Immune Globulin Therapy

Policy Number: 8.01.05  Last Review: 6/2014

Policy
BCBSKC will provide coverage for immune globulin replacement therapy when the following criteria are met.

When Policy Topic is covered
Intravenous Immune globulin (IV Ig) Therapy

IV Ig may be considered medically necessary for the following indications:

Primary immune deficiency syndromes, including combined immunodeficiencies.

- X-linked agammaglobulinemia (Bruton’s)
- X-linked hyper-IgM syndrome
- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome
- Ataxia telangiectasia
- Patients with primary immunodeficiency syndromes should meet all the following criteria for treatment with immune globulin:
  - Laboratory evidence of immunoglobulin deficiency (see Policy Guidelines)
  - 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;
- allogeneic post-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

Infectious diseases

- HIV [human immunodeficiency virus]-infected patients
- toxic shock syndrome
- Kawasaki disease
- 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

* FDA-labeled indications
Subcutaneous Immune Globulin (SCIg) Therapy

SCIg may be considered medically necessary for the treatment of primary immunodeficiencies*, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency (CVID), severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinemia (XLA).

When Policy Topic is not covered

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

Other applications of IVIg therapy are considered investigational, including, but not limited to, the following conditions:

- chronic progressive multiple sclerosis;
- refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus;
- recurrent spontaneous abortion (see below for related laboratory tests);
- 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;
- Diamond-Blackfan anemia;
- red cell aplasia;
- acquired factor VIII inhibitors;
- hemophagocytic syndrome;
- 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
• sepsis

Considerations
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.

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.
Patients with chronic inflammatory demyelinating neuropathy (CIDP) should meet the diagnostic criteria established by the American Academy of Neurology, particularly if the patient also is diagnosed with chronic fatigue syndrome. (See Appendix A for the diagnostic criteria.) In addition, by 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. 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.

Patients with multifocal motor neuropathy should meet established diagnostic criteria such as those published by Van Asseldonk and colleagues in *Lancet Neurology* in 2005 (See Appendix B for the diagnostic criteria).

The following is an adaptation of recommendations that have been made for IVIg dosing in a consensus report from the IVIg advisory committee. (1)

<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>

There are CPT and HCPCS codes that describe IVIg and SCIg products:

- 90283: Immune globulin (IgIV), human, for intravenous use
- 90284: Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
- J1459: Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
- J1557: Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
- J1559: Injection, immune globulin (Hizentra), 100 mg
- J1561: Injection, immune globulin (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
- J1562: Injection, immune globulin (Vivaglobin), subcutaneous, 100 mg
- J1566: Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
- J1568: Injection, immune globulin (Octagam) intravenous, non-lyophilized (e.g., liquid), 500 mg
- J1569: Injection, immune globulin (Gammagard Liquid) intravenous, non-lyophilized (e.g., liquid), 500 mg
- J1572: Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg
- J1599: Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg

The following CPT drug administration codes would be used for the administration of these products:

- 96365-96366 for intravenous infusions and
- 96369-96371 for subcutaneous infusions.

IVIg and SCIg are considered a medical benefit.

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy number 8.01.05.
Description of Procedure or Service

This policy addresses the use of human immune globulin therapy for preventing and/or treating a wide variety of disorders in the outpatient setting. Both intravenous infusion (IVIg) and subcutaneous infusion (SCIg) of immune globulin are addressed. However, the policy only considers nonspecific pooled preparations of IVIg, not other preparations used for passive immunization to specific antigens.

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.

Intravenous infusion immune globulin 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. Several IVIg products are available for clinical use in the United States. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the Policy section. 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 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.

Subcutaneous infusion immune globulin is used for treating 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. The first FDA-approved SCIg product, Vivaglobin, is a pasteurized, polyvalent human normal immune globulin product that is manufactured from large pools of human plasma by cold alcohol fractionation with no chemical or enzymatic alterations. Vivaglobin administration produces relatively stable steady-state serum levels of IgG that are representative of those seen in a normal human population. Applications of this product for conditions other than primary immunodeficiencies are considered off-label in the United States and are not addressed in this policy. In recent years, other SCIg products have also received FDA-marketing approval.

Regulatory Status

Several IVIg have been approved by the FDA. These include Carimune (ZLB Bioplasma), Flebogamma (Grifols), Gammagard (Baxter), Gamunex (Talecris Biotherapeutics), Octagam (Octapharma), Polygam S/D (Baxter) Privigen (CSL Behring LLC).

Several SCIg products have received FDA marketing approval for primary immunodeficiencies. These include Vivaglobin® (ZLB Behring LLC, Kankakee, IL), Hizentra® (ZLB Behring LLC, Kankakee, IL), Gamunex-C® (Talecris Biotherapeutics, Inc., Research Triangle Park, NC), and Gammaked® (Kedrion Biopharma, Cambridge, MA).
Rationale

This policy was created in 1996; the original policy incorporated findings from TEC Assessments on intravenous immune globulin therapy on a variety of conditions including multiple sclerosis (1994), rheumatoid arthritis (1994), recurrent fetal loss (1994), and inclusion body myositis (1995). The policy was updated regularly with searches of the MEDLINE database, most recently for the period December 2008 through October 2010. Following is a summary of the key literature to date:

IVIg Therapy

Given the heterogeneous nature and relapsing-remitting course of many of the diseases for which intravenous immunoglobulin infusion (IVIg) has been investigated as therapy, randomized controlled trials (RCTs) are important for evaluating true benefit. However, in the case of rare disease, RCTs may be less likely to evaluate benefit. In these cases, reports of series data from at least 10 patients and consistent trends in results may support conclusions. Therefore, the rationale includes some labeled indications but focuses on the use of IVIg for other conditions under investigation.

Primary Immune Deficiency

Primary immune deficiencies, a group of chronic disorders, are an FDA-approved indication for immune globulin therapy. Immunoglobulin is a longstanding treatment for these disorders.

X-linked agammaglobulinemia (XLA or Bruton’s) occurs in male patients who have less than 2% or absent circulating B cells and normal T lymphocytes. (2) There are mutations in the tyrosine kinase gene (BTK gene), the defect is on the mid-portion of the X chromosome (Xp22). XLA should be suspected in infants who present with life-threatening infections in the latter part of the first year of life. This is due to passively acquired maternal antibodies waning below protective levels. *H. influenzae* and *S. pneumoniae* are commonly associated infections of the sinopulmonary tract. Cellular immunity (T cell) is intact; therefore, viral and fungal infections and tuberculosis are not typically seen in XLA. It is important to recognize this condition early, using broad-spectrum antibiotics with IVIg, thereby changing the outcome and survival of these patients. (3) In order to prevent acute bacterial infections and bronchiectasis as an end organ disease in this condition, it is recommended that maintaining nadir serum IgG levels at greater than 500mg/dL is critical.

Common variable immunodeficiency (CVID) involves both B and T cell immune function. This disease presents with decreased immunoglobulin levels and abnormal antibody responses to antigens. Interestingly, CVID can affect any or all isotypes of immunoglobulin with specific antibodies affected due to inability to respond to antigen and there are diminished isohemagglutinin titers. The average age of onset is approximately 25 years. Unfortunately the mortality rate is high due to lymphoma and chronic pulmonary disease becoming more prominent with lower IgG and poorer T cell function. Similar to XLA, patients present with sinopulmonary infections and end organ bronchiectasis. In addition, the gastrointestinal tract is commonly affected, causing malabsorption or chronic diarrhea, protein-losing enteropathy, small bowel infection with *Campylobacter* or *Giardia lamblia*. There is a propensity to develop nodular lymphoid hyperplasia of the small bowel, peripheral lymph nodes, or the spleen. Incidence of malignancy is increased during the fifth and sixth decade of life. (4)

X-linked hyper-IgM is a T cell deficiency with a genetic defect in CD40 ligand molecule. Family consanguinity is frequent. These patients present with recurrent sinopulmonary and gastrointestinal tract infections in childhood. Serum IgM levels may be in excess of 1,000 mg/dL. The immunologic characteristic of this disorder is an abnormality in the process of immunoglobulin class switch recombination, therefore an inability to manufacture IgG, IgA, or IgE antibodies. Peripheral blood B cell counts (CD19) are normal. T lymphocyte counts and proliferative responses are normal. Molecular studies have shown a mutation in the AID gene (activation-induced cytidine deaminase gene).

IgG subclass deficiency has been questioned by clinical immunologists as to whether having low serum IgG subclass levels is a true immunodeficiency disease. The rationale is that low serum IgG
subclass levels may be found with more sensitive assays available today, and these individuals may be otherwise healthy. Therefore, IVIg replacement therapy would be considered investigational.

In 2010, the National Advisory Committee on Blood and Blood Products and Canadian Blood Services published a guideline on use of immune globulin therapy for patients with primary immune deficiency; recommendations were based on a systematic review of evidence that was reviewed by a panel of experts. (5) The search identified 3 RCTs, several cohort studies, and numerous case series. The panel agreed that there is sufficient evidence from 19 observational studies that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, which likely leads to a lower mortality and improved quality of life. Thus, IVIg therapy is considered medically necessary for treating primary immune deficiency diseases.

Other recommendations in the 2010 guideline in regards to IVIg treatment of primary immune deficiencies are:

- Consider the diagnosis of primary immune deficiency in patients (adults and children) with autoimmune hematological disease. To rule out primary immune deficiency in these patients, patients with autoimmune hematologic disease should have quantitative IgA, IgG, and IgM levels drawn before beginning immune globulin therapy.
- Treatment should be started at a dose of 400 to 600 mg/kg per 4 weeks for IVIg or 100 to 150 mg/kg per week for SCIG [by subcutaneous infusion] in most patients.
- If there is end-organ damage, the dose and/or frequency of immune globulin can be increased.
- Patients with primary immune deficiency may require immune globulin therapy indefinitely.

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disease characterized by thrombocytopenic purpura with small defective platelets, eczema, and infections with encapsulated bacteria. Clinically there is low serum IgM, elevated IgA and IgE with normal or low IgG, diminished isohemagglutinins and decreased antibody response to polysaccharide antigens. There are reduced T cells and lymphocyte response to antigens that are depressed. Identification in mutation of the WASP gene has been identified. Prenatal diagnosis of this disorder is made by chorionic villus sampling or amniocentesis if the WASP mutation occurs in the family. Mortality typically occurs in the teen years from vasculitis, infections, autoimmune cytopenias, and Epstein-Barr virus-induced lymphoreticular malignancy. (6) IVIg has been shown to increase platelet counts and prevent infections in those patients. (7)

Ataxia telangiectasia occurs because of a genetic defect in ATM (A-T mutated) that normally detects breaks in DNA. This leads to elevated serum alpha-fetoprotein. Patients present with cerebellar ataxia, ocularcutaneous telangiectasias, and immunodeficiency. (8)

Severe combined immunodeficiency (SCID) represents a profound defect of immunity, often with complete absence of lymphocyte function. Clinically, patients present with failure to thrive, chronic sinopulmonary infections, chronic diarrhea, and opportunistic and disseminated sepsis that is life-threatening. A series of genetic mutations have been described in the literature recognizing the heterogeneous molecular biology underlying both X-linked and autosomal recessive inheritance patterns. Bone marrow transplantation is recommended for long-term survival in patients with SCID. (9)
Prophylaxis in the Post-Stem-Cell Transplant Setting

Prevention of infection after bone marrow transplant is a labeled indication for IVIg. The FDA approval was based on data from a randomized but not a placebo-controlled study that compared the outcomes in 369 patients undergoing bone marrow transplant for both malignant and non-malignant disease (i.e., aplastic anemia). (10) In addition, patients underwent a variety of types of stem-cell support, including allogeneic stem-cell support (both HLA identical and non-identical, T-cell depleted or not), autologous, or syngeneic. The majority of patients received HLA-identical allogeneic stem-cell support. In addition to type of stem-cell support, patients were stratified according to transplant type, age, serological status for cytomegalovirus, and protective isolation. The study endpoints were acute graft-versus-host disease (GVHD), infections, interstitial pneumonia, and death. In patients older than age 20 years, IVIg administration was associated with decreased incidence or risk of interstitial pneumonitis, septicemia, or acute GVHD. There was no overall improvement in survival. Since this 1990 study, there has been further discussion of the role of IVIg in the post-stem-cell transplant setting, and there appears to be no consensus about its efficacy. (11,12) Criticisms of this study point out that the statistical significance did not take into account multiple endpoints and subgroup analyses such that some of the reported p values could be due to chance alone. In addition, the study included a heterogeneous group of patients and was not placebo controlled. Moreover, there have been improvements in supportive care, particularly prophylaxis for cytomegalovirus and fungal infection, which may attenuate any effect of IVIg. In addition, studies examining the effect of IVIg on GVHD have reported conflicting data. In 2003, Cordonnier and colleagues reported on the results of a trial that randomized 200 patients undergoing allogeneic stem-cell transplant with HLA-identical donors to receive either placebo or various doses of IVIg from 7 days prior to transplant weekly until 100 days after transplant. (13) Doses ranged from 50 mg/kg to 500 mg/kg. The authors reported that IVIg had no benefit over placebo in terms of infection, interstitial pneumonitis, or GVHD. The results of this study challenge the conclusions of the previous 1990 study, at least for the subgroup with HLA-identical donors.

A meta-analysis published in 2008 by the Cochrane Collaboration evaluated the role of IVIg in patients undergoing hematopoietic stem-cell transplantation and those with lymphoproliferative disorders to determine whether prophylaxis with IVIg reduces mortality or affects other outcomes in patients with hematological malignancies. (14) All RCTs included in the evaluation compared prophylaxis of IVIg with placebo, no treatment or another immunoglobulin preparation; different administration schedules or doses for patients with hematological malignancies were included. Of the 40 trials evaluated, 30 included patients who had hematopoietic stem-cell transplantation, and 10 included patients with lymphoproliferative disorders. The authors concluded that in patients undergoing hematopoietic stem-cell transplantation, routine prophylaxis with IVIg is not supported. Its use may be considered in patients with lymphoproliferative disorders who have hypogammaglobulinemia and recurrent infections to reduce clinically documented infections.

HIV-Infected Patients

One of the FDA-approved indications for IVIg is its use in HIV-infected children. A randomized study published in 1996 reported similar results in adults with HIV infection. For example, patients in the treatment group reported a longer duration of infection-free status, a reduction in the number and duration of hospital admissions, and frequency of diarrhea. (15) Thus, IVIg is considered medically necessary for prevention of infection in both children and adults who are HIV-infected. Clinical evidence indicates that IVIg administered at a dose of 400 mg/kg every 28 days decreases pediatric HIV morbidity when CD4 counts are less than 200 cells/mm². (1,12)
Kawasaki Syndrome and Other Vasculitides

Kawasaki syndrome is an FDA-approved indication for IVIg. 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. Randomized, multicenter studies have shown that high-dose IVIg plus aspirin, given within the first 10 days after the onset of fever, is safe and effective in reducing the prevalence of coronary artery abnormalities. (16) An RCT of single course IVIg (n=17) versus placebo (n=17) in patients with persistent active Wegener’s granulomatosis or microscopic polyangiitis associated with anti-neutrophil cytoplasmic antibody found significantly more responders in the IVIg treatment group at 3 months but no significant differences after 3 months or in the frequency of relapse or use of other medications. (17) Data are inadequate regarding the effectiveness of IVIg in other vasculitides including polyarteritis nodosa and rheumatoid arthritis. (18)

Chronic Inflammatory Demyelinating Neuropathy (CIDP)

CIDP is a labeled indication for IVIg. A double-blind placebo-controlled study comparing IVIg to placebo in patients with progressive or relapsing CIDP reported a significant effect of IVIg in 63% of patients compared to no effect in the placebo group. (19) A randomized single-blinded study comparing IVIg to plasma exchange (PE) reported equivalent beneficial outcomes for both therapies. Open-label treatment of 26 patients with type 2 diabetes and meeting electrophysiologic criteria for CIDP has shown significant improvement in 21, suggesting benefit in diabetic CIDP as well. (20) A possible advantage to IVIg treatment is the ability to administer the drug in the home.

Guillain-Barre Syndrome (GBS)

A meta-analysis by Hughes and colleagues reviewed the results of randomized trials of immunotherapy for GBS. (21) Most trials used a 7-point disability grade scale. In 4 trials with a total of 585 severely affected adult participants, those treated with plasma exchange (PE) improved significantly more on the scale 4 weeks after randomization than those who did not, weighted mean difference (WMD) -0.89 (95% confidence interval [CI]: -1.14 to -0.63). In 5 trials with 582 participants, the improvement on the disability grade scale with intravenous immunoglobulin (IVIg) was very similar to that with PE, WMD -0.02 (95% CI: -0.25 to 0.20). There was also no significant difference between IVIg and PE for any of the other outcome measures. In 1 trial with 148 participants, therapy that included PE followed with IVIg did not produce significant additional benefit. Limited evidence from 3 open trials in children suggested that IVIg hastens recovery compared with supportive care alone. Corticosteroids were compared with placebo or supportive treatment in 6 trials with 587 participants. The significant heterogeneity in the analysis of these trials could be accounted for by analyzing separately 4 small trials of oral corticosteroids, with a total of 120 participants, in which there was significantly less improvement after 4 weeks with corticosteroids than without, WMD was -0.82 (95% CI: -0.17 to -1.47). Two large trials of intravenous methylprednisolone with a total of 467 participants, in which there was no significant difference between corticosteroids and placebo, WMD was -0.17 (95% CI: 0.06 to -0.39). None of the treatments significantly reduced mortality. Approximately 20% of patients die or have persistent disability despite immunotherapy. The authors conclude more research is needed to identify better treatment regimens.

In 2010, the same research team led by Hughes published an updated meta-analysis of randomized trials evaluating IVIg to treat GBS for the Cochrane collaboration. (22) The Cochrane review identified 5 randomized trials comparing IVIg to PE in severely affected participants (mostly adults). A pooled analysis did not find a significant difference between groups in the change in disability level (using a 7-grade disability scale) after 4 weeks. The mean number of grades of change was 0.02 (95% CI: 0.25 to -0.20). There were also no significant differences in other outcome measures. Three studies conducted with children were identified (total n=75). Study findings were not pooled, but,
according to the investigators, findings suggest that IVIg hastens recovery compared to supportive care.

Dermatomyositis is an autoantibody end-complement attack against vascular endothelium. Clinically, patients develop weakness of the muscles and a skin rash. Literature has shown improvement in symptoms in a randomized, double-blind placebo-controlled trial using high-dose IVIg. (23) Treatment with IVIg has the advantage of being corticosteroid- and/or chemotherapy-sparing.

Eaton-Lambert is an autoimmune disease with antibodies directed against the neuromuscular junction. Patients have muscle weakness of the lower extremities, autonomic dysfunction, and extraocular muscle impairment. This is a paraneoplastic syndrome associated with small-cell carcinoma of the lung, most commonly. A number of studies have been cited in the literature improving disability and reducing muscle weakness, substantiating IVIg as beneficial. (24)

**Idiopathic Thrombocytopenic Purpura (ITP)**

In 2007, the National Advisory Committee on Blood and Blood Products and Canadian Blood Services issued guidelines on the use of IVIg for hematologic conditions, including ITP, based on 6 randomized controlled trials (RCTs) and one nonrandomized trial of IVIg for adult ITP. (25) Three of the trials compared IVIg with corticosteroids, and 4 trials evaluated different doses of IVIg. None of the trials compared IVIg with no therapy. The largest trial that compared IVIg with corticosteroids included 122 patients with severe acute ITP. The primary outcome, mean number of days with platelet count greater than 50 x 10^9/L at day 21, was significantly higher in the IVIg group compared with the high-dose methylprednisolone group. Two other trials, one nonrandomized (IVIg versus corticosteroids) and one randomized (IVIg alone versus oral prednisone alone versus IVIg plus oral prednisone) found no difference in platelet counts greater than 50 x 10^9/L at 48 hours or response rate between groups, respectively.

The recommendations from the National Advisory Committee on Blood and Blood Products and Canadian Blood Services for adults with ITP are as follows:

- Adult acute ITP with bleeding: IVIg strongly recommended as a part of multimodality therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.
- Adult acute ITP with severe thrombocytopenia but no bleeding: IVIg not recommended as first-line therapy alone, except for patients with contraindications to corticosteroids.
- Adult ITP with no or slow response to adequate dose corticosteroids: IVIg may be considered as a possible adjunctive therapy.
- Adult chronic ITP postsplenectomy: IVIg may be considered as a possible adjunctive therapy as a corticosteroid-sparing measure.

The 2007 Canadian Committee on Blood and Blood Products guidelines recommends IVIg for select patients with chronic ITP. (25) In particular, patients with a platelet count below 20 x 10^9/L despite treatment with corticosteroids should be considered for IVIg therapy. Also, the use of IVIg may be considered as a corticosteroid-sparing agent in patients who require long-term corticosteroids to maintain adequate platelet counts. For chronic ITP, the minimal dose of IVIg should be used that maintains a safe platelet count. Patients should be re-evaluated every 3 to 6 months, and alternative therapies to IVIg should be considered for patients who do not achieve a durable response for a minimum of 2 to 3 weeks.

**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 IVlg. Case series have shown that maternal IVlg infusions are associated with an increase in the fetal platelet count. A randomized trial compared weekly IVlg with and without associated dexamethasone. (26) Although there was no placebo-controlled arm, results can be compared to the course in a prior affected sibling, since the natural history of the disease suggests that subsequent births should be similarly if not more severely affected with thrombocytopenia. The study reported a mean increase in the platelet count of 69,000/mL. There were no instances of intracranial hemorrhages, although hemorrhage had occurred previously in 10 untreated siblings. Due to improvement found in the case series and RCT, IVlg is considered medically necessary.

Myasthenia Gravis

One RCT (total n=87) (27) and 1 retrospective chart review (total n=54) (28) compare IVlg treatment to plasma exchange in acute myasthenic crisis. Myasthenic crisis was defined as an acute episode of respiratory muscle weakness, defined by a forced vital capacity (FVC) of ≤ 1.0 liter or negative inspiratory force of ≤ 20 cm H20, or requirement of mechanical ventilation. One crossover study compared these therapies in 12 patients with moderate-to-severe disease in a stable phase. (29) Results for all 3 trials show that IVlg and plasma exchange had similar efficacy over time, although improvement may be more rapid with plasma exchange. Case series data support benefit with IVlg treatment in patients with acute exacerbations and with refractory disease or who are unable to tolerate standard treatment. One series of 10 children with refractory disease suggests short-term benefit with IVlg but limited long-term benefit. (30) Refractory myasthenia gravis has been defined as patients with persistent symptoms in spite of immunosuppressive treatment with prednisone and/or azathioprine or those unable to tolerate corticosteroid therapy. A review article explored myasthenia gravis management and concluded that, to determine appropriate pharmacotherapy, characterization of the disease based on degree of function and muscle regions affected was critical for therapy selection. (31) The existing evidence supports the use of IVlg as a treatment option for myasthenia gravis and myasthenic crisis.

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 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, IVlg has been widely used in the prevention and management of AMR, often in conjunction with plasma exchange (see policy No. 8.02.02). For example, in patients at high risk for AMR, IVlg 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. IVlg may be one component of therapy after transplant if AMR develops.

One RCT of 30 patients published in 2001 suggested that IVlg is at least as good as anti-CD3 in combating corticosteroid-resistant rejection of kidney transplants. (32) Later, in 2003-4, findings from the NIH IG02, a double-blind placebo-controlled trial, were published. (33) The trial randomized 101 highly sensitized renal transplant candidates to receive either 4 monthly infusions of IVlg or placebo prior to transplant. If transplanted, additional infusions were given monthly for 4 months. IVlg significantly reduced PRA levels in study subjects compared to placebo, resulting in a higher transplant rate. For example, a total of 24 patients subsequently underwent transplant, 16 in the IVlg group and 8 in the placebo group. There was acceptable graft survival in both groups. Desensitization protocols varied among transplant centers; certain protocols commonly used are
referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consisted of high-dose IVIg (2 g/kg) and was offered to patients awaiting either a deceased or live donor. (34) The Johns Hopkins protocol consisted of low-dose IVIg (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD-20 (i.e., Rituxan). (35)

A retrospective cohort study published in 2009 compared outcomes in pediatric liver transplant patients entered into a multicenter Registry who did (n=336) and did not (n=1,612) receive IVIg within 7 days of transplantation. (36) The investigators assumed that IVIg given within this timeframe was used for prophylaxis of AMR, rather than for treatment. The Kaplan-Meier probability of patient survival was not significantly different between groups (hazard ratio [HR]: 0.97, 95% CI: 0.71-1.39). However, the risk of graft rejection was significantly lower in patients treated with immunoglobulin. In the first 3 months after transplant, 31% of patients who received immunoglobulin and 40% of those not treated had an episode of graft rejection (p=0.02). Similarly, the proportion of patients with 2 or more episodes of graft rejection was significantly lower among those who received immunoglobulin (13.1%) than those who did not (19.2%), p=0.009. Patients were not randomized to treatment group, and there may have been differences in those treated or not treated with immunoglobulin that affected outcomes.

A variety of protocols also have been developed for the treatment of AMR, often in combination with other therapies, such as plasmapheresis or anti-CD-20. (37-40) The majority of studies of IVIg in the transplant setting are retrospective case series from single institutions. Therefore, it is not possible to compare immunomodulatory regimens to determine their relative efficacy. Nevertheless, in part based on the large volume of literature published on this subject, it appears that IVIg is a component of the standard of care for the management of AMR.

In 2010, the National Advisory Committee on Blood and Blood Products and Canadian Blood Services produced a guideline on the use of IVIg for solid organ transplantation; a panel of experts reviewed findings from a systematic review of evidence. (41) In their literature search, they identified 3 RCTs, all on kidney transplant, and numerous observational studies or case series on several types of organ transplantation. Key recommendations of the panel are as follows:

- When kidney transplantation involves use of a living donor, IVIg is recommended to decrease donor-specific sensitization.
- There is insufficient evidence to recommend for or against the use of IVIg for ABO-incompatible kidney transplantation.
- To reduce the risk of acute antibody-mediated rejection, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies.
- IVIg is recommended after plasmapheresis for patients who have received a living donor or deceased kidney donor transplant and who have acute antibody-mediated rejection. Consider IVIg when patients have corticosteroid-resistant rejection, when other therapies are deemed unacceptable or ineffective.
- There is insufficient evidence to recommend for or against the use of IVIg for desensitization for patients undergoing heart, lung, or liver transplantation.

**Multifocal Motor Neuropathy**

Multifocal motor neuropathy (MMN) is diagnosed based on clinical criteria, laboratory criteria including high anti-GMI antibody level and electrodiagnostic criteria e.g., motor conduction block.

A double-blind, placebo-controlled crossover trial of 12 patients with multifocal motor neuropathy and high titters of anti-GM1 antibody reports a significant increase in muscle strength associated with IVIg infusion. The effects were only seen in those patients with an associated conduction block. (42) Subsequent RCTs have reported similar results. (43,44); thus use of IVIg to treat multifocal motor neuropathy is considered medically necessary.
Multiple Sclerosis

Following an updated TEC Assessment in 1998 which concluded that IVIg for multiple sclerosis met the TEC criteria, it was considered medically necessary. (45) However, in 2002 the American Academy of Neurology (AAN) published a technology assessment on therapies for multiple sclerosis. (46) Their rating system was A (established as effective), B (probably effective, ineffective, or harmful), C (possibly effective, ineffective or harmful), or U (data inadequate). The assessment offered the following recommendations regarding IVIg:

1. 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).

2. 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 suggested that IVIg was no longer considered a drug of choice for relapsing-remitting multiple sclerosis, and thus the policy statement was changed to indicate that IVIg is not medically necessary for this type of multiple sclerosis. Due to insufficient data, IVIg for chronic progressive multiple sclerosis is considered investigational. The AAN guideline on treatments for multiple sclerosis was reaffirmed in July 2008. Updated literature searches did not identify any additional randomized trials that would prompt reconsideration of the conclusions of the American Academy of Neurology assessment.

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.

The policy on IVIg as a treatment of recurrent spontaneous abortion (RSA) is based on a 1998 TEC Assessment. (45) This review concluded: 1) The scientific evidence is not sufficient to support the conclusion that IVIg reduces spontaneous abortion in women with antiphospholipid antibodies who have a history of recurrent spontaneous abortion; and 2) The scientific evidence is not sufficient to support the conclusion that IVIg therapy is superior to no treatment in women without antiphospholipid antibodies who have a history of recurrent spontaneous abortion. The assessment cited 4 randomized, blinded, controlled trials of IVIg focusing on this patient population. Only 1 of these trials showed a significant treatment effect. The treatment effect of the 4 trials was summarized by meta-analysis; the overall relative risk and odds ratio values and their confidence intervals indicate no significant treatment effect.

Two subsequent meta-analyses of 5 trials and 6 trials, respectively, concluded that IVIg provides no significant beneficial effect over placebo in preventing further miscarriages. (47,48) A blinded RCT of
41 women treated with IVIg or saline placebo found no differences in live birth rates. (49) A multicenter RCT comparing heparin and low-dose aspirin with versus without IVIg in women with lupus anticoagulant, antiphospholipid antibody, or both, found no significant differences. (50) In addition, an RCT of 58 women with at least 4 unexplained miscarriages tested IVIg versus placebo and analyzed results by intention to treat. (51) The live birth rate was the same for both groups; also, there was no difference in neonatal data. Other non-randomized but controlled trials also report no benefit for IVIg treatment. There is insufficient evidence in RCTs or other trials to support benefit in secondary (live birth followed by consecutive spontaneous abortions) versus primary (no prior live births) spontaneous abortions. A variety of immunologic tests may precede the initiation of IVIg therapy. These tests, including various subsets of lymphocytes, human leukocyte antigen (HLA) testing, and lymphocyte functional testing (i.e., natural killer cell assays and the embryo cytotoxicity test), are research tools that explore subtle immunologic disorders that may contribute to maternal immunologic tolerance of the fetus. However no clinical data show that the results of these tests can be used in the management of patients to reduce the incidence of recurrent spontaneous abortion, particularly since IVIg therapy has not been shown to be an effective therapy.

**Asthma**

Two RCTs of IVIg therapy in patients with corticosteroid-dependent asthma found no significant decrease in corticosteroid use compared to placebo. (52,53) A subgroup analysis in one trial indicated a significant effect of IVIg on corticosteroid consumption in patients requiring corticosteroid doses greater than 2 g per year; however, this subgroup analysis was not stated as planned in advance and involved only 17 of 38 total patients. Thus, IVIg for asthma is considered investigational.

**Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections**

The National Advisory Committee on Blood and Blood Products and Canadian Blood Services convened a panel of national experts to develop an evidence-based practice guideline on the use of IVIg for neurologic conditions; findings were published in 2007. (54) Recommendations for use of IVIg were made for 14 conditions, including pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The Panel emphasized that this syndrome is not well-understood and diagnosis of PANDAS requires expert consultation. The optimum dose and duration of treatment is uncertain. The evidence review examining IVIg for PANDAS identified 1 RCT of 29 children who had new or severe exacerbations of obsessive-compulsive disorder (OCD) or tic disorder after streptococcal infections randomly assigned to IVIg plasma exchange or placebo. At 1-month follow-up, IVIg and plasma exchange had no significant differences and showed significant improvement in obsessive-compulsive symptoms. The improvement in symptoms was evident at 1-year follow-up. (55) Given that there is only 1 small study, there are insufficient data to support the use of IVIg for PANDAS.

**Autism**

The Canadian guideline on neurologic conditions, cited above, did not recommend IVIg for autism. (54) The evidence review examining IVIg for autism identified 3 case series. In 1 of the case series, 10 patients with abnormal immune parameters received IVIg monthly. After 6 months, 5 of 10 subjects showed marked improvement in several autistic characteristics. In the second case series, 1 of 10 subjects showed improvement in autistic symptoms after receiving IVIg. No improvement was observed in the third series. Given there are no randomized comparative trials evaluating IVIg in autism, a relatively common condition, data are insufficient to support the use of IVIg for autism.
Autoimmune Mucocutaneous Blistering Diseases (AMBDs)

Nonrandomized trials and a recent meta-analysis (56-58) showed that IVIg therapy for specific patients prevented the progression of disease and showed significant clinical benefit. The study identified critical parameters that define severity of illness, and then the conventional immunosuppressive therapy (CIST) group was compared to IVIg treatment to determine efficacy. The goal was to reduce systemic corticosteroid dose and duration and improve quality of life. This study showed that IVIg produced a favorable clinical response such as halting progression of disease and new mucocutaneous sites in the treatment of pemphigus and pemphigoid. The article suggests that IVIg be considered with the following criteria:

- Patients who are non-responsive to either high dose systemic corticosteroids and/or multiple immunosuppressive agents;
- Patients unable to tolerate due to effects of the drugs or the disease severity culminating in poor quality of life.

IVIg can be used as an adjunctive agent to taper or discontinue use of corticosteroids and/or immunosuppressive treatments. In effect, IVIg served as a corticosteroid-sparing agent. An important conclusion of this meta-analysis is that mucocutaneous blistering diseases carry with them high morbidity and mortality such that RCTs using large cohorts of patients are unsuitable for further study and may be considered unethical and morally challenging. Therefore the evidence to date has shown that IVIg is efficacious using the best available evidence in the treatment of AMBDs. (58)

Fisher Syndrome

In 2007, a Cochrane Collaboration systematic review was published on acute immunomodulatory therapies in Fisher syndrome or its variants. (59) Fisher syndrome is one of the regional variants of Guillain-Barré syndrome, characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). Intravenous immunoglobulin (IVIg) and plasma exchange are often used as treatments in this patient group. No RCTs were identified; the authors concluded that, due to the lack of controlled studies, there is insufficient evidence on which to base practice.

Refractory Dermatomyositis (DM)

An RCT comparing IVIg plus prednisone to placebo in 15 patients with refractory dermatomyositis reported significant increases in muscle strength, as measured by mean scores on the neuromuscular symptom scale (NSS) and the modified MRC scale, in the IVIg group. At 3 months IVIg versus placebo; mean modified MRC: IVIg, 84.6±4.6 versus placebo, 78.6±8.2, Mean NSS: IVIg 51.4±6.0 versus placebo, 45.7±11. (60) Repeated transfusions every 6 to 8 weeks may be required to maintain a benefit. In 2 case series of 18 and 19 patients, respectively, a significant number of patients (67%) had reduction in corticosteroid use or were otherwise considered responders. (61, 62) In a nonrandomized comparison of prednisone plus cyclosporine A, with or without IVIg, patients (12 with DM, 8 with polymyositis [PM]) given IVIg had a higher probability of remission. In a double-blind, placebo-controlled crossover trial in 15 patients with refractory DM with IVIg, 5 patients had improvement in muscle strength and histopathology, and additional patients had improvement in their rash. The authors noted that IVIg is not recommended as monotherapy but in combination with other immunosuppressive therapies for patients who have not adequately responded to other immunosuppressive agents. According to the Canadian guidelines, IVIg is appropriate in selected patients with resistant dermatomyositis disease, but there is insufficient evidence supporting primary or long-term treatment. (54)

Complex Regional Pain Syndrome

A double-blind RCT was published in 2010; the study was conducted at an academic pain management center in the U.K. (63) To be eligible, patients needed to be diagnosed with stable
complex regional pain syndrome (CRPS) of 6 to 30 months’ duration; patients were also eligible if their disease had a longer duration and had spread to a previously uninvolved limb within the past 30 months. Patients needed to have tried standard medical treatment and, despite other treatments, to report a pain intensity of 5 or higher on an 11-point scale (0-10 with 10=worst pain imaginable) for each of 7 days they completed a diary. Patients received an infusion of IVIg and saline (2 doses each) in random order, with a 28-day washout period between treatments. The primary outcome was 24-hour pain using the scale described above on days 6 to 19 after each treatment. A total of 13 patients were randomized; data on pain after IVIg were missing for 1 patient. According to the article’s Appendix Table 3, the median daily pain intensity score for each 14-day period was 6.21 after IVIg infusion and 7.35 after saline infusion, a mean difference of 1.14 points. In the text of the article, the authors report that the mean pain intensity was 1.55 points lower after IVIg than after saline (95% CI: 1.29 to 1.82, p<0.001). This is a short-term RCT with a small number of patients and findings need to be confirmed in larger trials with longer follow-up. Moreover, the optimum dose and treatment regimen are unknown.

Alzheimer’s disease (AD)

Several small studies have been published, most recently an open-label randomized study with 8 patients by Relkin and colleagues. (64) The goal of the trial was to evaluate the safety of repeated injections of IVIg in Alzheimer’s disease patients and examine change in the level of antibodies against beta-amyloid; it was not powered to detect changes in cognition. Eligibility criteria included a diagnosis of probably Alzheimer’s disease, ability to give informed consent and comply with the study protocol, assistance from a suitable caregiver and on a stable dose of an approved AD medication for at least 3 months. After an initial test dose of 0.4 g/kg of IVG, patients were randomly assigned to 6 months of treatment with one of 4 doses (0.4 g/kg per 2 weeks, 0.4 g/kg per week, 1 g/kg per 2 weeks, and 2 g/kg per 4 weeks). This was followed by a 3-month washout period and an additional treatment period in which all patients received 1 g/kg every 2 weeks for months 10-12 and 0.4 g/kg every 2 weeks for months 13-18. All patients completed the study; only 7 patients underwent sampling at the 9-month follow-up. Cerebrospinal fluid antibodies against beta-amyloid decreased significantly after 6 months of treatment, returned to baseline levels at the end of the 3-month washout and remained stable during the second treatment period. No serious adverse events occurred, and all mild symptoms resolved spontaneously and without sequelae. Although not a primary outcome, the authors reported patients’ scores on the Mini-Mental State Examination (MMSE). At baseline, the mean score was 23.5 (maximum possible score is 30). The mean score increased to 26.0 after 6 months of treatment, decreased to 23.9 at the end of the washout period, and was 24.0 after an additional 9 months of treatment. The authors conclude that further studies with larger samples are needed to determine efficacy, safety, and the optimal dosing regimen in Alzheimer’s disease patients.

Additional studies conducted by the Relkin research team are underway. In a Phase II study initiated in 2006, the researchers aim to recruit 24 patients with mild to moderate Alzheimer Disease patients. (65) The study involves random assignment to IVlg or placebo for 6 months, and then all patients have the option of an additional 6 months of IVlg treatment. The primary outcome is change in cognitive ability. A Phase III study was initiated in 2009. (66) In this study (target sample size not reported), patients will be randomly assigned to receive IVlg or placebo for 70 weeks. The primary outcome is change in cognition and global function after 9 months; a secondary outcome is cognitive change after 18 months. As of April 2010, the Phase II study is ongoing but not recruiting participants, and the Phase III study is recruiting participants. Due to the lack of published randomized trials with sufficiently large sample sizes to evaluate safety and efficacy, IVlg is considered investigational for treatment of Alzheimer’s disease.

Demyelinating Neuropathy Associated with Paraproteinemia or Paraneoplastic Syndromes

Results of a double-blind, placebo-controlled, crossover randomized study of IVlg versus placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients. (67) A subsequent randomized study of 22 patients focused on the short-term outcomes at 2 weeks. (68) No significant difference was found between the treatment and
placebo groups. Data are inadequate on the use of IVIg in paraneoplastic syndromes, such as Eaton-Lambert disease.

**Polymyositis (PM) and Refractory Polymyositis**
A case series of IVIg in patients with refractory PM showed significant clinical improvement in more than two thirds of patients. (69) However, comparative trials are lacking to validate the effectiveness of IVIg in patients with polymyositis. An RCT of IVIg for polymyositis has not been published, but a prospective study of IVIg in patients with refractory PM showed improvement in 25 of 35 patients and a 50% reduction of prednisone dose. With the lack of controlled trials, there is insufficient evidence to support the use of IVIg in polymyositis.

**Inclusion Body Myositis**
Dalakas and colleagues have reported on a double-blind, placebo-controlled crossover study comparing IVIg to placebo in 19 patients with inclusion body myositis. (70) There was no statistically significant improvement in overall muscle strength in the IVIg group compared to the control placebo group. Two more recent RCTs (combined n=58) also found no significant functional improvement when IVIg treatment was compared to placebo. (71, 72) Due to the lack of benefit found in RCTs, use of IVIg for inclusion body myositis is considered investigational.

**Chronic Fatigue Syndrome**
Vollmer-Conna and colleagues reported no therapeutic benefit of IVIg in 99 patients with chronic fatigue syndrome randomized to receive either IVIg or placebo. (73) Due to the limited data and the lack of benefit in one RCT, this indication for IVIg is investigational.

**Post-Infectious Sequelae**
RCTs of IVIg administered as postoperative prophylaxis in patients anergic to common recall antigens (n=40) (74) and trauma patients (n=39) (75) indicated significantly fewer infections in treated patients. Each of these trials addressed a different patient population, and the evidence is insufficient for conclusions. IVIg given as prophylaxis in patients with rheumatic fever did not appear to change cardiac outcomes (n=59). (76)

**Dilated Cardiomyopathy**
Sixty-two patients with recent-onset dilated cardiomyopathy were randomized to IVIg or placebo. (77) There was no significant difference in left ventricular ejection fraction between IVIg and placebo treatment arms. Due to the limited data and the lack of benefit in one RCT, this indication for IVIg is investigational.

**Systemic Lupus Erythematosus**
IVIg is proposed for the treatment of systemic lupus erythematosus because of its immunomodulatory properties and also to prevent infection in patients who are taking immunosuppressive drugs. Although this is a relatively prevalent autoimmune disease, only several small case series (78, 79) and 1 small RCT comparing IVIg to cyclophosphamide (80) have been published. These studies suggest some benefit; IVIg may be a good alternative to cyclophosphamide. However, results are inconsistent and short-lived in some cases, and RCTs are needed for confirmation. Thus, IVIg for systemic lupus erythematosus is considered investigational.

**Stiff Person Syndrome**
Dalakas et al. randomized 16 patients with disease and anti-BAD65 autoantibodies to IVIg or placebo for 3 months. (81) After a 1-month washout period, patients were crossed over to 3 months of the alternate treatment. Stiffness scores decreased significantly on IVIg, but not on placebo, regardless of order. Eleven patients were able to walk more easily or without assistance; the frequency of falls decreased; and patients were able to perform work-related or household tasks. The duration of benefit lasted 6 weeks to 1 year without additional treatment. Thus, results suggest benefit, but no other comparative trials or series data with at least 10 patients are available for confirmation.
Non-Infectious Uveitis

Two small series of 18 and 10 patients, respectively, report measurable improvement in visual acuity after IVlg therapy. (82, 83) These 2 studies represent insufficient data to draw conclusions about efficacy; therefore, IVlg for non-infectious uveitis is considered investigational.

Demyelinating Optic Neuritis

Noseworthy et al. conducted a double-blind RCT of 55 patients randomized to IVlg or placebo. The trial was terminated due to negative results. (84) Due to the findings of this study, and lack of other comparative trials, IVlg for demyelinating optic neuritis is considered investigational.

Other conditions

Outcome data are inadequate to validate the use of IVlg in other conditions including, but not limited to conditions listed in the Policy as investigational and not otherwise discussed in the Rationale.

Subcutaneous Immune Globulin (SClg) Therapy

SClg replacement therapy for primary immunodeficiency (PID) has been available outside the United States for decades and was cleared for use in the United States in 2006. Clinical data on the first SClg product (Vivaglobin) available in the U.S. were published the same year as the FDA approval. (85). An open-label, nonrandomized, prospective, multicenter study reported outcomes of SClg replacement therapy in adults and children (older than 2 years with bodyweight 10 kg or more) with common variable immune deficiency (CVID) or X-linked agammaglobulinemia (XLA) that had been treated with IVlg for at least 4 months. A total of 65 patients (mean age: 34 +/- 15 years, range: 2 to older than 65 years, 57% male) were enrolled. Most (78%) had CVID, 22% had XLA. The study included 3 phases: baseline (3–4 weeks), wash-in/wash-out (12 weeks), and efficacy (52 weeks). During the baseline period, each patient received usual IVlg treatment, during and after which vital signs were collected, baseline biochemical and viral tests were performed, and serum IgG trough levels were measured. One week following the last IVlg dose, once-weekly SClg therapy was administered for at least 3 months (wash-in/out phase), using a dose equivalent to 137% of the IVlg dose. The 12-month efficacy phase began after the wash-in/out phase, using a mean weekly dose of 158 mg/kg (range, 155–165 mg/kg). The mean pre-infusion IgG level increased from 7.9 g/L at baseline to 10.4 g/L during SClg treatment, representing a 39% increase. Trough levels remained relatively stable throughout the study. During the efficacy phase, 2 serious bacterial infections (pneumonias) were reported in 2 patients, resulting in an annual rate of 0.04 episodes per patient-year (upper 99% confidence limit: 0.14). Thirty-two patients (63%) missed a total of 192 days of school or work due to infections during the efficacy phase, resulting in an overall rate of 3.7 days per patient-year. Four patients were hospitalized due to infection (including the 2 with pneumonia), for a total of 12 days or 0.23 hospital days per patient-year. Of a total of 3,656 infusions, 2,584 treatment-emergent adverse events were reported (0.71 per infusion), with 1,901 considered to be treatment-related (0.52 per infusion). The most frequent type of adverse event, infusion-site reaction, was observed at least once in 60 cases (91%); the vast majority (96%) were of mild or moderate intensity and short duration (1 or 2 days). Importantly, the incidence of infusion-related adverse events declined by 50% over time, from 85% after the first infusion session to 41% after the 33rd session, after which the rate remained relatively stable. Three subjects withdrew from treatment due to infusion-site reactions. No deaths or notable changes in hematologic or other laboratory parameters were noted, nor were any virus-related safety issues reported.
A parallel study by Gardulf and colleagues of the same product (Vivaglobin) in Europe and Brazil among 60 patients (16 children, 44 adults, age range, 2–75 years) with a diagnosis of PID produced almost identical annualized rates of mild-to-moderate overall infections and serious bacterial infections (0.04 episodes per patient). (86) However, Gardulf used an SCIg dose equivalent to 100% of the previous IVIg dose, compared to 137% in the North American study. The rates, intensity, and types of adverse events in the Gardulf report were similar to the North American study and also showed a similar decline in incidence with subsequent infusions. Among children in the Gardulf study, serum IgG trough levels increased from a mean 7.8 g/L to a mean 9.2 g/L during the efficacy phase; adult levels rose from a mean 8.6 g/L to 8.9 g/L. Six of the children and 10 adults missed days from school (range, 1–9 days) or work (range, 1–36 days). No deaths or notable changes in hematologic or other laboratory parameters were noted, nor were any virus-related safety issues reported.

The results for the Vivaglobin SCIg replacement therapy were nearly identical (0.04 serious bacterial infections per patient-year) to those attained in a randomized, 2-year duration, crossover study conducted in Europe in the mid-1990s. (87) However, the pharmacokinetics of IVIg and SCIg are quite different. Thus, IVIg infusion results in very high peak serum concentrations that fall quickly as the Ig is distributed into the extravascular space. (88) In contrast, weekly SCIg administration results in smoother, more consistent serum IgG concentrations with greater stability in levels between infusions, due to a reservoir effect of SCIg in the subcutaneous tissues.

The clinical implications of the pharmacokinetic differences between IVIg and SCIg are not clear. However, it is plausible that they could be beneficial in terms of fewer systemic adverse effects and reduction in break-through infections secondary to rapid falls in serum Ig levels. (89) Furthermore, evidence is available to show that PID patients who switch from IVIg replacement therapy delivered in the hospital or other outpatient site to home-based SCIg self-infusions perceive their health-related quality of life as significantly improved. (90-92) Thus, taken together, the similar clinical efficacy of SCIg replacement therapy versus IVIg, in the context of more favorable pharmacokinetic parameters and a simpler delivery method for chronic therapy, suggests SCIg treatment may be considered medically necessary in lieu of IVIg to prevent recurrent infections in patients with PID who require lifelong immunoglobulin replacement therapy. A 2008 review article concluded that SCIg therapy may be advantageous for selected populations of patients with primary antibody deficiency, including pregnant women, children, and patients with poor intravenous access. (93) Given that there are no RCTs for these patient types and conditions, there is insufficient evidence to support these uses of SCIg.

**Practice Guidelines and Position Statements**

The National Advisory Committee on Blood and Blood Products and Canadian Blood Services has issued practice guidelines on the use of IVIg in several of the diseases discussed within the Rationale section of this policy. The recommendations were based on interpretation of available evidence and where evidence was lacking, consensus of expert clinical opinion. A select number of these recommendations are outlined under the individual diseases in the Rationale section; guidelines for treatment recommendations for additional diseases addressed in this policy can be found in the published guidelines of the National Advisory Committee on Blood and Blood Products and Canadian Blood Services. (5, 25)

**Medicare National Coverage**

In 2002, the Centers for Medicare and Medicaid Services (CMS) published a National Coverage Determination on IVIg for treatment of autoimmune mucocutaneous blistering diseases. (94) IVIg is covered for patients with biopsy-proven disease who failed conventional therapy or for whom conventional therapy is contraindicated, and to supplement conventional therapy in patients with rapidly progressive disease.
No National Coverage Determinations on other uses of intravenous or subcutaneous immune globulin were identified.

References:

42. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Intravenous immune globulin for multiple sclerosis. TEC Assessments 1998; Volume 13, Tab 19.


### Billing Coding/Physician Documentation Information

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<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour (new code number 1/1/09 - previously 90765)</td>
</tr>
<tr>
<td></td>
<td>96366</td>
<td>each additional hour (List separately in addition to code for primary procedure) (new code number 1/1/09 - previously 90766)</td>
</tr>
<tr>
<td></td>
<td>96369</td>
<td>Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump set-up and establishment of</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>96370</td>
<td>each additional hour (List separately in addition to code for primary procedure) (new code number 1/1/09 - previously 90770)</td>
<td></td>
</tr>
<tr>
<td>96371</td>
<td>additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure) (new code number 1/1/09 - previously 90771)</td>
<td></td>
</tr>
</tbody>
</table>

**ICD-9 Procedure**

- 99.29  | Injection or infusion of other therapeutic or prophylactic substance                                                                                                                                     |

**ICD-9 Diagnosis**

- 040.82 | Toxic shock syndrome                                                                                                                                                                                  |
- 041.00 - 041.9 | Bacterial infection, code range                                                                                                                   |
- 042     | Human immunodeficiency virus (HIV) disease                                                                                                                                            |
- 204.10 – 204.11 | Chronic lymphoid leukemia, code range                                                                                                       |
- 279.00  | Hypogammaglobulinemia, unspecified                                                                                                                                                                 |
- 279.04 – 279.05 | Immunodeficiency (X-linked), code range                                                                                                        |
- 279.06  | Common variable immunodeficiency                                                                                                           |
- 279.12  | Wiskott-Aldrich syndrome                                                                                                                                                                           |
- 279.2   | Combined immunity deficiency                                                                                                               |
- 279.3   | Unspecified immunity deficiency                                                                                                            |
- 283.0   | Autoimmune hemolytic anemias (includes warm antibody autoimmune hemolytic anemia)                                                            |
- 287.3   | Primary thrombocytopenia                                                                                                                   |
- 287.5   | Thrombocytopenia, unspecified                                                                                                               |
- 289.81  | Primary hypercoaguable state (includes anti-phospholipid syndrome)                                                                          |
- 340     | Multiple sclerosis                                                                                                                          |
- 354.0 – 355.9 | Mononeuritis, code range                                                                                                                   |
- 356.4 – 356.9 | Idiopathic peripheral neuropathy, code range                                                                                                  |
- 357.0   | Acute infective polyneuritis (includes Guillain-Barre syndrome)                                                                             |
- 358.01  | Myasthenia gravis with (acute) exacerbation (includes myasthenia gravis in crisis)                                                        |
- 358.1   | Myasthenic syndromes in diseases classified elsewhere (includes Eaton-Lambert syndrome from stated cause classified elsewhere)           |

**HCPCS**

- 90283  | Immune globulin (IgIV), human, for intravenous use                                                                                           |
- 90284  | Immune globulin (SCIg), human, for use in subcutaneous infusions, 100mg, each                                                             |
- J1459  | Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500mg                                                   |
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1556</td>
<td>Injection, immune globulin (Bivigam), 500 mg</td>
</tr>
<tr>
<td>J1557</td>
<td>Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1559</td>
<td>Injection, immune globulin (Hizentra), 100 mg (new code 1/1/11)</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1562</td>
<td>Injection, immune globulin (Vivaglobin), 100 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin (Octagam) intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin (Gammagard liquid) intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), 500mg</td>
</tr>
<tr>
<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>A48.3</td>
<td>Toxic shock syndrome</td>
</tr>
<tr>
<td>B20</td>
<td>HIV</td>
</tr>
<tr>
<td>B95.0-B95.8</td>
<td>Streptococcus, staphylococcus and enterococcus as the cause of diseases classified elsewhere code range</td>
</tr>
<tr>
<td>C91.10-C91.12</td>
<td>Chronic lymphocytic leukemia of b-cell type</td>
</tr>
<tr>
<td>D59.1</td>
<td>Other autoimmune hemolytic anemias (includes warm type)</td>
</tr>
<tr>
<td>D68.61</td>
<td>Anticardiolipin syndrome (includes antiphospholipid syndrome)</td>
</tr>
<tr>
<td>D80.0-D80.9</td>
<td>Immunodeficiency with predominantly antibody defects</td>
</tr>
<tr>
<td>D83.0-D83.9</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>D69.6</td>
<td>Thrombocytopenia, unspecified</td>
</tr>
<tr>
<td>G35</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>G60.0-G60.9</td>
<td>Hereditary and idiopathic neuropathy</td>
</tr>
<tr>
<td>G61.0</td>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>G70.01</td>
<td>Myasthenia gravis with (acute) exacerbation</td>
</tr>
<tr>
<td>G73.3</td>
<td>Myasthenic syndromes in other diseases classified elsewhere</td>
</tr>
<tr>
<td>I44.0-I45.9</td>
<td>Other conduction disorders</td>
</tr>
<tr>
<td>L10.0-L10.9</td>
<td>Pemphigus code range</td>
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<td>Code Range</td>
<td>Description</td>
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<tr>
<td>----------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>L12.0-L12.9</td>
<td>Pemphigoid code range</td>
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<tr>
<td>L51.3</td>
<td>Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome</td>
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<tr>
<td>M30.3</td>
<td>Mucocutaneous lymph node syndrome</td>
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<tr>
<td>M33.90-M33.99</td>
<td>Dermatopolymyositis unspecified</td>
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<tr>
<td>P61.0</td>
<td>Transient neonatal thrombocytopenia</td>
</tr>
<tr>
<td>Z94.81</td>
<td>Bone marrow transplant status</td>
</tr>
</tbody>
</table>

ICD-10-PCS (effective 10/1/13)

ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for this procedure.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3E013GC</td>
<td>Administration, introduction, subcutaneous tissue, percutaneous, other therapeutic substance</td>
</tr>
<tr>
<td>3E033GC</td>
<td>Administration, introduction, peripheral vein, percutaneous other therapeutic substance</td>
</tr>
<tr>
<td>3E033WK, 3E033WL</td>
<td>Administration, introduction, peripheral vein, immunotherapeutic, code by qualifier (immunostimulator or immunosuppressive)</td>
</tr>
</tbody>
</table>

**Type of Service**  Therapy  
**Place of Service**  Physician Office

**Additional Policy Key Words**
Immune Globulin, Intravenous Therapy, Intravenous Immune Globulin Therapy, IVIg

**Related Topics**
N/A

**Policy Implementation/Update Information**
- 06/1996  New policy titled Intravenous Immune Globulin Therapy
- 06/1999  Reviewed – no changes made.
- 06/2000  Reviewed – no changes made.
- 06/2001  Reviewed – no changes made.
- 06/2002  Reviewed – no changes made.
- 06/2003  Reviewed – no changes made.
- 06/2004  Policy updated to reflect BCBSA policy 8.01.05
- 06/2005  Policy updated to reflect BCBSA policy 8.01.05
- 06/2006  Reviewed – no changes made.
- 06/2007  Policy updated to reflect BCBSA policy 8.01.05
Appendix

Appendix A:

Diagnostic Criteria for Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The following criteria are adapted from the Task Force Report of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. (Neurology 1991; 41(5):617-8) The report included mandatory, supportive, and exclusionary diagnostic criteria. Only the mandatory criteria are excerpted here. The criteria are based on a combination of clinical observations, physiologic studies, pathologic features (i.e., nerve biopsy), and studies of the cerebrospinal fluid (CSF).

I. Clinical

Mandatory

1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than 1 limb or a peripheral nerve nature, developing over at least 2 months.
2. Hypo- or areflexia. This will usually involve all 4 limbs.

II. Physiologic Studies

Mandatory

Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination.

Must have 3 of 4:

1. Reduction in conduction velocity (CV) in 2 or more motor nerves:
   a. <80% of lower limit of normal (LLN) is amplitude >80% of LLN
   b. <70% of LLN is amplitude <80% of LLN
2. Partial conduction block or abnormal temporal dispersion in 1 or more motor nerves: either peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow.

Criteria suggestive of partial conduction block: <15% change in duration between proximal and distal sites and >20% drop in negative peak (p) area or peak to peak (p-p) amplitude between proximal and distal sites.

Criteria for abnormal temporal dispersion and possible conduction block: >15% change in duration between proximal and distal sites and >20% drop in p area or p-p amplitude between proximal and distal sites and >20% drop in p or p-p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block as they are derived from studies of normal individuals. Additional studies, such as stimulation across short segments or recording of individual motor unit potentials, are required for confirmation.

3. Prolonged distal latencies in 2 or more nerves:
   a. >125% of upper limit of normal (LEN) is amplitude >80% of LLN
   b. >150% of LEN if amplitude <80% of LLN.

4. Absent F waves or prolonged minimum
   a. >120% of ULN if amplitude >80% of LLN
   b. >150% of ULN if amplitude <80% of LLN.

III. Pathologic Features

Mandatory
Nerve biopsy showing unequivocal evidence of demyelination and remyelination.
Demyelination by either electron microscopy (>5 fibers) or teased fiber studies >12% of 50 fibers, minimum of 4 internodes each, demonstrating demyelination/remyelination.

IV. CSF Studies

Mandatory

1. Cell count <10 per cubic mm if HIV-seronegative or <50 per cubic mm is HIV seropositive
2. Negative VDRL

The following criteria are adapted from the Joint Task Force of the EFNS and the PNS. 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. J Peripher Nerv Syst. 2005;10:220-228. The EFNS/PNS diagnostic criteria were designed to balance specificity and sensitivity.

I. Inclusion Criteria

1. Typical CIDP - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities
2. Atypical CIDP

One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):

- Predominantly distal weakness (distal acquired demyelinating symmetric, DADS)
- Pure motor or sensory presentations, including chronic sensory immune polyradiculoneuropathy affecting the central process of the primary sensory neuron
- Asymmetric presentations (multifocal acquired demyelinating sensory and motor, MADSAM, Lewis-Sumner syndrome
- Focal presentations (e.g., involvement of the brachial plexus or of one or more peripheral nerves in one upper limb
- Central nervous system involvement (may occur with otherwise typical or other forms of atypical CIDP)

II. Exclusion Criteria

- Diphtheria, drug or toxin exposure likely to have caused the neuropathy
- Hereditary demyelinating neuropathy, known or likely because of family history, foot deformity, mutilation of hands or feet, retinitis pigmentosa, ichthyosis, liability to pressure palsy
- Presence of sphincter disturbance
- Multifocal motor neuropathy
- Antibodies to myelin-associated glycoprotein

III. Electrodiagnostic Criteria

1. Definite
   At least one of the following:
   - At least 50% prolongation of motor distal latency above the upper limit of normal values in two nerves, or
   - At least 30% reduction of motor conduction velocity below the lower limit of normal values in two nerves, or
   - At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves (>50% if amplitude of distal negative peak CMAP, 80% of lower limit of normal values), or
   - Absence of F-waves in two nerves if these nerves have amplitudes of distal negative peak CMAPs at least 20% of lower limit of normal values + at least one other demyelinating parameter* in at least one other nerve, or
   - Partial motor conduction block: at least 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve, or
   - Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in at least two nerves, or
   - Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) of at least 9 ms in at least one nerve + at least one other demyelinating parameter* in at least one other nerve

2. Probable
   At least 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve

3. Possible
   As in (1) but in only one nerve

CMAP, compound muscle action potential. 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. Temperatures should be maintained at least 33° C at the palm and 30° C at the external malleolus (good practice points).
* Any nerve meeting any of the criteria

IV. Supportive Criteria
Elevated cerebrospinal fluid protein with leukocyte <10/mm3 (level A recommendation)
Magnetic resonance imaging showing gadolinium enhancement and/or hypertrophy of the cauda equine, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexus (level C recommendation)
Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination in >5 fibers by electron microscopy or in >6 of 50 teased fibers
Clinical improvement following immunomodulatory treatment (level A recommendation)

Appendix B:
Diagnostic Criteria for Diagnosis of Multifocal Motor Neuropathy (MMN)
The following are proposed diagnostic criteria adapted from a 2005 article by Van Asseldonk and colleagues (Lancet Neurology; 4: 309-319)

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 titre
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 0.5 mV


**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