Title: Intravenous and Subcutaneous Immune Globulin Therapy

PRE-DETERMINATION of services is required.

Predetermination Request Form:

BCBSKS will review all prior authorization requests.

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

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

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

IVIg is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. 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-Barré 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. A genetic basis for more than 80 different types of primary immunodeficiencies has been discovered, the most common being primary antibody deficiency that is associated with low levels or total lack of normal circulating immunoglobulins. The first FDA-approved SCIg product, Vivaglobin®, is a pasteurized, polyvalent human normal immune globulin product that is manufactured from large pools of human plasma by cold alcohol fractionation with no chemical or enzymatic alterations. Vivaglobin administration produces relatively stable steady-state serum levels of IgG that are representative of those seen in a normal human population. Applications of this product for conditions other than primary immunodeficiencies are considered off-label in the United States and are not addressed in this policy. In recent years, other SCIg products have also received FDA-marketing approval.
Regulatory Status
Several IVIg have been approved by the FDA. These include Carimune® (ZLB Bioplasma), Flebogamma® (Grifols), Gammagard® (Baxter), Gamunex-C® (Grifols), Octagam® (Octapharma), Polygam® S/D (Baxter), Privigen® (CSL Behring LLC), and BIIVIGAM™ (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).

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

POLICY
A. Intramuscular immune globulin is not medically necessary for the indications listed in this policy.

B. Immune Globulin therapy may be medically necessary in the following conditions when the associated criteria are met:

1. **Primary Humoral Immunodeficiencies** (to include X-linked agammaglobulinemia [Bruton] X-linked hyper-IgM syndrome, severe combined immunodeficiency [SCID], Wiskott-Aldrich syndrome, and ataxia telangiectasia) with a history of significant recurrent infections and one of the following:
   a. A very low level of IgG (e.g., 200 mg per dl or less). Assessing vaccine response is not necessary; or
   b. Nonprotective levels of antibodies to pneumococcal vaccine serotypes documented with a 14-serotype panel. If antibodies are at nonprotective levels, a pneumococcal vaccine challenge is required.

   For a pneumococcal vaccine challenge, a 14-serotype panel should be done prior to the vaccine and repeated no earlier than one month after vaccination.

   The interpretation of response to pneumococcal vaccine is as follows:
   - in children 2 to 5 years of age, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 50% of the serotypes tested
   - in children > 5 years of age and in adults, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 70% of the serotypes tested

   Immunoglobulin replacement should be reserved for patients who have failed the following treatments:
   - immunization with conjugate vaccines.
• aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures).
• prophylactic antibiotics such as amoxicillin-clavulanate or cefdinir.
• increased vigilance and appropriate antibiotic therapy for infections.

Note: SCIg, instead of IVIg may be considered medically necessary for the treatment of primary immunodeficiencies when policy requirements are met.

2. **Acute Disseminated Encephalomyelitis** when response to intravenous corticosteroid treatment is insufficient.

3. **Antiphospholipid Syndrome**

4. **Autoimmune Hemolytic Anemia**, refractory to corticosteroids or splenectomy.

5. **Autoimmune Mucocutaneous Blistering Diseases** (includes pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [a.k.a. cicatricial pemphigoid], and epidermolysis bullosa acquisita) when corticosteroids, and immuno-suppressive agents have failed.

6. **Birdshot (vitiliginous) Retinochoroidopathy** not responsive to immunosuppressives (e.g., corticosteroids, cyclosporine).

7. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) Variant**

8. **Chronic Lymphocytic Leukemia (CLL) in Patients with Hypogammaglobulinemia:**
   a. Recurrent or persistent bacterial infections;
   b. Evidence of specific antibody deficiency to pneumococcal vaccine serotypes.

9. **Dermatomyositis, Polymyositis (includes Juvenile)** intolerant or refractory to:
   a. Corticosteroids; and/or
   b. Immuno-suppressants (e.g., methotrexate, azathioprine, cyclophosphamide, and cyclosporine).

10. **Enteroviral Meningoencephalitis**

11. **Fetal Alloimmune Thrombocytopenia (FAIT) or previous pregnancy affected by FAIT**

12. **Guillain-Barré Syndrome (GBS)** (includes GBS variants: Miller-Fisher syndrome [MFS], panautonomic polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropahty (AMSAN)). IVIg should usually be initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms.

13. **Hematopoietic Stem Cell Transplant (HSCT) or Bone Marrow Transplant (BMT)**
a. For prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIg is indicated for treatment of recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL) or who have CMV or RSV infection; or
b. IVIg is considered medically necessary for steroid-resistant graft-versus-host disease in BMT recipients 20 years of age or older, in the first 100 days post transplant, and who are hypogammaglobinemic (IgG level less than 400 mg/dL).

14. **HIV Infected Children** - who meet the following criteria:
   a. Serum IgG concentration less than 250 mg/dL;
   b. Recurrent serious bacterial infections;
   c. Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine;
   d. Single dose for HIV-infected children who are exposed to measles;
   e. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.

15. **HIV Associated Polyneuropathy**

16. **HIV Associated Thrombocytopenia**

17. **Hemolytic Disease of the Newborn**

18. **Hyperimmunoglobulin E Syndrome** with recurrent staphylococcal abscesses.

19. **Idiopathic Thrombocytopenic Purpura (ITP)**
   a. Unresponsive to corticosteroid therapy; or
   b. To defer or avoid splenectomy; or
   c. Platelet counts less than 20,000 u/l (risk of intracerebral hemorrhage); or
   d. Management of acute bleeding with platelet counts less than 30,000 u/l; or
   e. To increase platelet counts, prior to major surgical procedures.

20. **Immune Thrombocytopenic Purpura (ITP) in Pregnancy**

21. **Immunosuppressed Patients** associated immunosuppression (IgG < 400 mg/dL) with one of the following:
   a. Solid organ transplants or extensive surgery with immunosuppression; or
   b. Hematological malignancy; or
   c. Extensive burns; or
   d. Collagen-vascular disease.

22. **Kawasaki disease**

23. **Lambert-Eaton Myasthenic Syndrome (LEMS)** and inadequate response to anticholinesterases and dianinopyridine)

24. **Myasthenia gravis** when other treatments have been unsuccessful or are contraindicated (e.g., azathioprine, cyclosporine, cyclophosphamide, and myasthenic crisis).
25. **Moersch-Woltmann (Stiff-man) Syndrome** (positive Anti-GAD antibody) when benzodiazepines (e.g., Valium) and/or baclofen, phenytoin, clonidine, tizanidine have failed.

26. **Multifocal Motor Neuropathy with Conduction Block**-diagnosed on the basis of electrophysiologic findings.

27. **Multiple Myeloma (MM)**
   a. IgG level < 600mg/dL; and
   b. Recurrent significant infections in last year; or
   c. Evidence of specific antibody deficiency such as those to pneumococcal vaccine serotypes.

28. **Neonatal Hemochromatosis**

29. **Neuroblastoma Associated Paraneoplastic Opsoclonus-Myoclonus-Ataxia Syndrome**

30. **Refractory Opsoclonus-Myoclonus**

31. **Erythrovirus (formerly Parvovirus) B19 Infection, chronic, with severe anemia**

32. **Post-Transfusion Purpura (PTP)**

33. **Rasmussen Encephalitis** refractory to antiepileptic drugs and corticosteroids.

34. **Staphylococcal Toxic Shock Syndrome**

35. **Systemic Lupus Erythematosus** such as severe active SLE for whom first- and second-line therapies have been unsuccessful (non-steroidal anti-inflammatory drugs, corticosteroids, antimalarial compounds, methotrexate, azathioprine, or cyclophosphamide).

36. **Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome**

37. **Toxic Shock Syndrome or Toxic Necrotizing Fasciitis due to Group A Streptococcus**

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


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

D. Other application of IVIg therapy are considered **experimental / investigational**, including, but not limited to, the following conditions:
1. chronic progressive multiple sclerosis;
2. refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus;
3. recurrent spontaneous abortion (see below for related laboratory tests);
4. inclusion-body myositis;
5. polymyositis, including refractory polymyositis;
6. myasthenia gravis in patients responsive to immunosuppressive treatment;
7. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener’s granulomatosis, polyarteritis nodosa), Goodpasture’s syndrome, and vasculitis associated with other connective tissue diseases;
8. thrombotic thrombocytopenic purpura;
9. hemolytic uremic syndrome;
10. paraneoplastic syndromes, other than Lambert-Eaton myasthenic syndrome
11. demyelinating polyneuropathy associated with IgM paraproteinemia;
12. epilepsy;
13. chronic sinusitis;
14. asthma;
15. chronic fatigue syndrome;
16. aplastic anemia;
17. Diamond-Blackfan anemia;
18. red cell aplasia;
19. acquired factor VIII inhibitors;
20. hemophagocytic syndrome;
21. acute lymphoblastic leukemia;
22. multiple myeloma;
23. immune-mediated neutropenia;
24. nonimmune thrombocytopenia;
25. cystic fibrosis;
26. recurrent otitis media;
27. diabetes mellitus;
28. Behcet’s syndrome;
29. adrenoleukodystrophy;
30. organ transplant rejection;
31. uveitis;
32. demyelinating optic neuritis;
33. recent-onset dilated cardiomyopathy;
34. Fisher syndrome;
35. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS);
36. autism;
37. complex regional pain syndrome;
38. Alzheimer’s disease;
39. IgG sub-class deficiency;
40. Sepsis, including neonatal sepsis;
41. Crohn’s disease.
**Policy Guidelines**

**Primary Humoral Immune Deficiency diseases**

Antibody deficiency characteristically leads to recurrent, severe upper and lower respiratory tract infections with encapsulated bacteria (e.g., Streptococcus pneumoniae, Haemophilus influenzae).

Patients with suspected antibody deficiency should have measurement of total serum IgG, IgA, and IgM. Immunoglobulin levels should be repeated to confirm that the values are persistently low and that a laboratory error has not occurred.

Specific antibody titers to tetanus and to polysaccharide antigens (such as type specific pneumococcal capsular polysaccharides) should also be measured, unless the immunoglobulin levels are very low (e.g., IgG <200 mg/dL). If specific antibody levels are low, booster immunization should be administered and titers measured again four weeks later.

**Assessing the immunologic response to vaccination**

For most evaluations of suspected immunodeficiency, the patient's ability to respond to the two main types of antigens, protein and polysaccharide antigens, should be assessed. Tetanus and diphtheria are representative protein antigens while pneumococcus represents polysaccharide antigens. It is unusual for a patient to have an impaired response to protein antigens with a normal response to polysaccharide antigens. If specific titers are protective, then the immune response to it is normal and no further evaluation is necessary for that particular vaccine or pathogen.

If initial titers are not protective, a single dose of the vaccine is administered and post-vaccination titers are measures no earlier than ONE MONTH after vaccination. Pre- and post-vaccination titers are then analyzed. Assessing responses earlier than one month may result in low post vaccination titers. It is critical that any evaluations of pre- and post- vaccination titers be performed by the same laboratory.

The immunologic response to vaccination cannot be reliably evaluated in patients who have received gammaglobulin replacement within the past three or four months, or in those who have received single doses of immune globulins for prevention of specific infections (e.g., hepatitis A or measles) within the past three to four months, since the antibodies assessed may be either of donor or patient origin. Conditions and treatments that potentially interfere with immunoglobulin production and vaccine response include cancer, chemotherapy, and some immunosuppressive therapies (e.g., long-term glucocorticoids, rituximab, etc.).

For both tetanus and diphtheria, antibody concentrations of >0.1 IU/mL are usually considered indicative of long-term protection. If either tetanus or diphtheria titers are protective, then the patient can be assumed to have a normal response to protein antigens. If a patient does not have protective titers to either tetanus or diphtheria, then a booster should be administered and titers reassessed.

**Assessing polysaccharide responses in adults and children over two years**

The evaluation of a patient’s immune response to specific vaccinations serves as a correlate to their ability to fight natural infections and is a component of the diagnosis of several primary and secondary immunodeficiencies.

Measurement of at least 14 different antibodies to pneumococcal vaccine serotypes is recommended. A serotype-specific IgG concentration ≥1.3 micrograms/mL is considered
protective in all age groups. Vaccination is performed if a patient's pre-existing titers are not protective.

- Patients 2 to 5 years of age should be able to generate protective titers (≥1.3 micrograms/mL) to at least 50 percent of the serotypes administered.
- Patients 6 years of age and older should be able to generate protective titers (>1.3 micrograms/mL) to at least 70 percent of the serotypes administered.

Some patients who initially develop an adequate antibody response demonstrate a rapid decline in antibody titers over the ensuing year and remain susceptible to pneumococcal infections. Thus, retesting of antibody titers after 6 to 12 months may be indicated to determine if a patient's titers have dropped to below protective levels in this time period.

Children in the United States have been receiving conjugated vaccines (Prevnar) for prophylaxis against *Streptococcus pneumoniae* since 2001. Antibodies to the pneumococcal subtypes contained in Prevnar (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) are measured after vaccination to assess protective immunity and responsiveness to protein-conjugated polysaccharide antigens.

It is not possible to assess a pure response to polysaccharide antigens in a child under two years of age, because even children with normal immune systems do not respond well to pure polysaccharide antigens. Polysaccharide responsiveness normally increases with age.

**IgG subclass deficiency**

IgG subclass deficiency is defined as a significant decrease in the levels of one or more subclasses of IgG in a patient whose total IgG concentration is normal. It is a laboratory finding that does not necessarily equate to a clinical disorder, and up to 20 percent of the population may have subnormal levels of one or more subclasses.

Most individuals lacking one or more IgG subclasses are asymptomatic. However, some present with recurrent sinopulmonary infections of varying severity. Other infections include otitis media, osteomyelitis, meningitis, septicemia, diarrhea, and various skin infections.

Antibody responses to both protein and polysaccharide antigens are assessed in any patient suspected of having a clinically significant IgG subclass deficiency. Patients with low IgG subclass levels but normal immune responses to vaccination may be immunologically normal.

**Treatment of IgG Subclass Deficiency**

Once treatment is initiated, patients need to be monitored, as some will progress to more severe immune disorders, such as CVID.

Treatment of patients with IgG subclass deficiency includes the following:

- Immunization with conjugate vaccines in patients who have not responded to polysaccharide vaccines.
- Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis, anatomic abnormalities conducive to ENT interventions). A high percentage of patients have concurrent allergic disease.
- Prophylactic antibiotics such as amoxicillin-clavulanate or cefdinir.
- Increased vigilance and appropriate antibiotic therapy for infections.
- Immunoglobulin replacement — judicious use of immunoglobulin (Ig) replacement is appropriate for immune deficiencies when the above treatment measures do not adequately
control infections. This therapy should be reserved for patients with clearly impaired responses to both protein and polysaccharide antigens.(69, 70)

Ig replacement therapy for IgG subclass deficiencies should be administered for one to two years initially, at which point the patient’s status should be re-evaluated to determine if the number and/or severity of infections have been reduced. Not all patients with IgG subclass deficiencies benefit from Ig replacement and the therapy should be discontinued if not effective.

**Prognosis for IgG Subclass Deficiency**

- Evidence suggests that the majority of children younger than ages 6 to 8, with clinically significant IgG subclass deficiency and diminished specific antibody responses, will normalize both antibody responsiveness and IgG subclass level(s). In contrast, if the condition persists beyond the age of 6 years, it is likely to be permanent.
- Adults with clinically significant IgG subclass deficiency and diminished specific antibody responses will rarely achieve normalization of a deficient IgG subclass level.(2) A subset of these patients will progress to CVID.

**Monitoring IgG Subclass Deficiency**

- In affected younger children (up to 6 years of age), levels of immunoglobulins and IgG subclasses should be measured yearly. Vaccine response should be assessed again if levels normalize.
- In symptomatic older children with persistent deficiency and in adults, levels should be reevaluated annually for several years. If the condition persists throughout this period, then reassessment can be less frequent.
- In patients requiring Ig replacement therapy, treatment should periodically be held after one to two years for immunologic and clinical reassessment. When discontinuing Ig replacement, it is advisable to do so during the spring months to minimize exposure to viral infections. It is also advisable to wait three or four months after discontinuation before performing immune testing.

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. 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).

**RATIONALE**

**Intravenous Infusion 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) occurs in male patients who have less than 2% or absent circulating B cells and normal T lymphocytes. 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. *Haemophilus influenzae* and *Streptococcus 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. 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.
X-linked hyper-IgM is a T cell deficiency with a genetic defect in CD40 ligand molecule. Family consanguinity is frequent. These patients present with recurrent sinopulmonary and gastrointestinal tract infections in childhood. Serum IgM levels may be in excess of 1,000 mg/dL. The immunologic characteristic of this disorder is an abnormality in the process of immunoglobulin class switch recombination, therefore an inability to manufacture IgG, IgA, or IgE antibodies. Peripheral blood B cell counts (CD19) are normal. T lymphocyte counts and proliferative responses are normal. Molecular studies have shown a mutation in the AID gene (activation-induced cytidine deaminase gene).

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

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

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

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

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-
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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. 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/mm$^3$.

**KAWASAKI SYNDROME AND OTHER VASCULITIDES**
Kawasaki syndrome is an FDA-approved indication for IVIg. Although the mechanism of action of IVIg is not understood, its use early in the course of disease has been shown to reduce the prevalence of coronary artery abnormalities. The success of IVIg in Kawasaki disease has led to the investigation of IVIg in other vasculitides, such as those associated with rheumatoid arthritis, Wegener’s granulomatosis, and polyarteritis nodosa. Randomized, multicenter studies have shown that high-dose IVIg plus aspirin, given within the first 10 days after the onset of fever, is safe and effective in reducing the prevalence of coronary artery abnormalities. A 2013 Cochrane review identified 1 RCT on IVIg for Wegener granulomatosis. 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. Data are inadequate regarding the effectiveness of IVIg in other vasculitides including polyarteritis nodosa and rheumatoid arthritis.

**CHRONIC INFLAMMATORY DEMYELINATING NEUROPATHY (CIDP)**
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.(22)

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 and colleagues, updated in 2012, reviewed the results of randomized trials of immunotherapy for GBS.(23) The review identified 12 randomized trials; none of these were placebo-controlled. Seven trials compared IVIg to plasma exchange (PE), 3 trials compared IVIg to supportive treatment only and 2 trials compared PE and 2 compared IVIg to immunoabsorption (one of these compared the combination of IVIg and immunoabsorption to 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 to 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, e.g. the 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 over 16 years old to IVIg, PE, or the combination of IVIg and PE.(24) 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. Non-inferiority 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 pre-defined 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, e.g., 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 ITP, based on 6 randomized controlled trials (RCTs) and one 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 $50 \times 10^9/L$ at day 21, was significantly higher in the IVIg group compared with the high-dose methylprednisolone group. Two other trials, one nonrandomized (IVIg versus corticosteroids) and one randomized (IVIg alone versus oral prednisone alone versus IVIg plus oral prednisone) found no difference in platelet counts greater than $50 \times 10^9/L$ at 48 hours or response rate between groups, respectively.

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

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

The 2007 Canadian Committee on Blood and Blood Products guidelines recommends IVIg for select patients with chronic ITP.(29) In particular, patients with a platelet count below $20 \times 10^9/L$ 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. 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. Later, in 2003 to 2004, findings from the NIH IG02, a double-blind placebo-controlled trial, were published. 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. 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).

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. 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. 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. In their literature search, they identified 3 RCTs, all on kidney transplant, and numerous observational studies or case series on several types of organ transplantation. Key recommendations of the panel are as follows:
- When kidney transplantation involves use of a living donor, IVIg is recommended to decrease donor-specific sensitization.
- There is insufficient evidence to recommend for or against the use of IVIg for ABO-incompatible kidney transplantation.
• To reduce the risk of acute antibody-mediated rejection, IVIg is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIg is not recommended for kidney transplant patients who do not have donor-specific antibodies.
• IVIg is recommended after plasmapheresis for patients who have received a living donor or deceased kidney donor transplant and who have acute antibody-mediated rejection. Consider IVIg when patients have corticosteroid-resistant rejection, when other therapies are deemed unacceptable or ineffective.
• There is insufficient evidence to recommend for or against the use of IVIg for desensitization for patients undergoing heart, lung, or liver transplantation.

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

A double-blind, placebo-controlled crossover trial of 12 patients with multifocal motor neuropathy and high 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.(43) Subsequent RCTs have reported similar results.(44); thus use of IVIg to treat multifocal motor neuropathy is considered medically necessary.

MULTIPLE SCLEROSIS
Following an updated TEC Assessment in 1998 which concluded that IVIg for multiple sclerosis met the TEC criteria, it was considered medically necessary.(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:
1. The studies of intravenous immunoglobulin (IVIg) to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in relapsing-remitting multiple sclerosis (Type C recommendation).
2. The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (Type C recommendation).

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

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

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. A blinded RCT of 41 women treated with IVIg or saline placebo found no differences in live birth rates. A multcenter RCT comparing heparin and low-dose aspirin with versus without IVIg in women with lupus anticoagulant, anticardiolipin antibody, or both, found no significant differences. In addition, an RCT of 58 women with at least 4 unexplained miscarriages tested IVIg versus placebo and analyzed results by intention to treat. 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 IVIg therapy in patients with corticosteroid-dependent asthma found no significant decrease in corticosteroid use compared to placebo. A subgroup analysis in one trial indicated a significant effect of IVIg on corticosteroid consumption in patients requiring corticosteroid doses greater than 2 g per year; however, this subgroup analysis was not stated as planned in advance and involved only 17 of 38 total patients. Thus, IVIg for asthma is considered investigational.

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

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

**AUTOIMMUNE MUCOCUTANEOUS BLISTERING DISEASES (AMBDs)**
Nonrandomized studies and a systematic review on IVIg for autoimmune mucocutaneous blistering diseases (AMBDs) showed that IVIg therapy for specific patients prevented the progression of disease and showed significant clinical benefit. The 2010 systematic review by Gurcan et al identified 23 studies evaluating IVIg for AMBDs; 22 case series and 1 RCT. The studies included a total of 260 patients treated with IVIg; 191 patients with pemphigus and 69 patients with pemphigoid. Of the 260 patients, 245 improved after IVIg treatment. IVIg can be used as an adjunctive agent to taper or discontinue use of corticosteroids and/or immunosuppressive treatments. In effect, IVIg served as a corticosteroid-sparing agent.

The article suggests that IVIg be considered with the following criteria:
- Patients who are nonresponsive 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 and Chen focused on IVIg for treating toxic epidermal necrosis (TEN). The authors identified 17 studies with a total of 221 with TEN treated with IVIg; 5 studies were retrospective, non-randomized controlled studies and the remaining 11 studies were case series. Twelve out of the 17 studies supported use of IVIg. Overall, the mean time from initiation of IVIg to response was 2.4 days and the mean time from initiation of IVIg 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 IVIg 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. Fisher syndrome is one of the regional variants of Guillain-Barré syndrome, characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). Intravenous immunoglobulin (IVIg) and plasma exchange are often used as treatments in this patient group. No RCTs were identified; the authors concluded that, due to the lack of controlled studies, there is insufficient evidence on which to base practice.
REFRACTORY DERMATOMYOSITIS
Dermatomyositis is an autoantibody end-complement attack against vascular endothelium. Clinically, patients develop weakness of the muscles and a skin rash. In 2012, Wang and colleagues 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 studies included patients with refractory disease. Both RCTs found a benefit of IVIg treatment. For example, a trial by Dalakas and colleagues compared prednisone plus IVIg to 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 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 endpoint 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 American Academy of Neurology guideline on IVIg for treating neuromuscular disorders stated that IVIg may be considered as a treatment of non-responsive 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

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. (63) 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 beta-amyloid, 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 beta-amyloid 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. (64) 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 1.4 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. (65) 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. 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) and trauma patients (n=39) 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).

**DILATED CARDIOMYOPATHY**

Sixty-two patients with recent-onset dilated cardiomyopathy were randomized to IVIg or placebo. 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 and 1 small RCT comparing IVIg to cyclophosphamide 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.

**MOERSH-WOLTMAN (STIFF-MAN) SYNDROME**

Dalakas et al randomized 16 patients with disease and anti-GAD65 autoantibodies to IVIg or placebo for 3 months. 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.(80, 81) 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.(82) Due to the findings of this study, and lack of other comparative trials, IVIg for demyelinating optic neuritis is considered investigational.

NEONATAL SEPSIS
A 2013 Cochrane review addressed IVIg for the prevention of infection in preterm and/or low-birth weight infants.(83) 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.

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.(84) 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.(85)

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.(86) 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'S DISEASE**

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

**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**

**PRIMARY IMMUNE DEFICIENCIES**

SCIg is FDA-approved for the treatment of primary immune deficiencies. Clinical data on the first SCIg product (Vivaglobin) available in the U.S. were published in 2006, the same year as the FDA approval. An open-label, nonrandomized, prospective, multicenter study reported outcomes of SCIg replacement therapy in 65 adults and children (>2 years with bodyweight ≥10 kg) with CVID or X-linked agammaglobulinemia that had been treated with IVIg for at least 4 months. Most (78%) had CVID, 22% had or X-linked agammaglobulinemia. One week after the last IVIg dose administered during a 3 to 4 baseline period, 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 preinfusion 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). 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 3656 infusions, 2584 treatment-emergent adverse events were reported (0.71 per infusion), with 1901 considered to be treatment-related (0.52 per infusion). The most frequent type of adverse event was infusion-site reaction in 60 patients; most of these were of mild or moderate intensity and of short duration. 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. 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 et al of the same product (Vivaglobin) in Europe and Brazil among 60 patients (16 children, 44 adults) with a diagnosis of primary immunodeficiencies, also published in 2006, produced almost identical annualized rates of mild-to-moderate overall infections and serious bacterial infections (0.04 episodes per patient). (89) Gardulf et al used a SCIg dose equivalent to 100% of the previous IVIg dose, compared with 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. (90) 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. (91) 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.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received through 3 physician specialty societies and 5 academic medical centers in March 2013 following approval of the December 2012 update of the policy. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Input focused on IVIg treatment of 7 rare conditions. There was consensus, or near-consensus, that IVIg is investigational for 6 of these conditions: birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, opsoclonus-myoclonus, PANDAS and polyradiculoneuropathy (other than CIDP). Clinical input was mixed overall on the seventh condition, IVIg for treating severe anemia associated with parvovirus B19. Additional clinical input was obtained in June 2013, focusing on severe anemia due to parvovirus B19. Input was received from 3 reviewers, all hematologists, and there was consensus that IVIg is not investigational for this indication. There was a lack of consensus among the 3 reviewers on any specific clinical or patient characteristics that can be used to select patients with severe anemia due to parvovirus B19 for treatment with IVIg and on any treatments that should be used by these patients before IVIg.

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, 28)

In 2013, a updated joint guideline on prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children was published.(92) 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 HIV-infected children who have hypogammaglobulinemia.”

In 2012, the American Academy of Neurology published an evidence-based guideline on IVIg for treating neuromuscular disorders.(22) Specific recommendations are discussed in appropriate sections of the Rationale.

CODING
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.
### CPT/HCPCS

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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
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<td>90284</td>
<td>Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each (new code 1/1/08)</td>
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<td>96365</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour (new code number 1/1/09 - previously 90765)</td>
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<td>96369</td>
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<td>each additional hour (List separately in addition to code for primary procedure) (new code number 1/1/09 - previously 90770)</td>
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<td>additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure) (new code number 1/1/09 - previously 90771)</td>
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<td>J1556</td>
<td>Injection, tbo-filgrastim, 5 micrograms <em>(Effective January 1, 2014)</em></td>
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<td>Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg</td>
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<td>J1599</td>
<td>Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg</td>
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### DIAGNOSIS

These diagnoses are otherwise subject to medical policy as stated above

- **041.0-** Bacterial infection, code range
- **041.9**
- **042** Human immunodeficiency virus (HIV) disease
- **204.10-** Chronic lymphoid leukemia, code range
- **204.11**
- **204.12** Chronic lymphoid leukemia, in relapse
- **279.00** Hypogammaglobulinemia, unspecified
- **279.04-** Immunodeficiency (X-linked), code range
- **279.05**
- **279.06** Common variable immunodeficiency
- **279.12** Wiskott-Aldrich syndrome
- **279.2** Combined immunity deficiency
279.3 Unspecified immunity deficiency
287.3 Primary thrombocytopenia
287.31 Immune Thrombocytopenic purpura
287.32 Evans’ syndrome
287.5 Thrombocytopenia, unspecified
334.8 Telangiectasia, ataxic (cerebellar)
354.0- Mononeuritis, code range
355.9
356.4- Idiopathic peripheral neuropathy, code range
356.9
357.0 Acute infective polyneuritis (includes Guillain-Barré syndrome)
426.0- Conduction disorders, code range
426.9
446.1 Acute febrile mucocutaneous lymph node syndrome (Kawasaki disease)
710.3 Dermatomyositis
776.1 Transient neonatal thrombocytopenia
V42.81 Status post-bone marrow transplant

ICD-10 DIAGNOSIS (Effective October 1, 2015)
A48.3 Toxic shock syndrome
B20 Human immunodeficiency virus [HIV] disease
B95.0 Streptococcus, group A, as the cause of diseases classified elsewhere
B95.1 Streptococcus, group B, as the cause of diseases classified elsewhere
B95.2 Enterococcus as the cause of diseases classified elsewhere
B95.3 Streptococcus pneumoniae as the cause of diseases classified elsewhere
B95.4 Other streptococcus as the cause of diseases classified elsewhere
B95.5 Unspecified streptococcus as the cause of diseases classified elsewhere
B95.61 Methicillin susceptible Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.62 Methicillin resistant Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.7 Other staphylococcus as the cause of diseases classified elsewhere
B95.8 Unspecified staphylococcus as the cause of diseases classified elsewhere
C91.10 Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11 Chronic lymphocytic leukemia of B-cell type in remission
C91.12 Chronic lymphocytic leukemia of B-cell type in relapse
D59.1 Other autoimmune hemolytic anemias
D68.61 Antiphospholipid syndrome
D69.3 Immune thrombocytopenic purpura
D69.6 Thrombocytopenia, unspecified
D80.0 Hereditary hypogammaglobulinemia
D80.1 Nonfamilial hypogammaglobulinemia
D80.2 Selective deficiency of immunoglobulinemia
D80.3 Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4 Selective deficiency of immunoglobulin M [IgM]
D80.5 Immunodeficiency with increased immunoglobulin M [IgM]
D80.6 Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7 Transient hypogammaglobulinemia of infancy
D80.8 Other immunodeficiencies with predominantly antibody defects
D80.9  Immunodeficiency with predominantly antibody defects, unspecified
         Common variable immunodeficiency with predominant abnormalities of B-cell numbers
D83.0  Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.1  Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.2  Other common variable immunodeficiencies
D83.9  Common variable immunodeficiency, unspecified
G11.3  Telangiectasia (cerebellar) (Louis-Bar)
G35   Multiple sclerosis
G60.0  Hereditary motor and sensory neuropathy
G60.1  Refsum's disease
G60.2  Neuropathy in association with hereditary ataxia
G60.3  Idiopathic progressive neuropathy
G60.8  Other hereditary and idiopathic neuropathies
G60.9  Hereditary and idiopathic neuropathy, unspecified
G61.0  Guillain-Barré syndrome
G70.01 Myasthenia gravis with (acute) exacerbation
G73.3  Myasthenic syndromes in other diseases classified elsewhere
I44.0  Atrioventricular block, first degree
I44.1  Atrioventricular block, second degree
I44.2  Atrioventricular block, complete
I44.30 Unspecified atrioventricular block
I44.39 Other atrioventricular block
I44.4  Left anterior fascicular block
I44.5  Left posterior fascicular block
I44.60 Unspecified fascicular block
I44.69 Other fascicular block
I44.7  Left bundle-branch block, unspecified
I45.0  Right fascicular block
I45.10 Unspecified right bundle-branch block
I45.19 Other right bundle-branch block
I45.2  Bifascicular block
I45.3  Trifascicular block
I45.4  Nonspecific intraventricular block
I45.5  Other specified heart block
I45.6  Pre-excitation syndrome
I45.81 Long QT syndrome
I45.89 Other specified conduction disorders
I45.9  Conduction disorder, unspecified
L10.0  Pemphigus vulgaris
L10.1  Pemphigus vegetans
L10.2  Pemphigus foliaceous
L10.3  Brazilian pemphigus [fogo selvagem]
L10.4  Pemphigus erythematosus
L10.5  Drug-induced pemphigus
L10.81 Paraneoplastic pemphigus
L10.89 Other pemphigus
L10.9  Pemphigus, unspecified
L12.0  Bullous pemphigoid
L12.1 Cicatricial pemphigoid
L12.2 Chronic bullous disease of childhood
L12.30 Acquired epidermolysis bullosa, unspecified
L12.31 Epidermolysis bullosa due to drug
L12.35 Other acquired epidermolysis bullosa
L12.8 Other pemphigoid
L12.9 Pemphigoid, unspecified
L51.3 Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M30.3 Mucocutaneous lymph node syndrome [Kawasaki]
M33.90 Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91 Dermatopolymyositis, unspecified with respiratory involvement
M33.92 Dermatopolymyositis, unspecified with myopathy
M33.99 Dermatopolymyositis, unspecified with other organ involvement
P61.0 Transient neonatal thrombocytopenia
Z94.81 Bone marrow transplant status

REVISIONS

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<tr>
<td>01-12-2007</td>
<td>In “Policy” section 1., a., added “(patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization)” based on consultant review and recommended by the Medical Director.</td>
</tr>
<tr>
<td>04-01-2007</td>
<td>In “Policy” section, added #23 “Prior to renal transplantation with high levels of panel reactive antibodies (PRA)” as recommended by the Medical Director.</td>
</tr>
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<td></td>
<td>In “Coding” title deleted “NOTE: Use of any diagnosis code does not guarantee reimbursement. Medical necessity will be based on documentation in the clinical record.”</td>
</tr>
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<td></td>
<td>In “Coding” CPT/HCPCS section, added HCPCS codes J1562 due to the 2007 CPT changes.</td>
</tr>
<tr>
<td></td>
<td>In “Reference” Government Agency; Medical Society; and Other Authoritative Publications section added #2.</td>
</tr>
</tbody>
</table>
| 09-12-2007 | Revised wording of Policy #1 – Primary humoral immunodeficiencies: 1. Primary humoral immunodeficiencies  
|            | a. Normal or subnormal gamma globulin and/or subclasses with recurrent significant infections. A function immune deficiency needs to be demonstrated by lack of antibody response to pneumococcal vaccine with pre-vaccine antibody titers drawn just before vaccine and post vaccination titers drawn one month after vaccine. At least a two-fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization.  
|            | b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed.  
<p>|            | c. Transient hypogammaglobulinemia of childhood age less than 5 functional immune deficiency is transient, usually six months, then IVIg can be gradually withdrawn. Need testing for pneumococcal antibody response. |
|            | Moved to Policy #24 - Chronic B Cell Lymphocytic Leukemia, multiple myeloma, or B cell lymphoma with low immunoglobulin levels |</p>
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>02-28-2011</td>
<td>Significant updates to Policy Language section. The following policy language has been updated:</td>
</tr>
<tr>
<td></td>
<td>All immune globulin therapy will be reviewed for medical necessity prior to payment. See Utilization Section for details. Indications for immune globulin include:</td>
</tr>
<tr>
<td></td>
<td>1. Immunodeficiency states:</td>
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<td>One of the following six is required:</td>
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<tr>
<td></td>
<td>a. A functional immune deficiency manifested by recurrent serious infections. Needs to be demonstrated by the lack of antibody response to pneumococcal vaccine with pre and post antibody titers (patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization) and recurrent significant infections or</td>
</tr>
<tr>
<td></td>
<td>b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed.</td>
</tr>
<tr>
<td></td>
<td>c. B Cell Lymphocytic Leukemia (CLL) (e.g. multiple myeloma, chronic lymphocytic leukemia with low immunoglobulin levels or B cell lymphoma).</td>
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<tr>
<td></td>
<td>d. Transient hypogammaglobulinemia of childhood</td>
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<tr>
<td></td>
<td>• Similar to a functional immune deficiency but transient, usually six months, then IVIg should be gradually withdrawn. Need testing for pneumococcal antibody response.</td>
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<td></td>
<td>• Consider in children less than age 5.</td>
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<td>e. Partial antibody deficiency (subclass of deficiency)</td>
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<td></td>
<td>• This may refer to a deficiency of one of the four subclasses. This in itself does not indicate instituting IVIg therapy even if patient presents with multiple infection (sinusitis or other upper respiratory infection). Attempts need to be made to find underlying cause and to see if patient has normal immune response. By giving Pneumovax (pneumococcal at a minimum and may include tetanus or hemophilus influenza in addition) and checking antibody levels before and after ascertain if patient has normal immune response.</td>
</tr>
<tr>
<td></td>
<td>• If normal response is obtained, then subclass level deficiency should not be treated. The only exception to this would be in case of a life threatening hospitalization from a specific disease.</td>
</tr>
<tr>
<td></td>
<td>f. Profound neutropenia in neonatal sepsis (WBC 5,000 or below) –Allow for a single dose.</td>
</tr>
<tr>
<td></td>
<td>2. Idiopathic thrombocytopenia (ITP)</td>
</tr>
<tr>
<td></td>
<td>a. Acute Idiopathic thrombocytopenia (ITP)</td>
</tr>
<tr>
<td></td>
<td>1) Management of acute bleeding, due to severe thrombocytopenia (platelet counts usually less than 30,000/ul;</td>
</tr>
<tr>
<td></td>
<td>2) To increase platelet counts prior to invasive surgical procedures, e.g., splenectomy;</td>
</tr>
<tr>
<td></td>
<td>3) In patients with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage</td>
</tr>
<tr>
<td></td>
<td>b. Chronic Refractory ITP</td>
</tr>
<tr>
<td></td>
<td>1) Prior to treatment with corticosteroids and splenectomy and;</td>
</tr>
<tr>
<td></td>
<td>2) Duration of illness of greater than six months and;</td>
</tr>
</tbody>
</table>

Moved to Policy #25 - Profound neutropenia in neonatal sepsis (WBC 5,000 or below) – Allow for a single dose.
3) Age of 10 years or older and;
4) No concurrent illness/disease explaining thrombocytopenia and;
5) Platelet counts persistently at or below 20,000/ul.

3. HIV associated thrombocytopenia – Allow treatment (same as ITP)
4. Immune thrombocytopenic purpura of pregnancy – Allow for 5 days.
5. Neonatal alloimmune thrombocytopenia – Allow for 5 days.
6. Kawasaki Syndrome
7. Organ transplant – graft versus host disease. Allow treatment, but treatment should be short-term unless it is "chronic" graft versus host.
8. Guillain Barré Syndrome – Allow for no longer than 1 month.
9. Bone Marrow transplant
10. Landau-Kleffner Syndrome – Allow for six weeks with documented speech improvement, only if patient has completed a course of prednisone. Additional treatment requires prior approval.
11. Polymyositis – Allow for six months if no response to steroids and observe for relapse.
12. Dermatomyositis – Allow for six months if no response to steroids and observe for relapse.
13. HIV associated polyneuropathy.
15. Chronic inflammatory demyelinating polyneuropathy (CIDP)
16. Myasthenia gravis – Only when all other treatments fail.
17. Intractable seizure – Not recommended unless all other measures fail.
18. Rasmussen encephalitis
19. Systemic juvenile rheumatoid arthritis – Only for refractory patient cases.
20. Systemic lupus – Not recommended except for refractory cases.
21. Steroid dependent asthmatic, allow only if:
   a. All modalities have failed.
   b. Unstable patient requiring frequent hospital care. A trial should be allowed and if there is a decrease of frequency of hospital admissions and stabilization of patient's pulmonary function it should be allowed.
22. Pemphigus - only when all other treatments fail.
23. Prior to renal transplantation with high levels of panel reactive antibodies (PBA)

NOTE: When it is determined IVIg is to be given for the duration of the patient’s life, reviews will be conducted not for medical necessity but for patient benefits.

Denied Medical Conditions:
1. Infertility and Spontaneous abortion deny experimental/investigational.
2. Frequent sinus/pulmonary infection only, deny not medically necessary.
3. Shingles deny not medically necessary.
4. Prevention of bacterial infection associated with HIV (adults), deny not medically necessary.
5. Amyotrophic Lateral Sclerosis (ALS), deny experimental/investigational.

In Coding Section
▪ Added CPT Codes: 90284, 96365, 96366, 96369, 96370, 96371
▪ Added HCPCS Codes: C9270, J1459, J1561, J1568, J1569, J1572,
▪ Removed CPT Codes: 90399
▪ Removed HCPCS Codes: J1567, J3490, Q9941, Q9942, Q9943, Q9944
In the Medical Policy Section:
- Item B, #1, a: corrected “ml” to read “(e.g.200 mg per dl or less)”
- Item B, #1, b: first bullet, corrected “mg per” to read “>1.3 micrograms/ml”
- Item B, #1, b, second bullet: corrected “mg per” to read “>1.3 micrograms/ml”

In the Coding Section
- Added HCPCS code J1559

In the Description section:
- Added the fourth paragraph: “One SCIg product (Vivaglobin®, ZLB Behring LLC, Kankakee, IL) has received FDA marketing approval for the treatment of patients with primary immune deficiency.”

In the Policy section:
- Item 16, b, added “; or “at the end.
- Item 16, added the following:
  - “c. Platelet counts less than 20,000/ul (risk of intracerebral hemorrhage; or”
  - “d. Management of acute bleeding with platelet counts less than 30,000/ ul; or”
  - “e. Increase platelet counts, prior to major surgical procedures.”

Updated the Rationale section.
Updated the Reference section.

In the Coding section:
- Removed HCPCS code C9270
- Added HCPCS code J1561.
- Revised HCPCS code J1561: to include Gammaked

Updated Description section.

In the Policy section:
- In Item B, #1, b, fourth paragraph, removed “with clearly impaired responses to both protein and / or polysaccharide antigens and” and inserted “who” to read “Immunoglobulin replacements should be reserved for patients who have failed the following treatments:”
- In Item B, #1, b, fourth paragraph, second bullet, removed “A high percentage of patients have concurrent allergic disease.” and inserted “anatomic abnormalities conducive to ENT procedures” to read “(e.g. asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures).”
- In Item B, #5, removed “or the member has experienced significant complications” to read “…when corticosteroids, and immune-suppressive agents have failed.”
- In Item B, #8, removed “with IgG level less than 600 mg/dL; and:” to read “Chronic Lymphocytic Leukemia (CLL) in Patients with Hypogammaglobulinemia”
- In Item B, #8, a, removed “1 server bacterial infection within preceding 6 months or 2 or more bacterial infections in one year; or” and inserted “recurrent or persistent bacterial infections”
- In Item B, #11, inserted “or previous pregnancy affected by FAIT”
- In Item B, #14, removed “Bacterial Infection” and “infected children” to read
“HIV Infected Children who meet the following criteria:”

- In Item B, #14, b, removed “i.e., defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1 year period” to read “Recurrent serious bacterial infections;”
- In Item B, #14, c, removed “Living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live” to read “Failure to form antibodies to common antigens, such as measles, pneumococcal, and / or Haemophilus influenza type b vaccine;”
- In Item B, #14, e, removed “HIV infected children with” to read “Chronic bronchiectasis that is...”
- In Item B, #26, inserted “diagnosed on the basis of electrophysiologic findings.”
- In Item B, #27, b, removed “Two or more and “or a single life threatening infection” to read “Recurrent significant infections in last year;”
- In Item B, #33, removed “for children whose symptoms do not improve with” and inserted “refractory to” to read “Rasmussen Encephalitis refractory to antiepileptic drugs and corticosteroids.”
- In Item B, #34, removed “Sever cases of toxic shock syndrome that have not responded to fluids and vasopressors”
- In Item D, inserted the following conditions:
  1. chronic progressive multiple sclerosis;
  2. refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus;
  3. recurrent spontaneous abortion (see below for related laboratory tests);
  4. inclusion-body myositis;
  5. polymyositis, including refractory polymyositis;
  6. myasthenia gravis in patients responsive to immunosuppressive treatment;
  7. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener’s granulomatosis, polyarteritis nodosa), Goodpasture’s syndrome, and vasculitis associated with other connective tissue diseases;
  8. thrombotic thrombocytopenic purpura;
  9. hemolytic uremic syndrome;
 10. paraneoplastic syndromes, other than Eaton-Lambert myasthenic syndrome
 11. demyelinating polyneuropathy associated with IgM paraproteinemia;
 12. epilepsy;
 13. chronic sinusitis;
 14. asthma;
 15. chronic fatigue syndrome;
 16. aplastic anemia;
 17. Diamond-Blackfan anemia;
 18. red cell aplasia;
 19. acquired factor VIII inhibitors;
 20. hemophagocytic syndrome;
 21. acute lymphoblastic leukemia;
 22. multiple myeloma;
 23. immune-mediated neutropenia;
25. nonimmune thrombocytopenia;
26. cystic fibrosis;
27. recurrent otitis media;
28. diabetes mellitus;
29. Behcet’s syndrome;
30. adrenoleukodystrophy;
31. stiff person syndrome;
32. organ transplant rejection;
33. uveitis;
34. demyelinating optic neuritis;
35. recent-onset dilated cardiomyopathy;
36. Fisher syndrome
37. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS);
38. autism
39. complex regional pain syndrome
40. Alzheimer's disease
41. IGG sub-class deficiency
42. Sepsis

Updated Policy Guidelines.
Updated Coding nomenclature.
Updated Rationale section.
Updated Reference section.

07-30-2013
In Policy section:
- Added "and have not responded to polysaccharide vaccines".
- In Item D, #41, added "including neonatal sepsis" to read "Sepsis, including neonatal sepsis"
- In Item D, added "#42. Crohn's disease"

Updated Rationale section.

01-21-2014
In Coding section:
- Added new code: J1556 (Effective January 1, 2014)
- Removed code: C9130 (Deleted code, effective December 31, 2013)

09-12-2014
In Policy section:
- In Item B, #1, added "(to include X-linked agammaglobulinemia (Bruton) X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and ataxia telangiectasia)"
- In Item B, #5, added "pemphigus"
- In Item D, removed, "30. Stiff person syndrome;"

Updated Rationale section.

In Coding section:
- Added ICD-9 code 334.8
- Added ICD-10 code G11.3

Updated Reference section.
REFERENCES


Other References
1. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee; July 2010, July 2012.
2. Blue Cross and Blue Shield of Kansas OB/GYN Liaison Committee; July 2010, July 2013, July 2014.
4. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee; CB October 2010, August 2013, August 2014.
5. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee; CB October 2010, February 2014.