Immune Globulin Therapy

Description of Procedure or Service

Human immune globulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Three formulations of human IgG are available for delivery by intravenous infusion (IVIg), by subcutaneous infusion (SCIg), or by intramuscular (IMIg) depot injections. IMIg has been largely abandoned in the United States because volume constraints and pain preclude delivery of sufficient product weekly into each buttock to yield therapeutic serum levels of IgG, leaving recipients susceptible to infections. Thus, this policy focuses on IVIg and SCIg for conditions that typically would be treated in an outpatient setting.

IVIg is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the following section. A variety of off-label indications have been investigated; some of the most common are briefly profiled here. Several IVIg products are available for clinical use in the United States.

This policy only addresses nonspecific pooled preparations of IVIg, including Carimune® (ZLB Bioplasma), Flebogamma® (Grifols), Gammagard® (Baxter), Gamunex®-C® (Grifols), Octagam® (Octapharma), Polygam® S/D (Baxter) Privigen® (CSL Behring LLC) and BIVIGAM™ (Biotest Pharmaceuticals).

At least 1 IVIg product is FDA-approved to treat the following conditions:

- Primary humoral immunodeficiency
- Multifocal motor neuropathy
- B-cell chronic lymphocytic leukemia
- Immune (aka Idiopathic) thrombocytopenic purpura
- Kawasaki syndrome
- Chronic inflammatory demyelinating polyneuropathy

This policy DOES NOT address other immunoglobulin preparations that are specifically used for passive immunization to prevent or attenuate infection with specific viral diseases such as respiratory syncytial virus, cytomegalovirus, or hepatitis B. (Coverage for RSV immune globulin (e.g., Synagis) is summarized in the Medical policy titled, "Respiratory Syncytial Virus Prophylaxis").

Subcutaneous infusion immune globulin (SCIg) is used for the treatment of patients with primary immunodeficiencies (PID). A genetic basis for more than 80 different types of PID has been discovered, the most common being primary antibody deficiency (PAD) that is associated with low levels or total lack of normal circulating immunoglobulins. With SCIg, it is possible for patients to self-administer the therapy. Several SCIg products have received FDA marketing approval for primary immunodeficiencies. These include Vivaglobin® (ZLB Behring, Kankakee, IL, discontinued by the company in 2013), Hizentra® (ZLB Behring LLC, Kankakee, IL), Gamunex-C® (Grifols) and Gammaked® (Kedrion
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Biopharma, Cambridge, MA). On September 12, 2014, the FDA granted approval for HyQvia (immune globulin infusion 10% [human] with recombinant human hyaluronidase). HyQvia is a subcutaneous immune globulin derived from human blood plasma and is used to restore at least partial immune function for adults with a primary immunodeficiency

Related Policies:

Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
Extracorporeal Photopheresis

**IVIg Therapy**

**Inflammatory Myopathies**

Inflammatory myopathies are broadly subdivided into polymyositis (PM), dermatomyositis (DM), and inclusion-body myositis (IBM). PM and DM are characterized clinically by proximal muscle weakness and pathologically by an inflammatory microangiopathy leading to subsequent muscle ischemia. In DM, these symptoms are accompanied by a characteristic erythematous rash. The inflammatory infiltrate in DM contains a high percentage of B cells and components of the complement cascade. In contrast, in PM the inflammatory infiltrates are not perivascular in location and contain activated T cells, natural killer cells, and macrophages. PM has no unique clinical features, and is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness. Both PM and DM respond to corticosteroids or immunosuppressive drugs but can become refractory to such treatment. IBM is characterized clinically by slowly progressive muscle weakness and atrophy affecting proximal and distal muscle groups, particularly the quadriceps and the long finger flexors. Pathologically, IBM is characterized by granular inclusions within the muscle cells. Unlike DM or PM, IBM rarely responds to immunosuppressive therapy. For all of these conditions, IVIg has been investigated as a treatment, particularly for cases refractory to corticosteroids or immunosuppressive drugs.

**Neuropathies**

IVIg has been studied in a variety of neuropathies, most prominently Guillain-Barre syndrome (acute demyelinating neuropathy), chronic inflammatory demyelinating neuropathy (CIDP), and multifocal motor neuropathy. CIDP is a symmetrical polyneuropathy manifested as both motor and sensory deficits. The disease course may present as either a relapsing/fluctuating or slowly progressive disease. Some of the symptoms of CIDP may overlap with symptoms of chronic fatigue syndrome; therefore, when considering IVIg therapy, appropriate diagnosis is critical. In 1991, the American Academy of Neurology published criteria for the diagnosis of CIDP (See Appendix). Patients with both CIDP and Guillain-Barre syndrome may be initially treated with prednisone, followed by plasmapheresis or IVIg in more severe cases. The latest diagnostic criteria were proposed in 2005 by the Joint Task Force of the European Federation of Neurological Societies (EEFNS) and the Peripheral Nerve Society (PNS) based on available evidence and expert consensus in the medical literature. The Task Force members agreed to define clinical and electrophysiological criteria for CIDP with or without concomitant disease.

Multifocal motor neuropathy is characterized by a conduction block of the motor axons. Patients frequently exhibit antibodies to GM1 ganglioside. Clinically, the disease presents as a very slow onset of weakness and muscular atrophy with preservation of sensation. Unlike other neuropathic disorders, this disease does not respond to steroids or plasmapheresis. Stiff person syndrome is a rare central nervous system disorder characterized by fluctuating muscle rigidity of truncal and proximal limb muscles with periodic spasms, resulting in a significant disability. The condition is thought to be immunologic in origin; elevated levels of anti-GAD antibodies are detected in most patients. Initial therapy is typically diazepam, but frequently the high doses required are poorly tolerated. IVIg has been investigated as an alternative therapy.

IVIg has also been investigated in neuropathies associated with paraproteinemia or a variety of paraneoplastic syndromes, including Eaton Lambert syndrome or neuropathy associated with anti-Yo or anti-Hu antibodies, seen in association with a variety of cancers including ovarian or small cell lung cancer.

**Multiple Sclerosis**

Multiple sclerosis (MS) is a demyelinating disease accompanied by a lymphocytic infiltration in lesions.
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Evidence relating to pathogenesis suggests genetic, infective, and/or immune mechanisms. IVIg has been investigated in patients with relapsing/remitting MS, for whom the treatment goals are to decrease the frequency and severity of future attacks and, if possible, to improve the functional deficit to some extent in patients with chronic progressive disease.

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease characterized by autoantibodies directed against the acetylcholine receptors of the muscle end plate that induce muscle weakness and pronounced fatigability. Initial treatment focuses on the use of cholinesterase inhibitors to overcome the post-synaptic blockade. Immunosuppressant drugs, including corticosteroids and azathioprine, are also effective. In patients with severe weakness, plasma exchange is a short-term therapy. IVIg has also been investigated in patients with myasthenia gravis as a potential alternative to plasma exchange.

Kawasaki Syndrome and Other Vasculitides

Kawasaki syndrome is an acute multisystem vasculitis that primarily affects children, manifesting itself as a constellation of clinical signs and symptoms including fever, conjunctivitis, mucosal erythema, polymorphous rash, and cervical adenopathy. Although the symptoms are self-limited, up to 25% of untreated patients may develop potentially lethal coronary artery abnormalities. Although the mechanism of action of IVIg is not understood, its use early in the course of disease has been shown to reduce the prevalence of coronary artery abnormalities.

The success of IVIg in Kawasaki disease has led to the investigation of IVIg in other vasculitides, such as those associated with rheumatoid arthritis, Wegener’s granulomatosis, and polyarteritis nodosa.

Recurrent Spontaneous Abortion

Recurrent spontaneous abortion (RSA) is defined as 3 or more pregnancies resulting in a spontaneous abortion prior to 16–20 weeks of gestational age. Patients with RSA frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss. Since these antibodies are associated with clotting abnormalities, treatment has included aspirin and heparin. Other more subtle immune etiologies have also been investigated. For example, a variety of cytokines and other mediators may be toxic to the conceptus. These cytokines may be detected in an embryo cytotoxicity assay in which activated lymphocytes from women with RSA are shown to be toxic to placental cell lines. Elevated levels of natural killer cells, which may be associated with antiphospholipid antibodies, have also been implicated in RSA. Another theory proposes that a lack of maternal blocking antibodies to prevent immunologic rejection of the fetus may be responsible. IVIg has been explored as a treatment based on its ability to influence both T- and B-cell function. In fact, IVIg may be offered to those patients with antiphospholipid antibodies without a prior history of RSA who are currently pregnant or contemplating pregnancy.

Fetal Alloimmune Thrombocytopenia

Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage is identified in about 10%–30% of affected neonates. At the present time, screening for this condition is unavailable, and thus the thrombocytopenia is only identified at the time of birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia and, similar to erythroblastosis fetalis, the severity of the thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIg.

Solid Organ Transplantation

Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction (AMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AMR does not, and, as such, has also been referred to as “steroid-resistant rejection.” The risk of AMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a
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Panel reactive antibody (PRA) screen, which combines the recipient’s serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool. The percentage of PRA is the percentage of positive reactions. Those with a PRA greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of AMR. As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AMR, often in conjunction with plasma exchange. For example, in patients at high risk for AMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AMR develops.

SCIg Therapy

Primary immunodeficiencies (PID) are genetically caused immune system defects. A genetic basis for more than 80 different types of PID has been discovered, the most common being primary antibody deficiency (PAD) that is associated with low levels or total lack of normal circulating immunoglobulins. Individuals with PID are prone to recurrent bacterial infections, primarily in the upper and lower respiratory tract and in the gastrointestinal (GI) tract. In PID patients, infections are frequent and may cause progressive tissue damage that can be severe and life threatening. For example, recurrent infections in the lungs can cause bronchiectasis and respiratory failure. GI tract infections secondary to PID can result in nutritional deficiencies and poor growth. Less frequently, other infections may occur, such as enterovirus in the brain and muscle, or mycoplasma in bone and joint tissues. Antibiotics can be used to treat bacterial infections, but the majority of patients with PID require lifelong immunoglobulin replacement to prevent tissue damage.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Immune Globulin Therapy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Immune Globulin Therapy is covered

Intravenous Immune globulin (IVIg) Therapy

IVIg may be considered medically necessary for the following indications:

Primary Humoral Immune Deficiency Syndromes*, including Combined Immunodeficiencies.

- X-linked agammaglobulinemia (Bruton’s agammaglobulinemia)
- X-linked hyper-IgM syndrome
- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome
- Ataxia telangiectasia
- Hypogammaglobulinemia
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
  - Laboratory evidence of immunoglobulin deficiency (see Policy Guidelines)
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- Documented inability to mount an adequate immunologic response to inciting antigens (see Policy Guidelines)
- Persistent and severe infections despite treatment with prophylactic antibiotics

**Acute Humoral Rejection**

**Autoimmune Mucocutaneous Blistering Diseases**, in patients with severe, progressive disease despite treatment with conventional agents (corticosteroids, azathioprine, cyclophosphamide, etc.)

- pemphigus
- pemphigoid
- pemphigus vulgaris
- pemphigus foliaceus
- Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN)

**Autoimmune and inflammatory disorders**

- dermatomyositis refractory to treatment with corticosteroids; in combination with other immunosuppressive agents
- Kawasaki syndrome*

**Neuroimmunological**

- myasthenia gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange
- Guillain-Barre syndrome
- chronic inflammatory demyelinating polyneuropathy*; in patients with progressive symptoms for at least two months
- multifocal motor neuropathy
- Eaton-Lambert myasthenic syndrome; in patients who have failed to respond to anticholinesterase medications and/or corticosteroids.

**Hematologic**

- idiopathic thrombocytopenic purpura (ITP)*
  - treatment of acute, severe ITP (see policy guidelines)
  - treatment of chronic ITP; in patients with at least 6 months’ duration of disease, and with persistent thrombocytopenia despite treatment with corticosteroids and splenectomy
- neonatal alloimmune thrombocytopenia;
- hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)
- post allogeneic bone marrow transplant setting
- B cell chronic lymphocytic leukemia (CLL)*; in patients with hypogammaglobulinemia and persistent bacterial infections
- warm antibody autoimmune hemolytic anemia, refractory to corticosteroids and immunosuppressive agents
- anti-phospholipid syndrome
- severe anemia due to parvovirus B19

**Infectious diseases**

- HIV [human immunodeficiency virus]-infected patients
- toxic shock syndrome
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- patients with primary defective antibody synthesis

Transplantation

- prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ.
- following solid-organ transplant, treatment of antibody-mediated rejection

Prevention

- Prevention of infection in preterm (<37 weeks’ gestational age) and/or low-birth weight (<2500g) neonates

Subcutaneous immune globulin may be considered medically necessary for the treatment of patients with primary immunodeficiencies*, including:
- congenital agammaglobulinemia,
- hypogammaglobulinemia,
- common variable immunodeficiency,
- severe combined immunodeficiency,
- Wiskott-Aldrich syndrome,
- X-linked agammaglobulinemia.

* FDA-labeled indications

When Immune Globulin Therapy is not covered

IVIg is considered not medically necessary as a treatment of relapsing/remitting multiple sclerosis.

Intravenous immunoglobulin therapy is considered investigational for all other indications, including, but not limited to, the following conditions:
- refractory rheumatoid arthritis and other connective tissue diseases including systemic lupus erythematosus,
- chronic progressive multiple sclerosis,
- recurrent spontaneous abortion,
- inclusion body myositis,
- polymyositis, including refractory polymyositis,
- Myasthenia Gravis in patients responsive to immunosuppressive treatment,
- other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener’s granulomatosis, polyarteritis nodosa), Goodpasture’s syndrome, and vasculitis associated with other connective tissue diseases,
- thrombotic thrombocytopenic purpura,
- hemolytic uremic syndrome,
- paraneoplastic syndromes, other than Eaton Lambert myasthenic syndrome,
- demyelinating polyneuropathy associated with IgM paraproteinemia,
- epilepsy,
- chronic sinusitis,
- asthma,
- chronic fatigue syndrome,
- aplastic anemia,
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- Diamond-Blackfan anemia,
- red cell aplasia,
- acquired factor VIII inhibitors,
- hemophagocytic syndrome, i.e., hemophagocytic lymphohistiocytosis
- acute lymphoblastic leukemia,
- multiple myeloma,
- immune-mediated neutropenia,
- nonimmune thrombocytopenia,
- cystic fibrosis,
- recurrent otitis media,
- diabetes mellitus,
- Behcet’s syndrome,
- adrenoleukodystrophy,
- stiff person syndrome,
- organ transplant rejection,
- uveitis,
- demyelinating optic neuritis,
- recent-onset dilated cardiomyopathy,
- Fisher syndrome,
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),
- autism,
- complex regional pain syndrome,
- Alzheimer’s disease,
- IGG sub-class deficiency,
- Treatment of sepsis including suspected or proven infection in neonates,
- Crohn’s disease,
- opsoclonus-myoclonus,
- birdshot retinopathy,
- epidermolysis bullosa acquisita,
- necrotizing fasciitis,
- polyradiculoneuropathy (other than CIDP),
- postpolio syndrome.

Other applications of SCIg therapy are considered investigational, including, but not limited to chronic inflammatory demyelinating polyneuropathy (CIDP).

Immunoglobulin therapy is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency who have known antibody against IgA.

Policy Guidelines

See Appendix for Diagnostic Criteria for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor Neuropathy (MMN), Primary Immunodeficiency Syndromes, and Severe Idiopathic Thrombocytopenic Purpura (ITP)
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Organ Allografts

Acute antibody mediated rejection (acute humoral rejection; AHR) of organ allografts usually presents as severe dysfunction with a high risk of allograft loss. Peritubular capillary complement C4d deposition with renal dysfunction, associated with circulating donor-specific anti-human leukocyte antigen alloantibodies, is diagnostic of AHR in kidney allografts.

Hematopoetic Stem Cell Transplantation

Prophylaxis with IVIg in patients undergoing hematopoietic stem cell transplantation may reduce the incidence of infections, acute graft versus host disease, and interstitial pneumonitis. For BCBSNC policy, the source of hematopoietic stem cells may be from bone marrow, peripheral blood or umbilical cord blood.

Multiple Sclerosis

The previous policy statement regarding IVIg for multiple sclerosis was based on a 1998 BCBSA TEC Assessment, which concluded that IVIg met the TEC criteria. Therefore, it was considered medically necessary in the previous version of this policy. However, in 2002 the American Academy of Neurology published a technology assessment on therapies for multiple sclerosis. This assessment provided a rating of the recommendations, including A (established as effective), B (probably effective, ineffective, or harmful), C (possibly effective, ineffective or harmful), or U (data inadequate). This assessment offered the following recommendation regarding IVIg:

The studies of intravenous immunoglobulin (IVIg) to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in relapsing-remitting multiple sclerosis (Type C recommendation).

The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (Type C recommendation).

In contrast, the American Academy of Neurology recommended the use of interferon beta (Type B recommendation) and glatiramer acetate (Type A recommendation). This assessment suggests that IVIg is no longer considered a drug of choice for relapsing-remitting multiple sclerosis, and thus the policy statement in this policy has been revised to indicate that IVIg is not medically necessary. A literature search for the period of 2002 to December 2004 did not identify any additional randomized trials that would prompt reconsideration of the conclusions of the American Academy of Neurology assessment.

Chronic Inflammatory Demyelinating Neuropathy (CIDP)

Patients with chronic inflammatory demyelinating neuropathy (CIDP) should meet the diagnostic criteria in the appendix of this document. In addition, intravenous immunoglobulin infusion (IVIg) treatment should be limited to CIDP patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening documented by neurological exam. In patients treated for chronic diseases, such as CIDP, multifocal motor neuropathy, and dermatomyositis, the effect of IVIg is transitory and therefore periodic infusions of IVIg are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed. Continued treatment with IVIG is warranted only if it continues to be efficacious.

IVIg Site of Care Eligibility

1. IVIg administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of IVIg infusion is not medically necessary, OR
2. IVIg administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
   a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
   b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
   c. First infusion, OR
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d. Less than 3 months since first IVIg infusion, OR
e. First infusion after six months of no IVIg infusions, OR
f. Requirement of a change in IVIg product.

3. Members who do not meet the criteria above are appropriate for IVIg administration in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

### Dosing Guidelines

The following is an adaptation of recommendations that have been made for IVIg dosing in a consensus report from the IVIg advisory committee.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary immunodeficiency disorders</td>
<td>0.4-0.6 g/kg every 28 days</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>0.4 g/kg for 5 doses</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>0.25-0.4 g/kg × 5 doses</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>0.4 g/kg for 5 doses</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenia</td>
<td>0.4 g/kg/d × 5 days</td>
</tr>
<tr>
<td>Acute humoral rejection</td>
<td>1 g/kg/d for 2 doses</td>
</tr>
</tbody>
</table>

### Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

**Applicable service codes:** 90283, 90284, J1459, J1556, J1557, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1575, J1599

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

### Scientific Background and Reference Sources

**From Policy Entitled: Intravenous Immune Globulin Therapy**

TEC Bulletin 12/95

2/96 FDA approval of RespiGam (RSV-IGIV) to prevent respiratory syncytial virus in children under 24 months)

1/97 - Recommendations from the American Academy of Pediatrics, member alert

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American Academy of Neurology; *Intravenous Immunoglobulin for the Treatment of Acquired Myasthenia Gravis*; James F. Howard, Jr., M.D.; December 1998;51(Suppl 5)S30-S36
Consultant review - 2/2001
BCBSA Medical Policy Reference Manual - Policy 8.01.05-Review date 12/18/02

**Policy retitled: Immune Globulin Therapy**

Specialty Matched Consultant Review - 5/23/07
Venetz JP, Pascual M. New treatments for acute humoral rejection of kidney allografts; Expert Opin Investig Drugs. 2007 May;16(5):625-33
Specialty Matched Consultant Review – 2/29/12

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Immune Globulin Therapy


Medical Director review 11/2014


Senior Medical Director review 10/2015

Specialty Matched Consultant Advisory Panel – 2/24/16

Policy Implementation/Update Information

From Policy Entitled: Intravenous Immune Globulin Therapy


11/94 Evaluated: Investigational for treatment of recurrent fetal loss and chronic inflammatory demyelinating polyneuropathy

1/96 Evaluated: Investigational for treatment of refractory SLE related cytopenia, nephritis, CNS involvement, vasculitis, pericarditis, or pleural effusion (TEC Bulletin, June 1995)

6/96 Revised: Added FDA approval of REspiGam to prevent respiratory syncytial virus in children under 24 months

1/97 Revised: Updated RespiGam and indications for use. Added CHD to list under investigational.

9/99 Reformatted, Medical Term Definitions added.

12/99 Medical Policy Advisory Group

2/00 The policy was revised to include eligibility of coverage for Myasthenia Gravis based on specific criteria per information received from the December 1998 article written by Dr. Howard and the May 1999 publication stated above. Typographical error corrected. Last Review and Next Review dates changed. Coding system changes.

10/00 System coding changes.


03/01 Consultant review. No changes to policy. Reaffirm.
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4/01 Revised. Removed first statement under "what is not covered". It was a duplicate diagnosis.

5/03 Specialty Matched Consultant Review 4/03. Revised Description section for clarity. Typos corrected. Deleted codes J1561, J1562, 90288, 90371, 90379, 90386 from Billing/Coding section as codes have either been deleted or are not applicable to this policy. Added code J1564 to Billing/Coding section. Kawasaki Syndrome is now a labeled indication. Eaton-Lambert syndrome is now an off-label indication. Under "When covered" added "steroid" to 2.h.ii; added refractory polymyositis as 2.i; Toxic shock syndrome as 2.j; Hemolytic Disease of the newborn as 2.k. Under "When not covered" added diagnoses 30-38.

4/04 Benefits Application and Billing/Coding sections updated for consistency.

4/21/05 Specialty Matched Consultant review 3/28/05. Under When Covered section -added the following statement to Guillain-Barré syndrome - "when presenting within 4 weeks of neuropathic symptoms if nonambulant and 2 weeks if ambulant". New HCPCS codes, Q9941, Q9942, Q9943, Q9944 added in Billing/Coding section of policy. Notification given 4/21/05. Effective date 7/7/2005.

1/19/06 Removed deleted codes J1563, J1564, Q9941, Q9942, Q9943, & Q9944 from Billing/Coding section and added new 2006 CPT codes J1566 & J1567.

2/16/06 Removed #2.h.i-ii indications for Myasthenia Gravis under "When Covered" section and added the following: 2.h. Myasthenic crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange and 2.i. Myasthenia Gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complication from or failure of steroids and/or azathioprine. Removed #5 statement under "When not Covered" section. #5 now reads, "Myasthenia Gravis in patients responsive to immunosuppressive treatment." Notification given 2/16/06. Effective date 4/27/06.

3/2/06 Due to a scheduling change for the 4/27/06 website update, the effective date for the revisions to this policy noticed on 2/16/06 is 4/24/06.

4/24/06 Added the following statement to When Covered section; 1.c. and 1.e. second bullet-both regarding bone marrow transplant patients: "(for BCBSNC policy, the source of hematopoietic stem cells may be from bone marrow, peripheral blood or umbilical cord blood)".

7/10/06 Typos corrected.

Policy retitled: Immune Globulin Therapy

3/12/07 "Intravenous" dropped from name of policy. Policy section, When Covered section header and When Not Covered section header since policy now includes subcutaneous route of administration of immune globulin. Information regarding subcutaneous formulation of immunoglobulin added to Description section. Under When Covered section added criteria for intravenous immunoglobulin in the setting of solid organ transplant. Also added "Subcutaneous immune globulin may be considered medically necessary for the treatment of patients with primary immune deficiency diseases (PIDD)." Under When Not Covered section, added contraindication to immune globulin therapy. Code J1562 added to Billing/Coding section (previously deleted code reinstated for subcutaneous injection immune globulin). Key words, terms and definitions and reference sources added. (pmo)

7/2/07 Specialty Matched Consultant review. No changes to criteria. Added HCPCS codes Q4087, Q4088, Q4091 and Q4092 effective July 1, 2007 to Billing/Coding section. Reference source added. (pmo)

12/31/07 Coding update. Deleted codes 90291, Q4087, Q4088, Q4091 and Q4092. Added codes 90284, J1561, J1568, and J1569. (adn)

3/24/08 Added code J1572 (Flebogamma) and code Q4097 (Privigen) to the Billing/Coding section. (adm)

01/05/09 Coding update. Code Q4097 replaced with Code J1459. (adm)
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7/6/09 Description section revised for clarity. Reformatted "When IVIg Is Covered" section into an outline and added the following indications: in post-bone marrow transplant setting and refractory dermatomyositis in combination with other immunosuppressive agents. The following indications were deleted from the "When IVIg is Covered" section: refractory polymyositis, toxic shock syndrome, hemolytic disease of the newborn and Lambert-Eaton syndrome. Subcutaneous immune globulin may be considered medically necessary for treatment of patients with primary immune deficiency diseases including: congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and x-linked agammaglobulinemia. The following were added to the "When IVIg is Covered" section: refractory dermatomyositis as monotherapy, dermatomyositis in patients responsive to immunosuppressive therapy, polymyositis including refractory polymyositis, Fisher syndrome and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Deleted Code J1567. References updated. Specialty Matched Consultant review 4/8/09. (adm)

9/28/09 Description section extensively revised. Specific FDA-labeled indications noted in the When IVIg Is Covered section. Relapsing/remitting multiple sclerosis (formerly Item 12) was deleted from the list of covered indications. The following statement was added to the When IVIg is Not Covered section, "IVIg is considered not medically necessary as a treatment of relapsing/remitting multiple sclerosis." Notification given 9/28/09. Effective date 1/01/10. (adm)

6/22/10 Policy Number(s) removed (amw)

1/4/2011 Added new HCPCS codes J1559 and J1599 to Billing/Coding section. Also added HCPCS code J1460 due to deletion of J codes J1470-J1550. (lpr)

4/12/11 Added code C9270 to Billing/Coding section. Specialty Matched Consultant Advisory Panel review. The following information was added to the Policy Guidelines section: “Patients with chronic inflammatory demyelinating neuropathy (CIDP) should meet the diagnostic criteria established by the American Academy of Neurology. In addition, intravenous immunoglobulin infusion (IVIg) treatment should be limited to CIDP patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening documented by neurological exam. In patients treated for chronic diseases, such as CIDP, multifocal motor neuropathy, and dermatomyositis, the effect of IVIg is transitory and therefore periodic infusions of IVIg are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed. Continued treatment with IVIG is warranted only if it continues to be efficacious.” Added Appendix to policy with diagnostic criteria for CIDP. Specialty Matched Consultant review 2/2011. (adm)

4/17/12 Specialty Matched Consultant review 2/29/12. Description section updated. Related policies and Evidence-based guidelines added. Added the following indications to When Immune Globulin Therapy is Covered: “Ataxia telangiectasia; X-linked hyper-IgM syndrome; Acute Humoral Rejection; Autoimmune Mucoedematous Blistering Diseases; and Eaton-Lambert myasthenic syndrome.” Added Appendix B Diagnostic Criteria for Diagnosis of Multifocal Motor Neuropathy (MMN) Added new reference. Added the following clinical conditions to “When not Covered” section: “complex regional pain syndrome, Alzheimer’s disease, IGG sub-class deficiency, sepsis.” Removed the “European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy” from Appendix. Policy noticed on 4/17/12 to be effective 7/24/12. (sk)

10/30/12 Coding update. Code C9270 replaced with Code J1557 in Billing/Coding section. (sk)

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for effective date 6/11/2013. (sk)

4/1/13 Coding update. Code C9130 added to Billing/Coding section. (sk)

7/1/13 Medical Director review. Added “Sural nerve biopsy may be optional in selective cases in which there is no evidence of demyelination on the electrodiagnostic studies” to the Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) section of the Appendix. No change to policy statement. (sk)

10/29/13 Reference added. Medical Director review. Severe anemia due to parvovirus B19 added as medically necessary. Opioclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis and polyradiculoneuropathy (other than CIDP) added as investigational. Notification given 10/29/13 for policy effective date of 12/31/13. (sk)

12/31/13 Coding update. C9130 deleted and J1556 added effective 01/01/14. (sk)

7/15/14 Specialty Matched Consultant Advisory Panel review 2/25/14. Added hypogammaglobulinemia and prevention of infection in preterm infants and/or low-birth weight neonates to the list of covered indications. Reference added. (sk)

11/25/14 Information about HyQvia added to Description section. References added. J3490 and J3590 added to Billing/Coding section. Medical Director review. No change to Policy statements. (sk)


7/1/15 Reference added. Related Guideline “Therapeutic Apheresis” removed from policy. Hemolytic disease of the fetus and newborn (aka erythoblastosis fetalis) added to medically necessary statement. In investigational statement, “treatment of sepsis including neonatal sepsis” changed to “treatment of sepsis including suspected or proven infection in neonates.” Postpolio syndrome added to investigational statement. (sk)

10/30/15 Senior Medical Director review. Site of care eligibility guidelines added to Policy Guidelines section. Notification given 10/30/2015 for policy effective date 12/30/2015. (sk)

12/30/15 New code J1575 added to Billing/Coding section. Removed codes J3490 and J3590 from Billing/Coding section. (sk)

4/1/16 Specialty Matched Consultant Advisory Panel review 2/24/2016. Physician office setting removed from 2 and added to 3 under IVIg Site of Care Eligibility. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.

Appendix: Diagnostic Criteria

**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

The following criteria are adapted from the European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. (European Journal of Neurology 2010; 17:356-363).

**I. Mandatory Clinical Criteria**

Progressive symmetrical or asymmetrical polyradiculoneuropathy when the clinical course is relapsing
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and remitting, or progresses for more than 2 months, especially if there are positive sensory, proximal weakness, areflexia without wasting, or preferential loss of vibration or joint position sense.

II. Mandatory Electrodiagnostic Study Criteria

1. **Definite Diagnosis**: at least one of the following
   a. Motor distal latency prolongation greater than or equal to 50% above upper limit of normal values (ULN) in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
   b. Reduction of motor conduction velocity greater than or equal to 30% below lower limit of normal values (LLN) in two nerves, or
   c. Prolongation of F-wave latency greater than or equal to 30% above ULN in two nerves (greater than or equal to 50% if amplitude of distal negative peak compound muscle action potential (CMAP) <80% of LLN values), or
   d. Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes greater than or equal to 20% of LLN plus greater than or equal to one other demyelinating parameter* in greater than or equal to one other nerve, or
   e. Partial motor conduction block: Greater than or equal to 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP greater than or equal to 20% of LLN, in two nerves, or in one nerve plus greater than or equal to one other nerve plus greater than or equal to one other demyelinating parameter* in greater than or equal to one other nerve, or
   f. Abnormal temporal dispersion (greater than 30% duration increase between the proximal and distal negative peak CMAP) in greater than or equal to two nerves, or
   g. Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in greater than or equal to one nerve (median greater than or equal to 6.6 ms, ulnar greater than or equal to 6.7 ms, peroneal greater than or equal to 7.6 ms, tibial greater than or equal to 8.8 ms) plus greater than or equal to one other demyelinating parameter* in greater than or equal to one other nerve

2. **Probable Diagnosis**
   Greater than or equal to 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP greater than or equal to 20% of LLN, in two nerves, or in one nerve plus greater than or equal to one other nerve

3. **Possible Diagnosis**
   • As in 1. (Definite) but in only one nerve

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb’s point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33 degrees C at the palm and 30 degrees C at the external malleolus (good practice points).

Electrodiagnostic findings meeting probable diagnostic criteria must also meet at least one or more of the supportive pathology, laboratory, or imaging criteria noted below. Electrodiagnostic findings meeting possible diagnostic criteria must also meet at least two or more of the supportive criteria.

*Any nerve meeting any of the criteria (a–g).

III. Supportive Pathologic Feature Criteria

Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron
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microscopy or teased fibre analysis.

IV. Supportive Laboratory Criteria

Cerebrospinal fluid studies

1. Cell count <10 per cubic mm if HIV-seronegative or <50 per cubic mm if HIV seropositive; and
2. Negative VDRL; and
3. Elevated protein.

V. Supportive Imaging Criteria

MRI of spinal roots, brachial plexus, cauda equina, or lumbosacral plexus showing gadolinium enhancement and/or hypertrophy.

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**Multifocal Motor Neuropathy (MMN)**

Patients with multifocal motor neuropathy should meet established diagnostic criteria such as those published by Van Asseldonk and colleagues in *Lancet Neurology* in 2005

I. Clinical criteria

1. Slow or stepwise progressive limb weakness
2. Asymmetrical limb weakness
3. Fewer than seven affected limb regions (on each side: upper arm, lower arm, upper leg, or lower leg
4. Tendon reflexes in affected limbs are decreased or absent
5. Signs and symptoms more pronounced in arms than in legs
6. 20-65 years old at disease onset
7. No objective sensory abnormalities except for vibration sense
8. No bulbar signs or symptoms
9. No upper-motor-neuron features
10. No other neuropathies
11. No myopathy (e.g., dystrophy, inclusion-body myositis)

II. Laboratory criteria

1. CSF protein less than 1 g/L
2. High anti-GM1 titer
3. High signal intensity on T2-weighted MRI of the brachial plexus

III. Electrodiagnostic criteria

1. **Definite motor conduction block:** Compound muscle action potential (CMAP) area reduction on proximal versus distal stimulation of at least 50% over a long segment (between erb and axilla, upper arm, lower arm, lower leg), or a CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a short distance (2.5 cm) detected by inching CMAP amplitude on stimulation of the distal part of the segment with motor conduction block of at least 1 mV
2. **Probable motor conduction block:** CMAP amplitude reduction on proximal versus distal stimulation of at least 30% over a long segment of an arm nerve. CMAP amplitude on stimulation of the distal part of the segment with motor conduction block of at least 1 mV
3. **Slowing of conduction compatible with demyelination:** Motor conduction velocity (MCV) <75% of the lower limit of normal; DML or shortest F wave latency 130% of the upper limit of normal or absence of F waves all after 16-20 stimuli. CMAP amplitude on distal stimulation of at least 0.5mV
4. Normal sensory-nerve conduction in arm segments with motor conduction block. Normal sensory nerve action potential (SNAP) amplitudes on distal stimulation

**Definite MMN:** 1-11 on clinical criteria, 1 on laboratory criteria, and 1 and 4 on electrodiagnostic criteria

**Probable MMN:** 1-3 and 6-11 on clinical criteria, 1 on laboratory criteria, and 2 and 4 on electrodiagnostic criteria

**Possible MMN:** 1 and 7-11 on clinical criteria, 2 or 3 on laboratory criteria, and 3 and 4 on electrodiagnostic criteria

**Primary Immunodeficiency Syndromes**

The diagnosis of immunodeficiency and post immunization titers must be taken in context with the clinical presentation of the patient, and may vary dependent on the type of vaccine given and the prior immunization history of the patient. The following parameters are examples of criteria for diagnosis of the primary immunodeficiency syndromes.

Laboratory evidence of immunoglobulin deficiency may include the following definitions:

- Agammaglobulinemia (total IgG less than 200 mg/dL)
- Persistent hypogammaglobulinemia (total IgG less than 400 mg/dL, or at least two standard deviations below normal, on at least two occasions)
- Absence of B lymphocytes

Inability to mount an adequate antibody response to inciting antigens may include the following definitions:

- Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen. For example, an adequate response to the pneumococcal vaccine may be defined as at least a four-fold increase in titers for at least 50% of serotypes tested.
- Lack of appropriate rise in antibody titer following provocation with a protein antigen. For example, an adequate response to tetanus/diphtheria vaccine may be defined as less than a four-fold rise in titers 3-4 weeks after vaccine administration.

According to a 2010 national guideline from Canada on immune globulin for primary immune deficiency, although higher trough levels of IVIg may be associated with clinical response; the goal of IVIg dose increases should be to improve clinical effectiveness and not merely to increase trough levels.

**Severe ITP**

Acute, severe ITP may be defined by the following parameters:

- acute ITP with major bleeding, e.g., life-threatening bleeding and/or clinically important mucocutaneous bleeding
- acute ITP with severe thrombocytopenia and at high risk for bleeding complications
- acute ITP with severe thrombocytopenia and a slow or inadequate response to corticosteroids
- acute ITP with severe thrombocytopenia and a predictable risk of bleeding in the future, e.g., a procedure or surgery with a high bleeding risk.