

Corporate Medical Policy

Immunoglobulin Therapy

File Name:	immune_globulin_therapy
Origination:	07/1994
Last CAP Review:	2/2020
Next CAP Review:	2/2021
Last Review:	5/2020

Description of Procedure or Service

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immunodeficiency states and a variety of autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Two formulations of human IgG are available: intravenous infusion (IVIG) and subcutaneous infusion. Intramuscular immunoglobulin depot injections have been largely abandoned.

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 immunodeficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIG products are available for clinical use in the United States. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., Guillain-Barre syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

This policy only addresses nonspecific pooled preparations of IVIG; it does not address other immunoglobulin preparations specifically used for passive immunization to prevent or attenuate infection with specific viral diseases (e.g., respiratory syncytial virus, cytomegalovirus, hepatitis B). (Coverage for RSV immune globulin (e.g., Synagis) is summarized in the Medical policy titled, "Respiratory Syncytial Virus Prophylaxis").

IVIG is considered a mainstay of treatment for immunodeficiency conditions and bullous skin disorders. It has been prescribed off-label to treat a wide variety of autoimmune and inflammatory neurologic conditions.

Regulatory Status

Several intravenous immunoglobulin (IVIG) products have been approved by the U.S. Food and Drug Administration (FDA). They include Carimune® (CSL Behring AG), Flebogamma DIF® (Istituto Grifols), GammaSTAN S/D® (Grifols Therapeutics), Gammagard Liquid® (Baxter), Gammagard S/D® (Baxter), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), Privigen® (CSL Behring) and BIVIGAM™ (Biotest Pharmaceuticals).

Several subcutaneous immunoglobulin products have been approved by FDA. They include Gammagard Liquid® (Baxter), Gamunex-C® (Grifols Therapeutics), Cuvitru® (Baxalta), Hizentra® CSL (Behring AG), Hyqvia® (Baxter), Xembify® (Grifols Therapeutics), and Vivaglobin® CSL (Behring GmbH).

At least one 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

Immunoglobulin Therapy

- Kawasaki syndrome
- Chronic inflammatory demyelinating polyneuropathy

Related Policies:

Hematopoietic 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 (EFNS) 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

Immunoglobulin Therapy

Multiple sclerosis (MS) is a demyelinating disease accompanied by a lymphocytic infiltration in lesions. 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 acute antibody-mediated rejection (ABMR) related to the presence of anti-donor antibodies. Acute ABMR is an entity now better defined and often detected earlier in the clinical course, based on the recognition of characteristic histologic findings, positive C4d staining, and the detection of donor-specific antibodies. The risk of

Immunoglobulin Therapy

ABMR 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 panel reactive antibody (PRA) screen. Those with a PRA screen greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Recipients of ABO mismatched donor organs are also at risk of ABMR.

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 Immunoglobulin 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 Immunoglobulin Therapy is covered

INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY

IVIG may be considered **medically necessary** for the following indications:

Primary Immunodeficiencies

Patients with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked hyperimmunoglobulinemia M syndrome, and ataxia telangiectasia.

- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immunoglobulin:
 - Laboratory evidence of immunoglobulin deficiency (see Appendix)
 - Documented inability to mount an adequate immunologic response to inciting antigens (see Appendix)
 - Persistent and severe infections, despite treatment with antibiotics

Infections

- Patients with chronic lymphocytic leukemia who have IgG levels less than 400 mg/dL and persistent bacterial infections
- Patients with multiple myeloma who have recurrent life-threatening bacterial infections

Immunoglobulin Therapy

- Patients (children) with HIV who have IgG levels less than 400 mg/dL to prevent opportunistic infections
- Patients with severe anemia associated with human parvovirus B19.
- Patients with toxic shock syndrome.

Autoimmune and Inflammatory Conditions

- Patients with severe, progressive autoimmune mucocutaneous blistering diseases that include pemphigus, pemphigoid, pemphigus vulgaris, pemphigus foliaceus who have failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide.
- Patients with acute, severe idiopathic thrombocytopenic purpura (see Appendix) or chronic idiopathic thrombocytopenic purpura with at least 6 months of disease duration, presence of symptoms and with persistent thrombocytopenia (platelet <20,000 per microliter [adult] or 30,000 per microliter [child]), despite treatment with corticosteroids and splenectomy
- Adult patients with Guillain-Barré syndrome as an equivalent alternative to plasma exchange.
- Patients with Kawasaki syndrome.
- Patients with granulomatosis with polyangiitis, previously known as Wegener granulomatosis.
- Patients with chronic inflammatory demyelinating polyneuropathy with progressive symptoms for at least 2 months.
- Patients with multifocal motor neuropathy.
- Patients with Eaton-Lambert myasthenic syndrome who have failed to respond to anticholinesterase medications and/or corticosteroids.
- Patients with neuromyelitis optica, as an alternative for patients with contraindication or lack of response to first-line treatment, particularly in children.
- Patients with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- Patients with myasthenic exacerbation (ie, an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated.
- Patients with dermatomyositis or polymyositis that is refractory to treatment with corticosteroids; in combination with other immunosuppressive agents.
- Patients with warm antibody hemolytic anemia who are refractory to prednisone and splenectomy.
- Patients with antiphospholipid syndrome
- Patients with autoimmune encephalitis (AE), including but not limited to antibody-mediated AE, with an inadequate response to glucocorticoids, or in whom steroids are not tolerated or are contraindicated.

Alloimmune Processes

- Patients with neonatal alloimmune thrombocytopenia
- Patients with hemolytic disease of the fetus and newborn (erythroblastosis fetalis).

Transplant

- In hematopoietic cell transplantation recipients who are 180 days post-transplantation and who have serum immunoglobulin G (IgG) levels less than 400 mg/dL, for prevention of infection. (see Policy Guidelines for transplant recipients within 180 days post-transplantation)
- Prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection including highly allo-sensitized patients and those receiving an ABO incompatible organ
- Treatment of solid organ transplant antibody-mediated rejection

Miscellaneous

- Patients with stiff person syndrome not controlled by other therapies

Immunoglobulin Therapy

SUBCUTANEOUS IMMUNOGLOBULIN THERAPY

Subcutaneous immunoglobulin may be considered medically necessary for the following indications:

- Patients with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinemia.

When Immunoglobulin Therapy is not covered

IVIg is considered **not medically necessary** for:

- Patients with relapsing-remitting multiple sclerosis.

Intravenous immunoglobulin therapy is considered **investigational** for all other indications, including, but not limited to:

Infections

- Patients with neonatal sepsis (prophylaxis or treatment)
- Patients (adults) with sepsis.

Autoimmune and Inflammatory Conditions

- Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis
- Patients with inclusion body myositis
- Patients with systemic lupus erythematosus
- Patients with immune optic neuritis
- Patients with Crohn's disease
- Patients with hemophagocytic lymphohistiocytosis.

Alloimmune Processes

- Patients with recurrent spontaneous abortion.

Miscellaneous

- Patients with pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections
- Patients with autism spectrum disorder
- Patients with complex regional pain syndrome
- Patients with Alzheimer disease
- Patients with paraproteinemic neuropathy
- Patients with chronic fatigue syndrome
- Patients with acute myocarditis
- Patients with refractory recurrent pericarditis
- Patients with noninfectious uveitis
- Patients with postpolio syndrome
- Patients with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, paraneoplastic syndromes, epilepsy, chronic sinusitis, asthma, aplastic anemia, Diamond-Blackfan anemia, red cell aplasia, acquired factor VIII inhibitors, acute lymphoblastic leukemia, immune-mediated neutropenia, nonimmune thrombocytopenia, cystic fibrosis, recurrent otitis media, diabetes mellitus, Behçet syndrome, adrenoleukodystrophy, Fisher syndrome, IGG subclass deficiency, opsoclonus-myoelonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy), refractory rheumatoid arthritis, other vasculitides besides Kawasaki disease

Immunoglobulin Therapy

and granulomatosis with polyangiitis, including polyarteritis nodosa, Goodpasture syndrome, and vasculitis associated with other connective tissue diseases.

Applications of SCIG therapy other than those listed under when covered 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)

Organ Allografts

For individuals who are at risk of acute antibody-mediated rejection (ABMR) after solid organ transplant who receive IVIG therapy, the evidence includes of multiple RCTs, noncomparative observational studies, systematic reviews, and meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for prophylaxis of infection in patients with high panel reactive antibody level was not associated with survival benefit or reduction in infection. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective studies. Larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Hematopoietic Cell Transplantation

***For IVIG requests within 180 days post-transplantation date, please refer to internal protocol found within Blue Cross NC Clinical Transplant Process Guidelines.

For individuals who are undergoing hematopoietic cell transplantation who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs, systematic reviews, and a meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for routine prophylaxis of infection in patients undergoing hematopoietic cell transplantation was not associated with survival benefit or reduction in infection. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Multiple Sclerosis

For individuals who have relapsing-remitting multiple sclerosis (RRMS) who receive IVIG therapy, the evidence includes multiple RCTs and technology assessments. Relevant outcomes are overall survival, symptoms, disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. According to technology

Immunoglobulin Therapy

assessments, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Chronic Inflammatory Demyelinating Neuropathy (CIDP)

For individuals who have chronic inflammatory demyelinating polyneuropathy (CIDP) who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in disability. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes a single RCT. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, SCIG therapy has shown clinically meaningful improvements in disability. However, the relative benefits of SCIG therapy over IVIG remain unclear because of lack of direct comparison with IVIG. The evidence is insufficient to determine the effects of the technology on health outcomes.

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
 - 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.

Disorder	Dose
Primary immunodeficiency disorders	0.4-0.6 g/kg every 28 days
Chronic inflammatory demyelinating polyneuropathy (CIDP)	0.4 g/kg for 5 doses
Guillain-Barré syndrome	0.25-0.4 g/kg × 5 doses
Dermatomyositis	0.4 g/kg for 5 doses

Immunoglobulin Therapy

Idiopathic thrombocytopenia	0.4 g/kg/d × 5 days
Acute humoral rejection	1 g/kg/d for 2 doses

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, J1555, J1556, J1557, J1558, 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

BCBSA Medical Policy Reference Manual - 9/23/98

BCBSA Medical Policy Reference Manual - 11/1/98

USPDI - 19th Edition, 1999; Vol. 1, pp. 1686-1690, 3024-3025 & 3147.

Medical Policy Advisory Group - 12/99

Canadian Journal of Neurological Sciences; *IGIV in Neurology--Evidence and Recommendations*; Brill V, Allenby K, Midroni G, O'Connor PW, Vajsar J. May 26, 1999 (2):139-52

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

USPDI - 23rd Edition, 2003; Vol. 1, pp. 1527-1532

Specialty Matched Consultant Review - 4/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/16/04.

USPDI - 25th Edition, 2005; Vol. 1, pp. 1652-1658

Specialty Matched Consultant Review - 3/28/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/1/05.

Policy retitled: Immune Globulin Therapy

Immunoglobulin Therapy

U.S. Food and Drug Administration. Product Approval Information-Licensing Action for Immune Globulin Subcutaneous (Human). Retrieved on 1/17/07 from <http://www.fda.gov/cber/products/igsczlb010906.htm>

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 12/14/05.

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 4/25/06

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 7/20/06.

Specialty Matched Consultant Review - 5/23/07

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 12/11/08

U.S. Food and Drug Administration (FDA). Immune Globulin Intravenous (IGIV) Indications. Updated 8/1/07. Retrieved 2/12/09 from <http://www.fda.gov/cber/products/igivlist.htm>

Gibson J, Kornberg A, Riminton S. Criteria for the clinical use of intravenous immunoglobulin in Australia. Canberra, ACT: National Blood Authority 2007. Retrieved 2/12/09 from <http://www.nba.gov.au/ivig/Criteria/foreword.html>

Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525-S553. Retrieved 2/12/09 from http://www.aaaai.org/members/resources/initiatives/ivig_toolkit/2006_ivig_evidence_review.pdf

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. *Eur J Neurol.* 2010 Mar;17(3):356-63

Venez JP, Pascual M. New treatments for acute humoral rejection of kidney allografts; [Expert Opin Investig Drugs](#). 2007 May;16(5):625-33 BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 10/4/11

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 10/4/11.

Specialty Matched Consultant Review – 2/29/12

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 12/13/12.

Specialty Matched Consultant Advisory Panel – 2/20/13

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 6/13/13.

Specialty Matched Consultant Advisory Panel – 2/25/14

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 5/22/14

HyQvia Prescribing Information. September 2014. Available at http://www.baxter.com/downloads/healthcare_professionals/products/HYQVIA_PI.pdf

U.S. Food and Drug Administration. <http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsbilas/fractionatedplasmaproducts/ucm414117.htm>

Medical Director review 11/2014

Specialty Matched Consultant Advisory Panel – 2/25/15

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 5/21/15

Immunoglobulin Therapy

Senior Medical Director review 10/2015

Specialty Matched Consultant Advisory Panel – 2/24/16

For Policy retitled Immunoglobulin Therapy

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 11/10/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 1/12/2017

Specialty Matched Consultant Advisory Panel – 2/22/17

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 10/12/2017

Specialty Matched Consultant Advisory Panel – 2/28/18

Dalmau J, Graus F. Antibody-Mediated Encephalitis. *N Engl J Med*. 2018 Mar 1;378(9):840-851. doi: 10.1056/NEJMra1708712. Review. PubMed PMID:29490181.

Kelley BP, Patel SC, Marin HL, et al. Autoimmune Encephalitis: Pathophysiology and Imaging Review of an Overlooked Diagnosis. *AJNR Am J Neuroradiol*. 2017 Jun;38(6):1070-1078. doi: 10.3174/ajnr.A5086. Epub 2017 Feb 9. Review. PubMed PMID: 28183838.

Gastaldi M, Thouin A, Vincent A. Antibody-Mediated Autoimmune Encephalopathies and Immunotherapies. *Neurotherapeutics*. 2016 Jan;13(1):147-62. doi: 10.1007/s13311-015-0410-6. Review. PubMed PMID: 26692392; PubMed Central PMCID: PMC4720680.

Medical Director review 5/2018

Medical Director review 7/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 10/10/2018

Specialty Matched Consultant Advisory Panel – 2/20/19

Medical Director review 4/2019

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Multiple Myeloma, version 3.2019. Revised June 19, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed June 2019.

Medical Director review 6/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.05, 10/17/2019

Specialty Matched Consultant Advisory Panel – 2/19/2020

Medical Director review 5/2020

Policy Implementation/Update Information

From Policy Entitled: Intravenous Immune Globulin Therapy

Immunoglobulin Therapy

- 7/94 Evaluated: Eligible for coverage for the treatment of refractory dermatomyositis. Investigational for the treatment of chronic progressive or relapsing-remitting multiple sclerosis and refractory rheumatoid arthritis.
- 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.
- 12/00 New 2001 HCPCS code J1563 added. System coding changes.
- 03/01 Consultant review. No changes to policy. Reaffirm.
- 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.

Immunoglobulin Therapy

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. (adn)

01/05/09 Coding update. Code Q4097 replaced with Code J1459. (adn)

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 Not 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. (adn)

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. (adn)

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)

Immunoglobulin Therapy

- 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. (adn)
- 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 Mucocutaneous 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)
- 3/12/13 Reference added. “Refractory dermatomyositis, as monotherapy”, “dermatomyositis in patients responsive to immunosuppressive therapy”, and “post-infectious sequelae” removed from Not Covered section. “Neonatal sepsis” and “Crohn’s Disease” added to Not Covered section. Specialty Matched Consultant Advisory Panel review 2/20/13. Notification given 3/12/2013 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. Opsoclonus-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)
- 4/28/15 Specialty Matched Consultant Advisory Panel review 2/25/15. Diagnostic criteria for CIDP updated in Appendix. (sk)
- 7/1/15 Reference added. Related Guideline “Therapeutic Apheresis” removed from policy. Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis) added to medically

Immunoglobulin Therapy

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)

For Policy retitled Immunoglobulin Therapy

- 3/31/17 Title changed from Immune Globulin Therapy to Immunoglobulin Therapy. References added. The following were changed from investigational to medically necessary: polymyositis, granulomatosis with polyangiitis (formerly known as Wegener’s granulomatosis), and stiff person syndrome. The following were new indications added as medically necessary: patients with chronic lymphocytic leukemia who have IgG levels <400 mg/dL and persistent bacterial infections; and patients with neuromyelitis optica as an alternative for patients with contraindication or lack of response to steroids or plasma exchange particularly in children. (sk)
- 3/31/17 Formatting and organizational changes made. Description and Policy Guidelines updated. The following were changed from medically necessary to investigational: treatment of antibody mediated rejection following solid organ transplantation; patients with neonatal sepsis (prophylaxis or treatment); patients with Stevens-Johnson syndrome; and patients with toxic epidermal necrolysis. The following were new conditions added as investigational: patients with acute myocarditis, and patients with refractory recurrent pericarditis. Policy noticed 3/31/17 for effective date 6/30/17. (sk)
- 12/29/17 Code J1555 added to Billing/Coding section for effective date 1/1/2018. (sk)
- 5/11/18 Updated “When Covered” section to include the following statement as medically necessary: “Patients with autoimmune encephalitis (AE), including but not limited to antibody-mediated, with an inadequate response to glucocorticoids, or in whom steroids are not tolerated or are contraindicated.” References added. In medically necessary bullet point on neuromyelitis optica, “steroids or plasma exchange” changed to “first-line treatment”. Specialty Matched Consultant Advisory Panel review 2/28/2018. Medical Director review 5/2018. (krc)
- 7/27/18 Updated “When Covered” section to include treatment of solid organ transplant antibody-mediated rejection as medically necessary. Reorganized coverage headings for clarity. Removed “organ transplant rejection” as investigational from “When Not Covered” section. Reference added. Medical Director review 7/2018. (krc)
- 9/7/18 Removed the following investigational statement from “When Not Covered” section: “Patients who have received solid organ transplant for prophylaxis or treatment of acute antibody mediated rejection” to provide clarity in association with added indication for treatment of solid organ transplant antibody-mediated rejection as medically necessary. (krc)
- 3/12/19 Reference added. Specialty Matched Consultant Advisory Panel review 2/20/2019. (krc)
- 4/16/19 Under “When Covered” section for Primary Immunodeficiencies, removed ‘prophylactic’ from the following statement for clarity: “persistent and severe infections, despite treatment with prophylactic antibiotics.” Reference added. Medical Director review 4/2019. (krc)
- 7/1/19 Under “When Covered” section for Infections, the following indication was added as medically necessary: patients with multiple myeloma who have recurrent life-threatening

Immunoglobulin Therapy

- bacterial infections. Removed multiple myeloma from “When Not Covered” section. References added. Medical Director review 6/2019. (krc)
- 3/10/20 Minor typographical edits made for clarity. Reference added. Specialty Matched Consultant Advisory Panel review 2/19/2020. No change to policy statements. (krc)
- 5/26/20 Updated “When Covered” section for hematopoietic cell transplantation to clarify the following “hematopoietic cell transplantation recipients who are 180 days post-transplantation.” Updated Policy Guidelines to include the following statement: “For IVIG requests within 180 days post-transplantation date, please refer to internal protocol found within Blue Cross NC Clinical Transplant Process Guidelines.” Clarified definition of standard deviation for hypogammaglobulinemia diagnostic criteria within the Appendix. Medical Director review 5/2020. (krc)
- 6/30/20 Added HCPCS code J1558 to Billing/Coding section for Xembify subcutaneous immunoglobulin therapy effective 7/1/2020. (krc)

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 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^a 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

Immunoglobulin Therapy

- greater than or equal to one other demyelinating parameter^a 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 demyelinating parameter^a 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 1 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.

^aAny 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 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.

Multifocal Motor Neuropathy (MMN)

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

Immunoglobulin Therapy

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 below the lower limit of normal defined as at least two standard deviations below the age-adjusted mean, 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.