Clinical Policy Title: Stem cell transplants for autoimmune disease

Clinical Policy Number: 18.03.02

Effective Date: April 1, 2016
Initial Review Date: June 16, 2013
Most Recent Review Date: January 20, 2016
Next Review Date: January, 2017

Related policies:
CP# 14.02.06 Bone marrow transplants
CP# 05.03.02 Stem cell transplants for breast cancer

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s 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 Pennsylvania 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 Pennsylvania’s 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 Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage Policy

AmeriHealth Caritas Pennsylvania considers the use of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplantation (HSCT) (single or planned tandem) to be investigational, and not medically necessary as a treatment for autoimmune diseases and autoimmune-related diseases including, but not limited to:

- Celiac sprue disease.
- Crohn’s disease.
- Graves’ disease.
- Juvenile idiopathic arthritis (JIA).
- Multiple sclerosis (MS).
- Neuromyelitis optica.
- Pernicious anemia.
• Rheumatoid arthritis (RA).
• Sjögren’s syndrome.
• Systemic lupus erythematosus (SLE).
• Systemic sclerosis (SSc or scleroderma).
• Systemic vasculitis.
• Type 1 diabetes
• Ulcerative colitis.

Note: A complete list of autoimmune diseases is available at the American Autoimmune Related Diseases Association’s (AARDA) website, www.aarda.org/autoimmune-information/list-of-diseases/.

Limitations:
All other uses of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) HSCT, single or planned tandem, are not medically necessary.

Alternative covered services:
Plan approved treatment ordered by treating participating provider.

Background
Stem cells that form blood and immune cells are known as hematopoietic stem cells (HSCs). They are ultimately responsible for the constant renewal of blood — the production of billions of new blood cells each day. Physicians and basic researchers have capitalized on this fact for more than 50 years in treating many diseases. The first evidence and definition of blood-forming stem cells came from studies of people exposed to lethal doses of radiation in 1945.

A bone marrow transplant, also called a HSCT, is a procedure that replaces damaged or destroyed bone marrow with healthy bone marrow stem cells. Bone marrow is the soft, fatty tissue inside the bones. Stem cells are immature cells in the bone marrow that give rise to all blood cells.

There are three basic kinds of stem cell transplants:

Autologous bone marrow transplant:
• The term auto means self. Stem cells are removed from a patient prior to receiving high-dose chemotherapy (HDC) or radiation treatment. The stem cells are stored in a freezer (cryopreservation). After HDC or radiation treatments, stems cells are put back in the body to regenerate normal blood cells. This is called a rescue transplant.

Allogeneic bone marrow transplant:
• The term allo means other. Stem cells are removed from another person, called a donor. Most times, the donor’s genes must at least partly match the member’s genes. Special blood tests are done to see if a donor is a good match for the member. A brother or sister is most likely to be a good match. Sometimes parents, children, and other relatives are good
matches. Donors who are not related to members may be found through national bone marrow registries.

Syngeneic stem cell transplants:

- This is a special kind of allogenic transplant that can only be used when the recipient has an identical sibling (twin or triplet) who can donate — someone who has the same tissue type. An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem. No cancer cells should be present in a transplant, as there should be no cancer cells in an autologous transplant.

Some people may have a HSCT using stem cells from umbilical cord blood. There are cord blood banks that store blood taken from umbilical cords. After the baby is born and the umbilical cord has been cut, a doctor extracts blood from the umbilical cord, and placenta. The blood bank may give the donated stem cells to a person whose blood cells closely match the donated cells. These transplants are mostly used for children, because of the lower volume of cells collected. It may be possible for adults to have a HSCT from two different umbilical cords (double cord transplant).

HSCT refers to a procedure in which HSCs are infused to restore bone marrow function in cancer patients who receive bone-marrow, toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Bone marrow stem cells may be obtained from the transplant recipient (i.e., autologous HSCT) or from a donor (i.e., allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

**Autoimmune Disease**

The term autoimmune disease” refers to a varied group of illnesses that involve almost every human organ system. It includes diseases of the nervous, gastrointestinal, and endocrine systems, as well as skin and other connective tissues, eyes, blood, and blood vessels. In all of these ADs, the underlying problem is autoimmunity — the body’s immune system becomes misdirected and attacks the very organs it was designed to protect.

Autoimmune diseases are a group of highly heterogeneous disorders with variable organ system involvement, diverse etiologies and pathologies, and different prognoses (Burt, 2008). Standard treatment for autoimmune diseases generally consists of immunosuppression, anti-inflammatory and/or anti-malarial medication, and supportive care. Dose escalation of immunosuppressive medication utilizing HSCT is being proposed for individuals who are refractory to standard treatment, or have disease considered to be life-, or organ-threatening.

Autoimmune disease affects up to 50 million Americans, according to the AARDA. An autoimmune disease develops when your immune system, which defends your body against disease, decides your healthy cells are foreign. As a result, your immune system attacks healthy cells. Depending on the type, an autoimmune disease can affect one or many different types of body tissue. It can also cause abnormal organ growth and changes in organ function.
There are as many as 80 types of autoimmune diseases. Many of them have similar symptoms, which make them very difficult to diagnose. It’s also possible to have more than one at the same time. ADs usually fluctuate between periods of remission (little or no symptoms) and flare-ups (worsening symptoms). Currently, treatment for ADs focuses on relieving symptoms, because there is no curative therapy.

AD often runs in families, and 75 percent of those affected are women, according to AARDA. African Americans, Hispanics, and Native Americans also have an increased risk of developing an AD. The cause of AD is unknown. There are many theories about what triggers AD, including:

- Bacteria or virus.
- Chemical irritants.
- Drugs.
- Environmental irritants.

The most common ADs include:

- Addison’s disease — Adrenal hormone insufficiency.
- Celiac sprue disease — A reaction to gluten (found in wheat, rye, and barley) that causes damage to the lining of the small intestine.
- Graves’ disease — Overactive thyroid gland.
- Hashimoto’s disease — Inflammation of the thyroid gland.
- Inflammatory bowel diseases (IBDs)— A group of inflammatory diseases of the colon and small intestine.
- Pernicious anemia — Decrease in red blood cells caused by inability to absorb vitamin B-12.
- Psoriasis — A skin condition that causes redness and irritation as well as thick, flaky, silver-white patches.
- RA — Inflammation of joints and surrounding tissues.
- Reactive arthritis — Inflammation of joints, urethra, and eyes; may cause sores on the skin and mucus membranes.
- Scleroderma — A connective tissue disease that causes changes in skin, blood vessels, muscles, and internal organs.
- Sjögren’s syndrome — Destroys the glands that produce tears and saliva causing dry eyes and mouth; may affect kidneys and lungs.
- Systemic lupus erythematosus — Affects skin, joints, kidneys, brain, and other organs.
- Type 1 diabetes — Destruction of insulin producing cells in the pancreas.
- Vitiligo — White patches on the skin caused by loss of pigment.

Searches

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).
We conducted searches on October 27, 2015. Search terms were: "autoimmune diseases (MeSH)," "stem cells (MeSH)," and autologous hematopoietic stem cell transplantation."

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**

Currently, there are multiple ongoing clinical trials using autologous and allogeneic HSCT following high-dose immunotherapies for the treatment of AD. Burt and colleagues (2006) described lymphoablation or the removal of "autoreactive lymphocytes" through the process of autologous HSCT to promote the generation of new self-tolerant lymphocytes. Examples of ADs being studied in this manner include MS, SSc, RA, Crohn's disease, and lupus. These authors identified the need for further research with randomized controlled trials (RCTs) to verify the benefit and safety of this therapy.

A major issue for physicians dealing with AD is that although temporary remissions do occur, the conditions are painful and chronic for patients. A growing number of studies suggest that uncontrolled systemic inflammation leads to premature atherosclerosis and cardiovascular deaths, as well as toxicity from chronic immunosuppression, especially glucocorticoids. Despite this, it is still a challenge for a rheumatologist, neurologist, or gastroenterologist to accept an immediate TRM of 5 to 10 percent, especially because long-term benefits have yet to be demonstrated. The hypothesis is that in a randomized prospective trial of HSCT versus conventional treatment, early toxicity from TRM would eventually be surpassed by later deaths and/or organ failure from disease progression in the control arm, but this has yet to be proven.

The peer-reviewed, published scientific research consists of retrospective analyses, small case studies, feasibility studies, and phase I/II trials that limit the ability to generalize findings to the AD population. However, a number of phase III clinical trials are ongoing. Nonstandard patient selection criteria, small patient populations, variability of conditioning regimens used for transplantation, and lack of randomization are reported limitations of many published studies. Although results of published studies are promising, in the absence of outcomes from well-designed RCTs published in peer-reviewed scientific literature, the role of HSCT for any AD has not yet been established.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>de Carvalho JF, et al.</td>
<td>Key points:</td>
</tr>
<tr>
<td>(2009)</td>
<td></td>
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<tr>
<td>Hematopoietic cell transplants in</td>
<td>• There are two major areas of consideration in the analysis of autoimmunity in human patients. The first of course is etiology and the second, and of even greater importance, is therapy.</td>
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</table>
autoimmunity.  

- The role of HSCT to either reverse or modulate AD.
- It is a field that has far more promise than premise based on a variety of issues, including economics, health care delivery, and obviously efficacy and safety.
- Attempted to review some of the issues pertaining to this novel approach of the management of autoimmunity.
- The need to incorporate basic research into therapeutic trials, a vacuum all too often present in clinical intervention.

### Key points:

- Since 1996, more than 1300 AID patients were registered by the European Group for Blood and Marrow Transplantation (EBMT) and almost 500 patients by the Center for International Blood and Marrow Transplant Research (CIBMTR).
- Autologous HCT is most commonly performed on patients with MS or SSC. Systemic lupus, Crohn's disease, type I diabetes, and JIA are other common indications.
- The paucity of controlled studies, the short-term toxicities, and the upcoming availability of second-generation biologic and targeted immunotherapies argues that perhaps HSCT for AID should be limited to clinical trials.

### Atkins HL et al. (2012)

**Autologous hematopoietic stem cell transplantation for autoimmune disease--is it now ready for prime time?**

- 1000 transplants for AD in Europe along with the three major multinational randomized trials for SSc (the ASTIS study), MS (the ASTIMS study), and Crohn's disease (the ASTIC study).
- Completed U.S. phase II studies of transplantation for severe SSc, SLE, and MS yield promising results. For individuals with SSc, there is dramatic improvement/resolution of dermal fibrosis and stabilization/improvement of pulmonary dysfunction, reported up to eight years after lymphoablative conditioning, and autologous HCT.
- Randomized phase III studies are recruiting U.S. subjects with SSc, MS and CD. In addition, nine other U.S. phase I and II trials are recruiting patients with AD for nonmyeloablative transplants from allogeneic HSC donors.
- Within several NIH sponsored trials there are ongoing immunologic, genomic, and mechanistic studies to further understand the molecular mechanisms of autoimmunity, immune regulation, and response to treatment. These clinical trials will provide scientists with insight into immunoregulatory pathways and clinicians with a context to weigh the progress and evidence in this evolving treatment for ADs.

### Sullivan KM (2010)

**Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States**

- Twenty-two patients with progressive refractory JIA were monitored over a median period of 80 months after pretreatment with intensive immunosuppression, followed by ASCT in a multicenter, prospective, phase II clinical trial.
- HSCs were harvested from the patients' bone marrow, depleted of T cells, and kept frozen until used for ASCT.
- Pretreatment of patients consisted of a combination of antithymocyte globulin, cyclophosphamide, and low-dose total body irradiation. Patients were followed up for ASCT-related complications, recovery of hematologic and immune system parameters, and disease outcomes.
- Intensive immunosuppression followed by ASCT resulted in sustained complete remission or marked improvement, in 15 of 22 patients with progressive refractory JIA.

<table>
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<tr>
<td>- Ten patients were included in this pilot study. All had progressive disease that did not respond to disease modifying agents, including Mitoxantrone. Their Expanded Disability Status Scale (EDSS) score ranged from 3.5 to 6. Patients were injected intrathecally with culture expanded mesenchymal stem cells (MSCs). Follow up included a monthly neurological assessment and an MRI scan at the end of the first year.</td>
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<td>- After 12 months, the MRI assessment revealed the following: seven patients with no difference, two showed an extra plaque, and one patient showed decrease in the number of plaques.</td>
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<td>- This preliminary report emphasizes the feasibility of autologous MSC for treatment of MS patients. In order to draw a definitive conclusion, a larger sample size is required.</td>
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Glossary

**Ablative** — Very high dose of a treatment, calculated to kill a tumor.

**Bone marrow** — A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains hematopoietic stem cells, the precursors to platelets, red blood cells, and white cells.

**Chemotherapy** — Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

**Chimerism** — Cell populations derived from different individuals; may be mixed or complete.

**Cytotoxic** — Destructive to cells.

**Graft-versus-host disease** — A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

**Hematopoietic stem cells (HSC)** — Unique cells that mature into a number of blood cell types found in the body. Also referred to as stem cells, they are primarily located in bone marrow and give rise to all red and white blood cells and platelets.

**High-dose or myeloablative chemotherapy (HDC)** — The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

**Human leukocyte antigen (HLA)** — A group of protein molecules located on bone marrow cells that can provoke an immune response.

**Non-myeloablative chemotherapy** — Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects, to permit engraftment of donor cells.

**Tandem transplant** — Planned administration of more than one cycle of high-dose or non-myeloablative chemotherapy, alone or with total body irradiation. Each infusion is followed by a re-infusion of stem cells.
References

Professional society guidelines/other:


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on October 27, 2015 using terms “stem cell transplants “ and "autoimmune disease" | Open Studies. 24 studies found, 4 relevant.


CMS National Coverage Determinations (NCDs):
No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):
No LCDs 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 accordingly.

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<td>E05.00</td>
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