Clinical Policy Title: Bone marrow transplant for children with hyper IgM disorder

Clinical Policy Number: CCP.1226

Effective Date: July 1, 2016
Initial Review Date: April 20, 2016
Most Recent Review Date: March 5, 2019
Next Review Date: March 2020

Related policies:

CCP.1206 Stem cell transplants for autoimmune diseases
CCP.1402 Histocompatibility testing of potential hematopoietic stem cell donors

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of bone marrow transplant for children with hyper IgM disorder to be clinically proven and, therefore, medically necessary (de la Morena, 2017; Mitsui-Sekinaka, 2015; Petrovic, 2009).

Limitations:

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

Alternative covered services:

None.
Background

The hyper IgM syndrome is a rare, inherited immune deficiency disorder resulting from defects in the CD40 ligand (CD40L)/CD40-signaling pathway. 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 and IgA. Diagnosis is confirmed with genetic studies, which show mutation in either CD40 or CD40L.

The X-linked hyper IgM disorder is the most frequent type, is caused by mutations in the CD40L gene, and is regarded as a combined T and B immunodeficiency. The long-term outcome of X-linked hyper-IgM syndrome caused by mutations in CD40LG is poor, and the only curative treatment is hematopoietic stem cell transplantation.

Searches

AmeriHealth Caritas searched PubMed and the databases of:
• UK National Health Services Center for Reviews and Dissemination.
• Agency for Healthcare Research and Quality and other evidence-based practice centers.
• The Centers for Medicare & Medicaid Services.

We conducted searches on January 24, 2019. Search terms were: "CD40 (MeSH)," "CD40 ligand (MeSH)," and "hyper IgM syndrome."

We included:
• Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• Guidelines based on systematic reviews.
• Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Researchers retrospectively reviewed and analyzed data from five patients who received hematopoietic stem cell transplantation for hyper IgM disorder at King Faisal Specialist Hospital & Research Centre in Riyadh, Saudi Arabia, between 2005 and 2013 (Al-Saud, 2015). The transplants were from a human leukocyte antigen matched sibling donor at a median age of 41 months (range, nine – 72 months). The
median time from diagnosis to transplantation was 30 months (range, five – 58 months). The survival rate was 100 percent, with a median follow-up of 69 months (range, 13 – 100 months). Four patients showed complete immune recovery with positive CD40L expression in activated T-cells. The authors concluded that hematopoietic stem cell transplantation from an -matched sibling donor is effective at treating hyper IgM disorder.

A retrospective analysis (Allewelt, 2015) of seven patients who underwent allogeneic hematopoietic stem cell transplantation for hyper IgM disorder at Duke University Medical Center found that all patients are alive at a median follow-up of 9.7 years (range 9.7 – 16.1) post-transplantation. The median age at transplant was 5.2 years (range 0.7 – 19.3). None of the patients had active hepatic or pulmonary disease immediately prior to transplant, but all had a history of serious infections. Post-transplantation complications included veno-occlusive disease, hemorrhagic cystitis, adenoviremia, and cryptosporidium recurrence in one patient each. The authors concluded that allogeneic hematopoietic stem cell transplantation results in excellent survival and sustained immune reconstitution in patients with CD40L deficiency.

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 hematopoietic stem cell transplantation (overall survival rate at 40 years of age, 28.2 percent). The overall survival rate of patients undergoing hematopoietic stem cell transplantation (n = 29) was significantly higher than that of those not undergoing hematopoietic stem cell transplantation (n = 27, P = 0.0231). Moreover, event-free and disease-free survival rates were significantly greater in patients 5 years old or younger at the time of transplantation (n = 14) than in older patients (n = 15). The authors concluded that hematopoietic stem cell transplantation improved the outcomes of patients with hyper IgM disorder and that an age of 5 years or younger was optimal for the timing of hematopoietic stem cell transplantation because persistent infections and severe organ damage were frequently observed in patients older than 6 years.

A case study (Tsai, 2015) reported an 18-year-old male who was diagnosed initially with hypogammaglobulinemia in infancy, but developed repeated pneumonia, sepsis, cellulitis, perianal abscess, pericarditis, and bronchiectasis, despite regular intravenous immunoglobulin replacement therapy. The patient died at age 18 years due to pneumonia and tension pneumothorax. Post-mortem mutation analysis revealed CD40L gene mutation within Exon 5 at nucleotide position 476 (cDNA 476G > A). This nonsense mutation predicted a tryptophan codon (TGG) change to a stop codon (TGA) at position 140 (W140X), preventing CD40L protein expression. Sequence analysis in the family confirmed a de novo mutation.

A second case study (Tsai, 2015) of a 6-month-old male infant presented as Pneumocystis jiroveci pneumonia and acute respiratory distress syndrome. Gene analysis of the CD40L gene revealed G to C substitution in intron 4 (c.409 + 5G > C) and that the mother was a carrier. Hematopoietic stem cell transplantation was arranged for the patient as therapeutic management in the second case.
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 (18 patients, 90 percent), neutropenia (14 patients, 70 percent), oral ulcer (13 patients, 65 percent), and protracted diarrhea (13 patients, 65 percent). Six patients received hematopoietic stem cell transplantation and four of them had immune reconstructions and clinical remissions. Eighteen unique mutations in CD40L gene were identified, with 12 novel mutations.

Another case study (Jasinska, 2013) gave an account of a boy with X-linked hyper IgM disorder and a novel Y172C mutation within his CD40LG gene. He presented with severe neutropenia. His bone marrow showed maturation arrest at the promyelocyte/myelocyte stage, typical of congenital neutropenia. The child suffered from life-threatening infections and required high doses of recombinant human granulocyte stimulating factor, and a haploidentical hematopoietic stem cell transplantation was also successfully performed, leading to reconstitution of CD40L expression on activated CD4+ T cells (confirmed with flow cytometry six months after the procedure). Two low-dose T-cell add-backs were required to re-establish full donor chimerism and clear cytomegalovirus reactivation.

Petrovic (2009) retrospectively analyzed the transplantation outcomes of 31 patients with primary immunodeficiency diseases treated at All Children’s Hospital in Tampa, Florida. The hospital is affiliated with the University of South 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 transplant ranged from 1 month to 19 years, and conditioning regimens varied based on the patients 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.

Policy updates:

In 2018, we added three publications to the reference list.

In 2019, we added one publication to the reference list. The policy ID changed from 17.02.01 to CCP.1226.

References

Professional society guidelines/other:

**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Commonly submitted codes**

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

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