beneficial, though the limited follow-up time for more recently diagnosed patients restricts the ability to draw definitive conclusions about contemporary practice.

Timing and age at transplantation

On the question of when transplantation should be performed, the evidence converges. De la Morena and colleagues (2017) found that among transplanted patients, younger age at transplantation was a significant predictor of better post-transplant survival, with the association reaching statistical significance at age thresholds of 5 and 10 years. Mitsui-Sekinaka and colleagues (2015) similarly reported that event-free and disease-free survival rates were significantly greater in patients aged 5 years or younger at transplantation (n = 14) compared with those older than 5 years (n = 15). Additionally, all four transplant-related deaths in the Mitsui-Sekinaka and colleagues (2015) study occurred in patients who were older than 15 years at the time of transplantation, and three of these four patients had organ damage before the procedure. Ferrua and colleagues (2019), in their analysis of 130 transplanted patients with CD40 ligand deficiency from an international multicenter registry, likewise found that outcomes were better in patients younger than 10 years at transplantation.

These consistent findings across three large cohorts support the clinical conclusion that if transplantation is pursued, it should be done early, ideally before age 5 to 10 years and before the development of organ damage. This principle has direct bearing on the clinical utility of transplantation: its benefit appears greatest when patients are identified and transplanted before the disease has caused irreversible complications.

<u>Organ damage as a risk factor</u>

All three major retrospective studies agree that pre-existing organ damage, particularly liver disease and sclerosing cholangitis, is a significant predictor of poor outcomes. De la Morena and colleagues (2017) identified liver and biliary involvement as the only significant negative predictor of survival in multivariable analysis (hazard ratio, 4.9; 95% confidence limits [the range within which the true effect likely falls], 2.2 to 10.8; P-value less than .001). Ferrua and colleagues (2019) found that sclerosing cholangitis was the most important risk factor negatively influencing event-free survival, both in historical and more recent transplantation cohorts. Mitsui-Sekinaka and colleagues (2015) reported that organ damage was observed in five transplanted patients, all of whom were older than 6 years, and noted that three of the four transplant-related deaths occurred in patients with pre-existing organ damage. This convergence of evidence reinforces that transplantation has the greatest clinical utility when performed before organ damage accumulates, and that the therapeutic window narrows as the disease progresses.

<u>Transplantation outcomes: engraftment, conditioning, and complications</u>

Ferrua and colleagues (2019) provide the most detailed analysis of transplant-specific variables, having collected data on 130 patients from 36 centers in 18 countries who underwent transplantation between 1993 and 2015. Overall survival, event-free survival, and disease-free survival at 5 years were 78.2%, 58.1%, and 72.3%, respectively. Several transplant-related findings emerged from this study.

Regarding conditioning regimen, myeloablative conditioning was associated with superior overall survival, event-free survival, and disease-free survival compared with reduced-intensity or non-myeloablative conditioning. Most graft rejections occurred after reduced-intensity or non-myeloablative conditioning, which were also associated with poorer donor cell engraftment. This finding is significant because the choice of conditioning intensity is a key clinical decision; Ferrua and colleagues (2019) suggest that a more intensive approach, though carrying higher short-term toxicity, yields better long-term disease control.

Regarding donor type, Ferrua and colleagues (2019) found that after the year 2000, superior overall survival was achieved with matched donors. Event-free survival was best with matched sibling donors. De la Morena and colleagues (2017) did not find a statistically significant effect of donor relationship, stem cell source, or conditioning regimen on post-transplant survival in their cohort, though this analysis may have been underpowered given the smaller number of transplanted patients (n = 67) and the heterogeneity of transplant practices.

Regarding graft-versus-host disease, De la Morena and colleagues (2017) reported that 40% of transplanted patients (27 of 67) developed graft-versus-host disease, predominantly acute, and Ferrua and colleagues (2019) reported a graft rejection rate of 15%. Most transplant-related deaths in both studies occurred early after transplantation, predominantly from infections. These complication rates are clinically meaningful because they represent the risks patients accept in exchange for potential cure.

The interval between diagnosis and transplantation also appears relevant. Ferrua and colleagues (2019) found that transplantation performed within 2 years of diagnosis was associated with higher overall survival and disease-free survival compared with longer intervals, further supporting early intervention.

Quality of life

De la Morena and colleagues (2017) found that among surviving patients, those who had undergone transplantation had significantly higher Karnofsky/Lansky scores (a measure of functional capacity and activity of daily living) compared with non-transplanted survivors (median 100% versus 90%, P-value less than .001). This finding is notable because even in the absence of an overall survival difference, transplantation was associated with greater functional well-being. Mitsui-Sekinaka and colleagues (2015) noted that 22 of 25 surviving transplanted patients (88%) were free of immunoglobulin replacement, suggesting successful immune reconstitution and independence from chronic therapy. These quality-of-life data support the clinical utility of transplantation beyond survival alone, suggesting that successfully transplanted patients may experience fewer chronic disease manifestations and greater independence from ongoing medical intervention.

Malignancy

De la Morena and colleagues (2017) reported that 8 of 176 patients (4.5%) developed malignancy, with a 75% mortality rate among those with cancer (6 of 8 died). Critically, malignancy as a cause of death was only observed in the non-transplanted group. This observation, while based on small numbers, raises the possibility that transplantation may prevent the long-term malignancy risk associated with chronic immunodeficiency and recurrent infection, particularly of the biliary tract. If confirmed in larger studies, this would represent an important additional argument for the clinical utility of transplantation.

Immune Reconstitution and Chimerism

Ferrua and colleagues (2019) reported that among survivors who discontinued immunoglobulin replacement at 2 or more years after the last procedure, T-lymphocyte chimerism was complete or predominantly donor in 85.2%. Viral infections after transplantation were associated with decreased donor chimerism, with 91.7% of transplants showing decreasing T-lymphocyte chimerism having experienced viral infections in early follow-up. This suggests that viral infections may promote expansion of residual host T cells, reducing the completeness of immune reconstitution. These data indicate that while transplantation can achieve meaningful immune reconstitution, the completeness of donor cell engraftment varies and may be influenced by post-transplant infectious complications.

Case Series

CD40 Deficiency (Autosomal Recessive Form)

Al-Saud and colleagues (2019) reported a single-center experience of transplantation in 6 patients with hyper-immunoglobulin M syndrome due to CD40 deficiency (the autosomal recessive form, as distinct from the more common X-linked CD40 ligand deficiency). This case series is notable as the largest reported cohort of transplanted patients with this specific genetic subtype. All 6 patients received myeloablative conditioning with busulfan and cyclophosphamide, and in 5 of 6 cases, the donor was an HLA-identical sibling. The overall survival and cure rate was 100% at a median follow-up of 54 months. All patients engrafted, discontinued immunoglobulin replacement within the first year, showed complete immune recovery with positive CD40 expression on B cells, and demonstrated positive vaccination responses. Only one patient developed acute graft-versus-host disease, and it resolved with treatment.

These results are the strongest evidence of transplantation efficacy for CD40 deficiency specifically, though the study is limited by its small size, single-center design, and the fact that nearly all donors were matched siblings. Two patients had cryptosporidium infection and sclerosing cholangitis before transplantation, yet both had complete recovery of liver function afterward, suggesting that transplantation may be beneficial even in the presence of some degree of organ compromise, at least when performed with a matched sibling donor and myeloablative conditioning.

Wang and colleagues (2014) reported clinical features and genetic analysis of 20 patients with X-linked hyper-immunoglobulin M syndrome (n = 20) diagnosed between 1999 and 2013. Of these, 6 received transplantation, with a median age at transplantation of 6 years. Four of the 6 transplanted patients (67%) achieved immune reconstitution and clinical remission, having received hematopoietic stem cells from HLA-identical unrelated donors, with follow-up ranging from months to 6 years. The other 2 patients had HLA-half-identical sibling donors and died from severe infections. This finding is consistent with the broader evidence that donor match quality significantly influences transplant outcomes. The study primarily contributes data on the clinical and genetic spectrum of X-linked hyper-immunoglobulin M syndrome and reinforces the association between donor match quality and transplant success, supporting the principle that well-matched donors are essential for optimal transplant outcomes.

Single-Center Transplant Experience

Petrovic and colleagues (2009) reported transplant outcomes for 31 patients with primary immunodeficiency diseases at a single center (All Children's Hospital, University of South Florida) spanning 1986 to 2009. Among these, 3 patients had X-linked hyper-immunoglobulin M syndrome. Two of 3 patients survived, and one surviving patient who received reduced-intensity conditioning showed only 4% CD40 ligand expression, indicating incomplete immune reconstitution. The authors concluded that transplantation at a younger age, before significant infections, autoimmune manifestations, and malignant transformation, was beneficial. They also

observed that patients with intact T-cell responses transplanted with reduced-intensity conditioning regimens did not fare as favorably, with poor donor chimerism in the surviving patients, consistent with the findings of Ferrua and colleagues (2019) regarding the superiority of myeloablative conditioning.

Case Report

Leone and colleagues (2002) described the case of a 10-month-old boy diagnosed with X-linked hyper-immunoglobulin M syndrome after presenting with life-threatening acute respiratory distress syndrome caused by Pneumocystis carinii pneumonia. Despite having no prior clinical history suggestive of immunodeficiency and initially normal immunoglobulin G levels, the patient was found to lack specific antibodies to vaccine antigens, leading to further investigation and a molecular diagnosis. After recovery from the acute episode and when the patient's overall condition was good, elective bone marrow transplantation from an HLA-matched older brother was performed successfully using busulfan-based myeloablative conditioning. The patient engrafted on day 16, developed neither acute nor chronic graft-versus-host disease, achieved full donor chimerism confirmed by molecular analysis showing absence of the pathogenic mutation, and normalized immunoglobulin levels. At 18 months post-transplant, the patient was in excellent condition and free of immunoglobulin replacement.

This case illustrates several principles that emerge from the broader evidence. First, it demonstrates the feasibility and success of early, elective transplantation performed before the development of liver disease or other organ damage, with a matched sibling donor and myeloablative conditioning. Second, it underscores the importance of timely diagnosis, as the authors emphasized that transplantation before the onset of liver complications is critical because hepatic involvement both worsens prognosis and makes transplantation more difficult. Third, the case is consistent with the theme across the evidence base that optimal outcomes are achieved when transplantation is performed early, electively, and with a well-matched donor.

Narrative Review

Meng and colleagues (2017) published a review summarizing the molecular pathology, clinical manifestations, and therapeutic approaches for hyper-immunoglobulin M syndrome, with a focus on prospects for modulating the CD40/CD40 ligand pathway. The review confirms the consensus view that transplantation is more likely to be successful when the donor is a sibling and that immunoglobulin replacement, while partially effective for all subtypes, is an inadequate long-term solution because it does not address the underlying T-cell dysfunction. The review notes that approximately 70% of patients respond to standard supportive therapy, but a majority still die in the second decade of life as a consequence of impaired T-cell function, supporting the rationale for pursuing a curative intervention.

Regarding emerging therapeutic approaches, Meng and colleagues (2017) describe clinical trials involving recombinant CD40 ligand and a CD40 agonist monoclonal antibody for X-linked hyper-immunoglobulin M syndrome. Both approaches activated B cells and improved some aspects of T-cell immune function in vitro and in small numbers of patients, but neither restored specific antibody synthesis. The review also discusses gene therapy, noting that while successful correction of the CD40 ligand gene has been achieved in vitro and in animal models, aberrant CD40 ligand expression in gene-corrected mice led to lymphoproliferative disease, and no gene therapy clinical trial for hyper-immunoglobulin M syndrome has been conducted. The authors conclude that gene therapy remains premature for this condition due to an insufficient understanding of CD40 ligand gene expression regulation.

In 2026, we reorganized the findings section and added Al-Saud (2019), which represents the largest reported cohort of transplanted patients with CD40 deficiency specifically, and Leone (2002), which provides a seminal account of successful early elective transplantation performed before the onset of organ damage.

References

On February 11, 2026, 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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3/2023: Policy references updated.

3/2024: Policy references updated.

3/2025: Policy references updated.

3/2026: Policy references updated.

Related Codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1226. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code Description
CPT Codes	
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation (aspiration only); autologous
HCPCS Codes	
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 (global definition including pheresis, cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization, and follow-up)