Immune Globulin Therapy

Policy Number: 8.01.05               Last Review: 6/2017

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for immune globulin replacement therapy when the following criteria are met.

When Policy Topic is covered

Please refer to Drug Infusion Site of Care Policy 5.02.538 for approved site of service.

Drug must be sourced from an approved specialty infusion provider

Intravenous immunoglobulin (IVIg) therapy may be considered medically necessary for the following indications.

- **Immunodeficiency States**—patients with Primary Immunodeficiencies, including
  - Congenital agammaglobulinemia
  - Hypogammaglobulinemia
  - Common variable immunodeficiency
  - Severe combined immunodeficiency (SCID)
  - Wiskott-Aldrich syndrome
  - X-linked agammaglobulinemia (Bruton agammaglobulinemia)
  - X-linked hyper-IgM 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 Considerations section)
  - Documented inability to mount an adequate immunologic response to inciting antigens (see Considerations section)
  - Persistent and severe infections, despite treatment with prophylactic antibiotics

Patients undergoing/undergone hematopoetic cell transplantation who have immunoglobulin G (IgG) levels less than 400 mg/dl.

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

- **Infections**
  - Patients with chronic lymphocytic leukemia who have IgG levels less than 400mg/dl and persistent bacterial infections.
  - Patients (children) with HIV who have IgG levels less than 400mg/dl to prevent opportunistic infections.
  - Patients with severe anemia associated with human parvovirus B19.
  - Patients with toxic shock syndrome.
• **Autoimmune and Inflammatory Conditions**
  o Patients with severe, progressive autoimmune mucocutaneous blistering diseases that include pemphigus, pemphigoid, pemphigus vulgaris, pemphigus foliaceus who have failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide.
  o Patients with acute, severe idiopathic thrombocytopenic purpura (see Considerations section) or chronic idiopathic thrombocytopenic purpura with at least 6 months of disease duration, presence of symptoms and with persistent thrombocytopenia (platelet <20,000 per microliter [adult] or 30,000 per microliter [child]), despite treatment with corticosteroids and splenectomy.
  o Adult patients with Guillain-Barre syndrome as an equivalent alternative to plasma exchange.
  o Patients with Kawasaki syndrome.
  o Patients with Wegener granulomatosis.
  o Patients with chronic inflammatory demyelinating polyneuropathy with progressive symptoms for at least 2 months.
  o Patients with multifocal motor neuropathy.
  o Patients with Eaton-Lambert myasthenic syndrome who have failed to respond to anticholinesterase medications and/or corticosteroids.
  o Patients with neuromyelitis optica as an alternative for patients with contraindication or lack of response to steroids or plasma exchange particularly in children.
  o Patients with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
  o Patients with myasthenic exacerbation (ie, an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated.
  o Patients with dermatomyositis or polymyositis that is refractory to treatment with corticosteroids; in combination with other immunosuppressive agents.
  o Patients with warm antibody hemolytic anemia who are refractory to prednisone and splenectomy.
  o Patients with antiphospholipid syndrome.

• **Alloimmune Processes**
  o Patients with neonatal alloimmune thrombocytopenia.
  o Patients with hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis).

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

• **Miscellaneous**
  o Patients with stiff person syndrome not controlled by other therapies.

Subcutaneous immune globulin therapy (SCIg) may be considered medically necessary for the following indications:

• Patients with primary immunodeficiencies, including:
  o congenital agammaglobulinemia
  o hypogammaglobulinemia
  o common variable immunodeficiency
  o severe combined immunodeficiency
  o Wiskott-Aldrich syndrome
  o X-linked agammaglobulinemia
When Policy Topic is not covered

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

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

- Patients who have received solid organ transplant for prophylaxis or treatment of acute antibody mediated rejection.
- Patients with neonatal sepsis (prophylaxis or treatment)
- Patients (adults) with sepsis.
- Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis
- Patients with inclusion body myositis
- Patients with systemic lupus erythematosus
- Patients with immune optic neuritis
- Patients with Crohn disease
- Patients with hemophagocytic lymphohistiocytosis
- Patients with recurrent spontaneous abortion.
- Patients with pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections
- Patients with autism spectrum disorder
- Patients with complex regional pain syndrome
- Patients with Alzheimer disease
- Patients with paraproteinemic neuropathy
- Patients with chronic fatigue syndrome
- Patients with acute myocarditis
- Patients with refractory recurrent pericarditis
- Patients with noninfectious uveitis
- Patients with postpolio syndrome
- Patients with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, paraneoplastic syndromes, epilepsy, chronic sinusitis, asthma, aplastic anemia, Diamond-Blackfan anemia, red cell aplasia, acquired factor VIII inhibitors, acute lymphoblastic leukemia, multiple myeloma, immune-mediated neutropenia, nonimmune thrombocytopenia, cystic fibrosis, recurrent otitis media, diabetes mellitus, Behçet syndrome, adrenoleukodystrophy, organ transplant rejection, Fisher syndrome, IGG subclass deficiency, opsoclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy), refractory rheumatoid arthritis, other vasculitides besides Kawasaki disease, including polyarteritis nodosa, Goodpasture syndrome, and vasculitis associated with other connective tissue diseases.

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

**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
- J1460: Injection, gamma globulin (GamaSTAN S/D), intramuscular, 1 cc
- J1556: Injection, immune globulin (Bivigam), 500 mg
- J1557: Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
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 products have been approved by FDA. These include Carimune® (ZLB Bioplasma), Flebogamma® (Grifols), Gammagard® (Baxter), Gamunex-C® (Grifols), Octagam® (Octapharma), Polygam® S/D (Baxter) Privigen® (CSL Behring LLC) and BIVIGAM™ (Biotest Pharmaceuticals).

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® (Grifols), 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 through April 20, 2015. 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. influenza* 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 the 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.
- Immunologic disorders of the T cell present with clinically, more severe disease that often lead to mortality in infancy or childhood. It is essential to diagnose these conditions early by screening for lymphopenia in cord blood at birth.

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, oculocutaneous 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 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) A 2013 Cochrane review identified 1 RCT on IVIg for Wegener granulomatosis. (17) This trial, published by Jayne et al, compared a single course IVIg (n=17) with placebo (n=17) and 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. (18) Data are inadequate regarding the effectiveness of IVIg in other vasculitides including polyarteritis nodosa and rheumatoid arthritis. (19)

**Chronic Inflammatory Demyelinating Neuropathy (CIDP)**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a labeled indication for IVIg. In 2013,
Eftimov et al published a Cochrane systematic review of RCTs on IVIg for treating CIDP. The authors identified 8 RCTs that enrolled patients with definite or probable CIDP and that compared IVIg with placebo, corticosteroid, or plasma exchange. Three of the trials compared IVIg with another active treatment and the other 5 were placebo-controlled. The primary study outcome was proportion of participants with a significant improvement in disability within 6 weeks of starting treatment. Studies used a variety of disability measures. When possible, the Cochrane authors transformed the data on disability to a modified 6-point Rankin disability scale. Data from the 5 placebo-controlled RCTs were pooled. The pooled risk ratio (RR) for improvement in the IVIg group compared with placebo was 2.40 (95% confidence interval [CI], 1.72 to 3.36; p<0.001). When data were pooled from 3 studies on IVIg versus placebo in which the disability measures could be converted to the Rankin scale, the RR was similar at 2.40 but did not quite reach statistical significance (95% CI, 0.98 to 5.83; p=0.054). Pooled analyses of data from these 3 placebo-controlled studies found a statistically higher rate of any side effect with IVIG, but not serious side effects. Data from studies comparing IVIg with an active treatment were not pooled due to differences in the comparator. Limitations of the meta-analysis include that a variety of different disability scales and definitions of clinical response were used.

The most recently published RCT was a 2012 multicenter double-blind study that assigned patients with CIDP to IVIg (n=22) or IV methylprednisolone (n=24). One patient dropped out of the IVIg group; the remaining patients were included in the analysis. The primary study outcome was the proportion of patients who discontinued therapy due to inefficacy or intolerance during the 6 months of therapy. A total of 3 (13%) of patients in the IVIg group and 11 (52%) of patients in the corticosteroid group discontinued treatment over 6 months. The difference between groups was statistically significant favoring the IVIg group (RR=0.54; 95% CI, 0.34 to 0.87). Secondary outcomes, including quality-of-life, time on 10-meter walk, grip strength, etc., did not differ significantly between groups, but the study may have been underpowered to detect clinically significant differences on these outcomes.

A 2012 evidence-based guideline on IVIg for treating neuromuscular disorders, prepared by a subcommittee of the American Academy of Neurology (AAN) stated that IVIg should be offered for the long-term treatment of CIDP.

Evidence from multiple RCTs and a meta-analysis of RCTs has found that IVIg is effective for treating CIDP. Thus, IVIg for treating CIDP may be considered medically necessary.

Guillain-Barre Syndrome (GBS)

A Cochrane review Hughes et al, updated in 2012, reviewed the results of randomized trials of immunotherapy for Guillain-Barré syndrome (GBS). The review identified 12 randomized trials; none of these were placebo-controlled. Seven trials compared IVIg with plasma exchange (PE), 3 trials compared IVIg with supportive treatment only, and 2 trials compared PE and 2 compared IVIg with immunoabsorption (1 of these compared the combination of IVIg and immunoabsorption with immunoabsorption only). Four trials included adults only, 5 included children only, 1 included both and 2 included adults and possibly children. The primary outcome of the review was between-group change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIg with PE did not find a significant difference between groups in change in the number of disability grades at 4 weeks (mean difference [MD], -0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIg versus PE, eg, number of patients improved by 1 or more grades. There were insufficient data to pool results for comparisons of IVIg with other types of alternative interventions or for a subgroup analysis by age. Most of the trials had small sample sizes. The largest trial was multicenter and randomized 383 adults older than 16 years of age to IVIg, PE, or the combination of IVIg and PE. The objectives of the trial were to establish that IVIg is equivalent to or superior to PE and to establish that PE followed by IVIg is superior to a single treatment. Noninferiority was defined as no more than a 0.5-grade difference in change in disability grade at 4 weeks. At 4 weeks, the difference in improvement between the IVIg group and PE group was 0.09 grade (CI, -0.23 to 0.42); this meets the predefined criteria for equivalence of these treatments. The difference between the IVIg plus PE group and the IVIg only group was 0.29 grade (95% CI, -0.04 to
0.63) and between the IVIg plus PE group and PE only was 0.20 grade (95% CI, -0.14 to 0.54). Thus, neither of the combined treatment groups was superior to either treatment only.

The 2012 AAN guideline, first cited earlier, concluded that IVIg should be offered to adults with GBS but that there is insufficient evidence to support or refute the use of IVIg in children.(22)

Based on the findings of the large RCT and the Cochrane review, IVIg appears to have similar efficacy to PE.

Multifocal Motor Neuropathy
Multifocal motor neuropathy is diagnosed based on clinical criteria, laboratory criteria including high anti-GMI antibody level, and electrodiagnostic criteria eg, motor conduction block.

A double-blind, placebo-controlled crossover trial of 12 patients with multifocal motor neuropathy and high titers 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.(25) Subsequent RCTs have reported similar results.(26,27)

The 2012 AAN guideline stated that IVIg should be considered for the treatment of multifocal motor neuropathy but that there are insufficient data to determine the optimal treatment interval, dosing and duration.(22)

Eaton-Lambert Myasthenic Syndrome
Eaton-Lambert is an autoimmune disease with antibodies directed against the neuromuscular junction. Patients have muscle weakness of the lower extremities, autonomic dysfunction, and extra-ocular 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.(28) The 2012 AAN guideline stated that IVIG is possibly effective and may be considered as a treatment for patients with Eaton-Lambert syndrome.(22)

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 idiopathic thrombocytopenic purpura (ITP), based on 6 RCTs and 1 nonrandomized trial of IVIg for adult ITP.(29) 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 50 109/L at day 21, was significantly higher in the IVIg group compared with the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIg versus corticosteroids) and 1 randomized (IVIg alone versus oral prednisone alone versus IVIg plus oral prednisone) found no difference in platelet counts greater than 50 109/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 firstline 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.\(^{29}\) In particular, patients with a platelet count below 20 \(10^9/L\), 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 IVIg. Case series have shown that maternal IVIg infusions are associated with an increase in the fetal platelet count. A randomized trial compared weekly IVIg with and without associated dexamethasone.\(^{30}\) 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, IVIg is considered medically necessary.

**Myasthenia Gravis**
In 2012, a Cochrane systematic review was published on IVIg for myasthenia gravis (MG).\(^{31}\) The review identified 7 RCTs. The trials varied in their inclusion criteria, comparison interventions and outcome measures and thus study findings were not pooled. Five trials evaluated IVIg for treating MG worsening or exacerbation and 2 evaluated IVIG for treatment of stable IVIg. Several of the trials were small, with insufficient statistical power. This review concluded that there was some evidence for efficacy in exacerbations of MG, and that the evidence for treatment of chronic MG was insufficient to form conclusions on efficacy. A representative trial was published by Gajdos et al and compared IVIg with PE in 87 patients with an MG exacerbation.\(^{32}\) The study did not find a statistically significant difference in the efficacy of the 2 treatments, but found that IVIg was better tolerated. Nine patients experienced adverse events, 8 in the PE group and 1 in the IVIg group. Case series data support use of IVIg treatment in patients with acute exacerbations and with refractory disease and in patients who are unable to tolerate standard treatment.\(^{33}\) Overall, the existing evidence supports the use of IVIg as a treatment option for MG.

**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, IVIg 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, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AMR develops.

One RCT of 30 patients published in 2001 suggested that IVIg is at least as good as anti-CD3 in combating corticosteroid-resistant rejection of kidney transplants. (34) Later, in 2003-4, findings from the NIH IG02, a double-blind placebo-controlled trial, were published. (35) The trial randomized 101 highly sensitized renal transplant candidates to receive either 4 monthly infusions of IVIg or placebo prior to transplant. If transplanted, additional infusions were given monthly for 4 months. IVIg 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 IVIg 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). (37)

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. (34, 39-41) 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. (42) 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.
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. (43) However, in 2002 the American Academy of Neurology (AAN) published a technology assessment on therapies for multiple sclerosis. (44) 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:

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

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

In contrast, the American Academy of Neurology recommended the use of interferon beta (Type B recommendation) and glatiramer acetate (Type A recommendation). This assessment 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.

A 2006 Cochrane systematic review of various immunotherapies for treating recurrent miscarriage concluded that IVIg provides no significant beneficial effect over placebo in preventing further miscarriages. (45) A blinded RCT of 41 women treated with IVIg or saline placebo found no differences in live birth rates. (46) A multicenter RCT comparing heparin and low-dose aspirin with versus without IVIg in women with lupus anticoagulant, anticardiolipin antibody, or both, found no significant differences. (47) In addition, an RCT of 58 women with at least 4 unexplained miscarriages tested IVIg versus placebo and analyzed results by intention to treat. (48) The live birth rate was the same for both groups; also, there was no difference in neonatal data. Other nonrandomized 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 (ie, 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 because IVIg therapy has not been shown to be an effective therapy.

Asthma
Two RCTs of IVlg therapy in patients with corticosteroid-dependent asthma found no significant decrease in corticosteroid use compared to placebo. (49,50) A subgroup analysis in one trial indicated a significant effect of IVlg 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, IVlg 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 IVlg for neurologic conditions; findings were published in 2007. (51) Recommendations for use of IVlg 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 IVlg 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 IVlg plasma exchange or placebo. At 1-month follow-up, IVlg 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 IVlg for PANDAS.

**Autism**

The Canadian guideline on neurologic conditions, cited above, did not recommend IVlg for autism. (51) The evidence review examining IVlg for autism identified 3 case series. In 1 of the case series, 10 patients with abnormal immune parameters received IVlg 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 IVlg. No improvement was observed in the third series. Given there are no randomized comparative trials evaluating IVlg in autism, a relatively common condition, data are insufficient to support the use of IVlg for autism.

**Autoimmune Mucocutaneous Blistering Diseases (AMBDs)**

Nonrandomized trials and a recent meta-analysis (53-55) showed that IVlg 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 IVlg treatment to determine efficacy. The goal was to reduce systemic corticosteroid dose and duration and improve quality of life. This study showed that IVlg 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 IVlg 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.

A 2012 systematic review by Huang et al focused on IVlg for treating toxic epidermal necrosis (TEN). (56) The authors identified 17 studies with a total of 221 with TEN treated with IVlg; 5 studies were retrospective, nonrandomized controlled studies, and the remaining 11 studies were case series. Twelve out of the 17 studies supported use of IVlg. Overall, the mean time from initiation of IVlg to response was 2.4 days, and the mean time from initiation of IVlg to remission was 10.9 days. The mean length of hospital stay was 17.4 days, and the mortality rate was 19.9%.

In summary, the literature available to date has shown that IVlg can be efficacious in the treatment of AMBDs and can be a corticosteroid-sparing agent.

**Fisher Syndrome**

In 2007, a Cochrane Collaboration systematic review was published on acute immunomodulatory therapies in Fisher syndrome or its variants. (57) 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 (IVlg) 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)**

Dermatomyositis is an autoantibody end-complement attack against vascular endothelium. Clinically, patients develop weakness of the muscles and a skin rash. In 2012, Wang et al published a systematic review of the literature on IVIg for treating adults with dermatomyositis/polymyositis. The authors identified 14 studies including 2 RCTs, 9 prospective case series and 3 retrospective case series. Eleven out of 14 included patients with refractory disease. Both RCTs found a benefit of IVIg treatment. For example, a trial by Dalakas et al compared prednisone plus IVIg with prednisone plus placebo in 15 patients with refractory dermatomyositis. There were significant increases in muscle strength in the IVIg group, as measured by mean scores on the neuromuscular symptom scale (NSS) and the modified Medical Research Council (MRC) scale. 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. Repeated transfusions every 6 to 8 weeks may be required to maintain a benefit. An additional RCT was published in 2012 by Miyasaka et al in Japan. The study included 26 patients with corticosteroid-resistant polymyositis/dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month. Patients were randomly assigned to treatment with IVIg (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary end point was the difference in mean manual muscle test (MMT) scores between baseline and 8 weeks. Change in mean MMT was 11.8 points in the IVIg group and 9.9 points in the placebo group. There was not a statistically significant between-group difference: 1.9 points (95% CI, -4.8 to 8.5). Other outcomes were also not significantly different between groups.

The 2012 AAN guideline on IVIg for treating neuromuscular disorders stated that IVIG may be considered as a treatment of nonresponsive dermatomyositis in adults.

Most but not all of the published studies on refractory dermatomyositis found a benefit of IVIg, and national guidelines support use of this therapy. Treatment with IVIg has the advantage of being corticosteroid- and/or chemotherapy-sparing.

**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. 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)**

To date, published studies have focused on the safety of administering IVIg to patients with Alzheimer disease. Some cognitive outcomes have been reported as secondary outcomes but these have not been the focus of study. In 2013, Dodel et al published an industry-sponsored double-blind placebo-controlled dose-finding trial that included 58 patients with mild-to-moderate Alzheimer disease. Patients were assigned to 1 of 8 groups. Injections of 0.2 g/kg, 0.5 g/kg, 0.8 g/kg, or placebo IVIg every 4 weeks, or half of this dose (or placebo) every 2 weeks for 24 weeks. There were 5 to 7 patients in each group. Fifty-five patients (95%) were included in the primary analysis. The median area under the
curve of plasma betaamyloid, the primary outcome, did not differ significantly from placebo for 5 of the 6 intervention groups. In the sixth group, those who received 0.4 g/kg every 2 weeks, the difference in the median of plasma betaamyloid was significantly different from placebo (p=0.02).

Twenty-five of 42 (60%) of patients in an intervention group and 9 of 14 (64%) in the placebo groups had an adverse event. Serious adverse events (not necessarily related to treatment) occurred in 4 (10%) of patients in the intervention group and 4 (29%) in the placebo group. Serious adverse events in the IVI group included postsurgery delirium (n=1), stroke (n=1), nausea and vomiting (n=1), and progressively severe Alzheimer disease (n=1). In the placebo group, serious adverse events were knee replacement surgery (n=1), gastric antral vascular ectasia (n=1), acute aggression (n=1), and possible seizure (n=1).

As secondary outcomes, the authors reported several cognitive outcomes at 12 and 24 weeks including scores on the Mini-Mental State Examination (MMSE), the Alzheimer’s Disease Cooperative Study activities of daily living scale and the Alzheimer’s disease assessment scale, cognitive subscale score. Scores on these outcomes did not differ significantly between any of the IVIg groups and placebo. When data from the IVIg groups were pooled, there was a significantly higher clinical dementia rating-sum of boxes at week 24 in the IVIg groups than the placebo group (p=0.02). No other statistically significant differences were found between pooled IVIg groups and the placebo groups.

Previously, in 2009, Relkin et al published an open-label randomized study with 8 patients who had probable Alzheimer disease. After an initial test dose of 0.4 g/kg of IVG, patients were randomly assigned to 6 months of treatment with 1 of 4 doses (0.4 g/kg per 2 weeks, 0.4 g/kg per week, 1 g/kg per 2 weeks, 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 to 12 and 0.4 g/kg every 2 weeks for months 13 to 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 wash-out and remained stable during the second treatment period. No serious adverse events occurred, and all mild symptoms resolved spontaneously and without sequelae. The authors reported patients’ scores on the MMSE as a secondary outcome. 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.

**Demyelinating Neuropathy Associated with Paraproteinemia or Paraneoplastic Syndromes**

Results of a double-blind, placebo-controlled, crossover randomized study of IVIg versus placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients. A subsequent randomized study of 22 patients focused on the short-term outcomes at 2 weeks. 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. 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. 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. 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. (70) 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) (71) and trauma patients (n=39) (72) 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). (73)

Dilated Cardiomyopathy

Sixty-two patients with recent-onset dilated cardiomyopathy were randomized to IVIg or placebo. (74) 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 (75,76) and 1 small RCT comparing IVIg to cyclophosphamide (77) 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. (78) 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 IVIg therapy. (79,80) These 2 studies represent insufficient data to draw conclusions about efficacy; therefore, IVIg for non-infectious uveitis is considered investigational.

Demyelinating Optic Neuritis

Noseworthy et al. conducted a double-blind RCT of 55 patients randomized to IVIg or placebo. The trial was terminated due to negative results. (81) Due to the findings of this study, and lack of other comparative trials, IVIg for demyelinating optic neuritis is considered investigational.

Prevention of Neonatal Sepsis

A 2013 Cochrane review addressed IVIg for the prevention of infection in preterm and/or low-birth weight infants. (82) The investigators identified 19 RCTs in which IVIg was compared with a placebo or no intervention for preterm (<37 week’s gestational age) and/or low birth weight (<2500 g) infants. The trials included a total of about 5000 infants. Five of the 19 studies were considered to be high-quality and the remaining studies had potential biases eg, lack of caregiver blinding in 10 studies.

In a pooled analysis of the findings of 10 studies, IVIg was associated with a statistically significant reduction in sepsis (1 or more episodes) (RR=0.85; 95% CI, 0.74 to 0.98). Moreover, a pooled analysis of 16 studies, IVIg was associated with a significant reduction in serious infection (≥1 episodes) (RR=0.82; 95% CI, 0.74 to 0.92). However, IVIg was not associated with a significant reduction in mortality. A pooled analysis of 15 studies reporting all-cause mortality found an RR of 0.89 (95% CI, 0.75 to 1.05), and a pooled analysis of 10 studies reporting mortality due to infection found an RR of 0.83 (95% CI, 0.56 to 1.22). No major adverse effects related to IVIg administration were reported in any of the studies.
Treatment of Neonatal Sepsis
Two systematic reviews of RCTs on IVIg for treatment of neonatal sepsis were identified. A 2013 Cochrane review identified 8 trials comparing IVIg with placebo or no intervention.(83) Studies included a total of 3871 infants; the largest study had a sample size of 3493 and contributed 90% of the data. A pooled analysis of data from the 8 trials found no statistically significant difference in the mortality rate with IVIg versus control (RR=0.94; 95% CI, 0.80 to 1.12). A pooled analysis of 3 trials found the IVIg reduced hospital stay significantly more than a control intervention (mean difference, -4.08; 95% CI, -6.47 to -1.69). Results were not pooled for other outcomes. A 2012 systematic review by Franco et al had similar findings.(84)

The study with the large sample size was published by the International Neonatal Immunotherapy Study group in 2011; it was a multicenter study and was conducted in 9 countries.(85) Infants receiving antibiotics for suspected or confirmed serious infection were randomly assigned to receive 2 infusions of IVIg at a dose of 500 mg per kg of body weight (n=1759) or a matching volume of placebo (n=1734). Infusions were given 48 hours apart. The primary study outcome was the rate of death or major disability (defined according to predefined criteria) at age 2 years. By age 2, 686 of 1759 (39.0%) children in the IVIg group had died or had major disability compared with 677 of 1734 (39.0%) of children in the placebo group (RR=1.00; 95% CI, 0.92 to 1.08). There were also no statistically significant differences in the primary outcome when prespecified subgroups eg, birthweight, gestational age at birth, gender, etc. were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIg group (including 2 deaths) and 10 in the placebo group (including 4 deaths).

Data from multiple RCTs including a large multinational trial, and meta-analyses of RCTs have not found a significant benefit of IVIg on outcomes in infants with neonatal sepsis.

Crohn Disease

A 2012 systematic review of IVIg for treating Crohn disease did not identify any randomized or nonrandomized controlled trials.(86) There were 5 published case reports of IVIg used for single patients with Crohn disease, and the remaining articles identified by the authors were conference papers, abstracts-only, or a nonsystematic review. Thus, there is insufficient evidence of effectiveness, and IVIg is considered investigational for treating Crohn disease.

Severe Anemia Associated with Parvovirus B19

No controlled trials have evaluated IVIg for severe anemia associated with parvovirus B19. Only case reports and small case series are available.(87-89) One of the larger case series, published in 2013 by Crabol et al, retrospectively reported on 10 patients with documented human parvovirus B19 and pure red cell aplasia.(90) Following a mean of 2.7 courses of IVIg treatment, hemoglobin level was corrected in 9 of 10 patients. Four patients had adverse effects associated with IVIG, 2 cases of acute reversible renal failure and 2 cases of pulmonary edema. In the same article, Crabol et al reported on findings of a literature search in which they identified a total of 123 cases of pure red cell aplasia treated with IVIg (other than the 10 patients in their series). Among the 86 of 123 (70%) patients available at a 12-month follow-up, hemoglobin was corrected in 36 patients (42%) and the remaining 50 patients (58%) had persistent anemia. Based on case series data and supportive clinical input from hematologists (see section on Clinical Input next), IVIg may be considered medically necessary for patients with severe anemia due to parvovirus B19.

Hemophagocytic syndrome

Hemophagocytic lymphohistiocytosis is an uncommon but potentially fatal disease of overactive histiocytes and lymphocytes that and may be familial or acquired. The published literature is limited to
small case series on the use of IVIg in hemophagocytic syndrome. (91-93) A 2012 systematic review on diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics identified a total of 156 cases; a portion of these patients were treated with IVIg. (94) A total of 156 published cases of hemophagocytic syndrome were identified. Steroids were the most common treatment. IVIG was used in 30% of children and 4% of adults. Hemophagocytic syndrome-related mortality occurred in 32% of children and 28% of adults. Due to the limited data and lack of controlled studies, IVIg is considered investigational for treatment of hemophagocytic syndrome.

Other conditions
Outcome data are inadequate to validate the use of IVIg 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 (SCIg) Therapy
SCIg 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 SCIg product (Vivaglobin) available in the U.S. were published the same year as the FDA approval. (95) An open-label, nonrandomized, prospective, multicenter study reported outcomes of SCIg 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 IVIg 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 IVIg 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 IVIg dose, once-weekly SCIg therapy was administered for at least 3 months (wash-in/out phase), using a dose equivalent to 137% of the IVIg 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 SCIg 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). (96) 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. In 2013, Lingman-Framme and Fasth published a systematic review of the literature on SCIg compared with IVIg for treatment of primary and secondary immunodeficiencies. (97) The authors identified 20 studies; 2 were RCTs and 19 of the studies included patients with primary immunodeficiencies. The
primary outcome of interest was the number of serious bacterial infections, defined as bacterial pneumonia, meningitis, osteomyelitis, septicemia, and peritonitis. Only 3 studies reported on serious bacterial infections during both SCiG and IVIg administration, and no serious bacterial infections identified. Five studies reported the annual number of infections (bacterial and/or viral) and no significant difference was found in the infection rate associated with SCiG and IVIg. Four studies compared health related quality of life in patients who changed the route of administration from IV to subcutaneous. All 4 of these studies found that patients reported a better quality of life with home-based SCiG compared with hospital-based IVIg. Moreover, all 11 studies that reported IgG trough levels found higher levels with SCiG compared with IVIg.

Thus, taken together, the similar clinical efficacy of SCiG replacement therapy versus IVIg, in the context of a simpler delivery method for chronic therapy and some evidence of improved quality of life, suggests SCiG treatment may be considered medically necessary in lieu of IVIg to prevent recurrent infections in patients with primary immunodeficiency who require lifelong immunoglobulin replacement therapy.

**CIDP**

CIDP is not a labeled indication for SCiG. No RCTs comparing SCiG with IVIg were identified; there was 1 RCT comparing SCiG with placebo. This study, published in 2013 by Markvardsen et al in Denmark, included 30 patients with CIDP with motor involvement who were on maintenance therapy with IVIg.(98) Patients were randomized to SCiG at a dose comparable with their prestudy IVIg dose or to placebo (subcutaneous saline), 2 to 3 times a week for 12 weeks. If patients experienced unacceptable deterioration, they were treated with rescue IVIg. The primary study outcome was change in muscle strength evaluated by isokinetic dynamometry. At the end of the 12 weeks, there was an increase in isokinetic muscle strength in the SCiG group and a decrease in the placebo group; the difference between groups was statistically significant (p<0.01). Secondary outcomes also favored the SCiG group. For example, the mean score on the Overall Disability Sum Score (which ranges from 0, no signs of disability to 12, most severe disability) increased 0.4 points (SD=0.7) in the SCiG group and decreased 0.7 points (SD=1.5) in the placebo group (p=0.04). Six patients in the SCiG group and 2 in the placebo group reported mild adverse events localized to the injection site. No serious adverse events were reported, and no patient appeared to need rescue IVIg therapy.

With only 1 small trial comparing SCiG with placebo following IVIg for CIDP, SCiG for treatment of CIDP is considered investigational.

**Practice Guidelines and Position Statements**

The National Advisory Committee on Blood and Blood Products and Canadian Blood Services 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.(5,29)

In 2013, a updated joint guideline on prevention and treatment of opportunistic infections among HIVexposed and HIV-infected children was published.(99) The guideline was endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and other agencies/societies and included the following statement:

“Intravenous (IV) immune globulin is recommended to prevent serious bacterial infections in HIVinfected children who have hypogammaglobulinemia.”

In 2012, the American Academy of Neurology published an evidence-based guideline on IVIg for treating neuromuscular disorders.(22)
References:
11. Kozlowski T, Andreoni K. Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time? Ann Transplant. Apr-Jun 2011;16(2):19-25. PMID 21716181


**Billing Coding/Physician Documentation Information**

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Common variable immunodeficiency
Cerebellar ataxia with defective DNA repair (includes ataxia telangiectasia)
Stiff-man syndrome
Multiple sclerosis
Hereditary and idiopathic neuropathy
Guillain-Barre syndrome
Chronic inflammatory demyelinating polyneuritis
Multifocal motor neuropathy
Myasthenia gravis with (acute) exacerbation
Myasthenic syndromes in other diseases classified elsewhere
Other conduction disorders
Pemphigus code range
Pemphigoid code range
Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
Mucocutaneous lymph node syndrome
Wegener's granulomatosis
Polymyositis code range
Dermatopolymyositis unspecified
Disorders of newborn related to short gestation and low birth weight, not elsewhere classified code range
Bacterial sepsis of newborn, code range
Transient neonatal thrombocytopenia
Bone marrow transplant status
ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for this procedure.
Administration, introduction, subcutaneous tissue, percutaneous, other therapeutic substance
Administration, introduction, peripheral vein, percutaneous other therapeutic substance
Administration, introduction, peripheral vein, immunotherapeutic, code by qualifier (immunostimulator or immunosuppressive)
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.
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.
   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