Name of Policy:
Immune Globulin Replacement Therapy

Policy #: 043
Category: Medication/Drugs

Latest Review Date: June 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Immune globulin is an antibody-containing solution obtained from the pooled plasma of healthy blood donors. 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. Immunoglobulins are administered intravenously to provide immediate antibody levels. The dosage and administration schedule varies by diagnosis. Office records should clearly document current history and physical exam, results of pertinent lab tests such as gamma globulin blood levels. Documentation should include a history of recurrent and severe sinus and/or pulmonary infections (such as bronchitis, pneumonia, or bronchiectasis) and/or diarrhea in association with hypogammaglobulinemia, if any, or all have been present.

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 U.S. 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. This policy addresses only IVIg and SCIg, for conditions that typically would be treated in an outpatient setting. It does not address conditions treated in the acute care setting.

Intravenous infusion immune globulin is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIg has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIg products are available for clinical use in the United States. The labeled indications approved by the U.S. Food and Drug Administration (FDA) for IVIg are listed in the Policy section. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

Subcutaneous infusion immune globulin is used for treating patients with primary immunodeficiencies (PID). A genetic basis for more than 80 different types of PID has been discovered, the most common being primary antibody deficiency (PAD) that is associated with low levels or total lack of normal circulating immunoglobulins. The first immune globulin for subcutaneous use was FDA approved in 2006. SCIg 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. SCIg 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.
Policy:

Intravenous Immune globulin (IVIg) therapy meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the following indications:

- **Primary immune deficiency syndromes** (see below), including combined immunodeficiencies, must meet all the following criteria for treatment with immune globulin:
  a. Immunologic evaluation including documented serum IgG below the lower limits of normal on at least two occasions; and
  b. Documented inability to mount an adequate immunologic response to inciting antigens; and
  c. Persistent and severe infections despite treatment with prophylactic antibiotics.

**Syndromes:**
- X-linked agammaglobulinemia (Bruton’s)
- X-linked hyper-IgM syndrome (effective 05/01/2012)
- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome
- Common variable immunodeficiency (CVID)
- Hyperimmunoglobulin E syndrome (hyper-IgE, Job syndrome)
- Ataxia telangiectasia
- Maintenance treatment of patients unable to produce sufficient amounts of IgG antibodies to include IgG subclasses.

- **Acute Humoral Rejection**

- **Autoimmune and inflammatory disorders:**
  - Dermatomyositis refractory to treatment with corticosteroids; in combination with other immunosuppressive agents. Treatment should be for three months, initially. If further treatment is requested, the physician must submit objective evidence of the effectiveness of the initial three month treatment.
  - Kawasaki syndrome
  - Autoimmune neutropenia (AIN)

- **Autoimmune Mucocutaneous Blistering Diseases**, in patients with severe, progressive disease despite treatment with conventional agents (corticosteroids, azathioprine, cyclophosphamide, etc.):
  - Pemphigus
  - Pemphigoid (effective 05/01/2012)
  - Pemphigus vulgaris
  - Pemphigus foliaceus
  - Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) (effective 05/01/2012)
**Hematologic:**
- Idiopathic thrombocytopenic purpura (ITP), acute or chronic
- Fetal or neonatal alloimmune thrombocytopenia
- Allogeneic post-bone marrow transplant setting (**effective 05/01/2012**)
- B cell chronic lymphocytic leukemia (CLL); in patients with hypogammaglobulinemia and persistent bacterial infections.
- Multiple myeloma patients with stable disease and at high risk of recurrent infections despite prophylactic antibiotic
- Warm antibody autoimmune hemolytic anemia (AIHA), refractory to corticosteroids and immunosuppressive agents.
- Anti-phospholipid syndrome for those that have experienced repeated fetal loss.
- Patients with hematologic malignancies (i.e., chronic lymphocytic leukemia, acute lymphocytic leukemia, multiple myeloma) who are taking chemotherapy.
- Severe anemia due to parvovirus B19 (**effective 05/01/2013**)

**Infectious diseases:**
- HIV (human immunodeficiency virus)-infected patients
- Toxic shock syndrome (**effective 05/01/2012**)
- Kawasaki disease
- Patients with primary defective antibody synthesis.
- Treatment of chronic parvovirus B19 (fifth disease) for immunodeficient patients with anemia or patients with sickle cell disease.

**Neuroimmunological:**
- Multiple sclerosis (MS), as a second line treatment in relapsing-remitting MS when standard approaches (i.e., interferons) have failed, become intolerable or are contraindicated.
- Myasthenia gravis in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- Acute inflammatory demyelinating polyneuropathy, including Guillain-Barré syndrome, when one of the following criteria is met:
  - Deteriorating pulmonary function tests, or;
  - Rapid deterioration with symptoms for less than 2 weeks, or;
  - Rapidly deteriorating ability to ambulate, or;
  - Frank inability to ambulate for 10 meters.
- Chronic inflammatory demyelinating polyneuropathy (CIDP) in patients with severe disability, and diagnosed by slowing of nerve conduction velocity. Retreatment will be covered with documented evidence of significant improvement in clinical condition and/or electrophysiological parameter.
- Multifocal motor neuropathy (**effective 05/01/2012**)
- Lambert-Eaton myasthenic syndrome (LEMS)
- Polymyositis
- Stiff person syndrome
Transplantation:
- Prior to solid organ transplant, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving and ABO incompatible organ.
- Following solid organ transplant, treatment of antibody-mediated rejection.
- Bone marrow transplant patients for the following indications:
  - Acute graft versus host disease
  - Development of hypogammaglobulinemia
  - Prevention of risk of septicemia
  - Prevention of the risk of interstitial pneumonia

Prevention:
- Prevention of infection in pre-term (<37 weeks’ gestational age) and/or low birth weight (<2500g) neonates. (effective 05/01/2014)

The use of IVIG therapy is considered investigational for, but not limited to, the following conditions:
- Acute renal failure
- Acquired factor VIII inhibitors (effective 05/01/2012)
- Adrenoleukodystrophy
- Aplastic anemia
- Asthma
- Autism
- Alzheimer’s Disease
- Behçet’s syndrome
- Chronic fatigue syndrome
- Chronic, progressive multiple sclerosis
- Chronic sinusitis
- Complex regional pain syndrome (effective 05/01/2012)
- Cystic fibrosis
- Demyelinating optic neuritis (effective 05/01/2012)
- Demyelinating polyneuropathy associated with IgM paraproteinemia (effective 05/01/2012)
- Diabetes mellitus
- Diamond-Blackfan syndrome (effective 05/01/2012)
- Epilepsy
- Hemolytic uremic syndrome (effective 05/01/2012)
- Hemophagocytic syndrome i.e., hemophagocytic lymphohistiocytosis (effective 05/01/2012)
- Immune-mediated neutropenia (effective 05/01/2012)
- Inclusion-body myositis (effective 05/01/2012)
- Myasthenia gravis in patients responsive to immunosuppressive treatment (effective 05/01/2012)
- Organ transplant rejection (effective 05/01/2012)
• 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 (effective 05/01/2012)
• Paraneoplastic syndromes, other than Lambert-Eaton myasthenic syndrome (effective 05/01/2012)
• Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (effective 05/01/2012)
• Recent-onset dilated cardiomyopathy (effective 05/01/2012)
• Recurrent otitis media
• Recurrent spontaneous abortion (effective 05/01/2012)
• Red cell aplasia (effective 05/01/2012)
• Refractory rheumatoid arthritis and other connective tissue disease, including systemic lupus erythematosus (effective 05/01/2012)
• Sepsis, including neonatal sepsis (effective 05/01/2012)
• Thrombotic thrombocytopenic purpura
• Uveitis (effective 05/01/2012)

Subcutaneous Immune Globulin (SCIg) (e.g. Hizentra) Therapy meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency (CVID), severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked immunodeficiency.

Other applications of SCIg therapy do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational, including, but not limited to chronic inflammatory demyelinating polyneuropathy (CIDP).

According to policy, SCIg must meet medical criteria for coverage. SCIg is administered subcutaneously and is considered a self-administered drug. Per the manufacturer this drug may be administered at the patient’s convenience. The initial administration may be in the physician’s office and will be covered as a medical benefit per the patient’s contract. When administered in the home, this is covered under the pharmacy benefit per the patient’s contract. Home health services will not be covered to administer a self-administered drug, in this instance SCIg. (effective 09/29/2009)

Hizentra, a newly approved SCIg, product meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of primary immunodeficiencies as above. The criteria regarding self-administration also apply to this product. This will be considered a pharmacy benefit, please refer to the pharmacy policy for coverage. (effective 03/04/2010)

Benefits are not provided for patients:
• Known to have had a previously anaphylactic reaction or severe systemic response to Ig and in individuals with selective IgA deficiencies or in class-specific anti-IgA.
Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

**Key Points:**
Antibodies are composed of proteins called immunoglobulins and there are five types of immunoglobulins: IgG, IgA, IgD, and IgE. Most of the antibodies are of the IgG class and this class is composed of IgG subclasses. The subclasses are designated as IgG1, IgG2, IgG3 and IgG4. While all the IgG subclasses contain antibodies, each subclass serves somewhat different functions in protecting the body against infection. The IgG circulating in the bloodstream is 60-70% IgG1, 20-30% IgG2, 5-8% IgG3 and 1-3% IgG4. The amount of the different subclasses varies with age.

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.

**Intravenous Immune Globulin (IVIg) therapy**

**Alzheimer’s Disease (AD)**
To date, published studies have focused on the safety of administering IVIg to patients with Alzheimer disease. Some cognitive outcomes have been reported as secondary outcomes but these have not been the focus of study. In 2013, Dodel et al published an industry-sponsored double-blind placebo-controlled dose-finding trial that included 58 patients with mild-to-moderate Alzheimer disease. Patients were assigned to one of eight groups. Injections of 0.2 g/kg, 0.5 g/kg, 0.8 g/kg, or placebo IVIg every four weeks, or half of this dose (or placebo) every two weeks for 24 weeks. There were five to seven 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 five of the six intervention groups. In the sixth group, those who received 0.4 g/kg every two 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 four (10%) patients in the intervention group and four (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 eight patients who had probable Alzheimer disease. After an initial test dose of 0.4 g/kg of IVG, patients were randomly assigned to six months of treatment with one of four doses (0.4 g/kg per two weeks, 0.4 g/kg per week, 1 g/kg per two weeks, 2 g/kg per four weeks). This was followed by a three-month washout period and an additional treatment period in which all patients received 1 g/kg every two weeks for months 10 to 12 and 0.4 g/kg every two weeks for months 13 to 18. All patients completed the study; only seven patients underwent sampling at the nine-month follow-up. Cerebrospinal fluid antibodies against beta-amyloid decreased significantly after six months of treatment, returned to baseline levels at the end of the three-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 six months of treatment, decreased to 23.9 at the end of the washout period, and was 24.0 after an additional nine months of treatment.

**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.

**Autism**

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

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

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

A 2012 systematic review by Huang and colleagues focused on IVIg for treating toxic epidermal necrosis (TEN). The authors identified 17 studies with a total of 221 with TEN treated with IVIg; five 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.

**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.

**Chronic Inflammatory Demyelinating Neuropathy (CIDP)**

CIDP is a labeled indication for IVIg. In 2010, Goebel and colleagues published a systematic review of RCTs on IVIg for treating CIDP. The authors identified nine RCTs meeting the following inclusion criteria: enrolled patients with definite or probably CIDP; compared IVIg to placebo, corticosteroid, or plasma exchange; reported a change from baseline in both a disability score and an electrophysiological measure, e.g., velocity, latency etc. Three of the trials compared IVIg with another active treatment and the other six were placebo-controlled. A pooled analysis of data from four of the six placebo-controlled trials found a significantly larger change in disability score with IVIg compared to placebo (standardized mean difference [SMD]: 0.65, 95% confidence interval [CI]: 0.23 to 1.08). Moreover, a pooled analysis of the proportion of patients with a response to treatment in these same studies also found a significantly greater benefit of IVIg versus placebo (relative risk [RR]: 2.74, 95% CI: 1.80 to 4.16). Data from studies comparing IVIg to an active treatment were not pooled. Limitations of the meta-analysis include that a variety of different disability scales and definitions of clinical response were used.
A 2012 multicenter double-blind RCT 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 six months of therapy. A total of three (13%) of patients in the IVIg group and 11 (52%) of patients in the corticosteroid group discontinued treatment over 6 months. The difference between groups was statistically significant favoring the IVIg group (RR: 0.54, 95% CI: 0.34 to 0.87). Secondary outcomes, including quality-of-life, time on 10-meter walk, grip strength, etc., did not differ significantly between groups, but the study may have been underpowered to detect clinically significant differences on these outcomes.

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

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

**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 six 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 five or higher on an 11-point scale (0-10 with 10=worst pain imaginable) for each of seven days they completed a diary. Patients received an infusion of IVIg and saline (two 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 six to 19 after each treatment. A total of 13 patients were randomized; data on pain after IVIg were missing for one 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.

**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 five 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.
**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 three patients. A subsequent randomized study of 22 patients focused on the short-term outcomes at two 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 Lambert-Eaton disease.

**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. Due to the findings of this study, and lack of other comparative trials, IVIg for demyelinating optic neuritis is considered investigational.

**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.

**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. The 2012 AAN guideline stated that IVIG is possibly effective and may be considered as a treatment for patients with Eaton-Lambert syndrome.

**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. 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.
**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.

**Guillain-Barre Syndrome (GBS)**
A Cochrane review Hughes and colleagues, updated in 2012, reviewed the results of randomized trials of immunotherapy for GBS. The review identified 12 randomized trials; none of these were placebo-controlled. Seven trials compared IVIg to plasma exchange (PE), three trials compared IVIg to supportive treatment only, and two trials compared PE and two compared IVIg to immunoabsorption (one of these compared the combination of IVIg and immunoabsorption to immunoabsorption only). Four trials included adults only, five included children only, one included both and two 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 four weeks. A pooled analysis of seven trials comparing IVIg to PE did not find a significant difference between groups in change in the number of disability grades at four 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 one or more grades. There were insufficient data to pool results for comparisons of IVIg with other types of alternative interventions or for a subgroup analysis by age. Most of the trials had small sample sizes. The largest trial was multicenter and randomized 383 adults older than 16 years of age to IVIg, PE, or the combination of IVIg and PE. The objectives of the trial were to establish that IVIg is equivalent to or superior to PE and to establish that PE followed by IVIg is superior to a single treatment. Non-inferiority was defined as no more than a 0.5-grade difference in change in disability grade at four weeks. At four 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 Guillain-Barre syndrome but that there is insufficient evidence to support or refute the use of IVIg in children.

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

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

**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/mm².

**Hyperimmunoglobulin E Syndrome**

Hyperimmunoglobulin E syndrome is a suspected genetic defect that produces high levels of the antibody immunoglobulin (IgE). This disorder is also known as Job syndrome and Hyper IgE syndrome. It is extremely rare and the cause is unknown. It causes serious skin and lung infections as well as eczema. The goal of treatment is to control the recurrent infection. Systemic antibiotics and antifungals are used both for prophylactic and symptomatic treatment in conjunction with topical therapy. Other treatment modalities include interferons, immunoglobulin supplementation and low-dose cyclosporine A.

**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 six randomized controlled trials (RCTs) and one nonrandomized trial of IVIg for adult ITP. Three of the trials compared IVIg with corticosteroids, and four trials evaluated different doses of IVIg. None of the trials compared IVIg with no therapy. The largest trial that compared IVIg with corticosteroids included 122 patients with severe acute ITP. The primary outcome, mean number of days with platelet count greater than 50 x 10⁹/L at day 21, was significantly higher in the IVIg group compared with the high-dose methylprednisolone group. Two other trials, one nonrandomized (IVIg versus corticosteroids) and one randomized (IVIg alone versus oral prednisone alone versus IVIg plus oral prednisone) found no difference in platelet counts greater than 50 x 10⁹/L at 48 hours or response rate between groups, respectively.

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

- Adult acute ITP with bleeding: IVIg strongly recommended as a part of multimodality therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.
- Adult acute ITP with severe thrombocytopenia but no bleeding: IVIg not recommended as 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. In particular, patients with a platelet count below 20 x 10^9/L despite treatment with corticosteroids should be considered for IVIg therapy. Also, the use of IVIg may be considered as a corticosteroid-sparing agent in patients who require long-term corticosteroids to maintain adequate platelet counts. For chronic ITP, the minimal dose of IVIg should be used that maintains a safe platelet count. Patients should be re-evaluated every three to six months, and alternative therapies to IVIg should be considered for patients who do not achieve a durable response for a minimum of two to three weeks.

**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.

**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 ten days after the onset of fever, is safe and effective in reducing the prevalence of coronary artery abnormalities. An RCT of single course IVIg (n=17) versus placebo (n=17) in patients with persistent active Wegener’s granulomatosis or microscopic polyangiitis associated with anti-neutrophil cytoplasmic antibody found significantly more responders in the IVIg treatment group at three months but no significant differences after three 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.

**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. Subsequent RCTs have reported similar results.
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.

**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. However, in 2002 the American Academy of Neurology (AAN) published a technology assessment on therapies for multiple sclerosis. 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.

**Myasthenia Gravis**
In 2012, a Cochrane systematic review was published on IVIg for myasthenia gravis. The review identified seven 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 two 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 and colleagues and compared IVIg to plasma exchange in 87 patients with an MG exacerbation. The study did not find a statistically significant difference in the efficacy of the two treatments, but found that IVIg was better tolerated. Nine patients experienced adverse events, eight in the plasma exchange group and one 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. Overall, the existing evidence supports the use of IVIg as a treatment option for myasthenia gravis.
Neonatal Sepsis (Prevention)
A 2013 Cochrane review addressed IVIg for the prevention of infection in preterm and/or low-birth weight infants. 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 ten studies.

In a pooled analysis of the findings of ten studies, IVIg was associated with a statistically significant reduction in sepsis (one 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 ten 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.

Neonatal Sepsis (Treatment)
Two systematic reviews of RCTs on IVIg for treatment of neonatal sepsis were identified. A 2013 Cochrane review identified eight trials comparing IVIg with placebo or no intervention. 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 eight 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 three 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.

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 nine countries. Infants receiving antibiotics for suspected or confirmed serious infection were randomly assigned to receive two 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 two years. By age two, 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 e.g., 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 two deaths) and ten in the placebo group (including four 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.
**Non-Infectious Uveitis**
Two small series of 18 and 10 patients, respectively, report measurable improvement in visual acuity after IVIg therapy. These two studies represent insufficient data to draw conclusions about efficacy; therefore, IVIg for non-infectious uveitis is considered investigational.

**Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)**
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 one 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 one-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 one-year follow-up. Given that there is only one small study, there are insufficient data to support the use of IVIg for PANDAS.

**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.

**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).

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

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

Common variable immunodeficiency (CVID) involves both B and T cell immune function. This disease presents with decreased immunoglobulin levels and abnormal antibody responses to antigens. Interestingly, CVID can affect any or all isotypes of immunoglobulin with specific antibodies affected due to inability to respond to antigen and there are diminished isoheamagglutinin 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. The search identified three 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 four weeks for IVIg or 100 to 150 mg/kg per week for SCIG [by subcutaneous infusion] in most patients.
- If there is end-organ damage, the dose and/or frequency of immune globulin can be increased.
- Patients with primary immune deficiency may require immune globulin therapy indefinitely.

Immunologic disorders of the T cell present with clinically, more severe disease that often lead to mortality in infancy or childhood. It is essential to diagnose these conditions early by screening for lymphopenia in cord blood at birth.

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

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.

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.

**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). 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. 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 seven days prior to transplant weekly until 100 days after transplant. 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. 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 ten 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.

**Recurrent Spontaneous Abortion**

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

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

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 multicenter RCT comparing heparin and low-dose aspirin with versus without IVIg in women with lupus anticoagulant, antiphospholipid antibody, or both, found no significant differences. In addition, an RCT of 58 women with at least four 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 non-randomized but controlled trials also report no benefit for IVIg treatment. There is insufficient evidence in RCTs or other trials to support benefit in secondary (live birth followed by consecutive spontaneous abortions) versus primary (no prior live births) spontaneous abortions. A variety of immunologic tests may precede the initiation of IVIg therapy. These tests, including various subsets of lymphocytes, human leukocyte antigen (HLA) testing, and lymphocyte functional testing (i.e., natural killer cell assays and the embryo cytotoxicity test), are research tools that explore subtle immunologic disorders that may contribute to maternal immunologic tolerance of the fetus. However no clinical data show that the results of these tests can be used in the management of patients to reduce the incidence of recurrent spontaneous abortion, particularly since IVIg therapy has not been shown to be an effective therapy.

**Refractory Dermatomyositis (DM)**

Dermatomyositis is an autoantibody end-complement attack against vascular endothelium. Clinically, patients develop weakness of the muscles and a skin rash. In 2012, Wang and colleagues published a systematic review of the literature on IVIg for treating adults with dermatomyositis/polymyositis. The authors identified 14 studies including two RCTs, nine prospective case series and three 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 Medical Research Council (MRC) scale. At three 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 six to eight weeks may be required to maintain a benefit.

An additional RCT was published in 2012 by Miyasaka and colleagues in Japan. The study included 26 patients with corticosteroid-resistant polymyositis/dermatomyositis who had received high-dose corticosteroid therapy for at least one month. Patients were randomly assigned to treatment with IVIg (n=12) or placebo (n=14) once daily for six consecutive days. The primary endpoint was the difference in mean manual muscle test (MMT) scores between baseline and eight 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.

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

Solid Organ Transplantation
Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common antibody-mediated rejection reaction (AMR) related to the presence of anti-donor antibodies. While ACR typically responds to immunologic therapy directed at T cells, AMR does not, and, as such, has also been referred to as “steroid-resistant rejection.” The risk of AMR is related to the presence of preformed allo-antibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of allo-antibodies is assessed by using a panel reactive antibody (PRA) screen, which combines the recipient’s serum with samples of antigen containing cells taken from 60 individuals representative of the potential donor pool. The percentage of PRA is
the percentage of positive reactions. Those with a PRA greater than 20% are referred to as “sensitized,” and these patients often have prolonged waiting times to identify a compatible donor. Living donor kidney transplants have also been performed using ABO mismatched donor organs. These recipients are also at risk of AMR. As an immunomodulatory agent, IVIg has been widely used in the prevention and management of AMR, often in conjunction with plasma exchange (see policy No. 8.02.02). For example, in patients at high risk for AMR, IVIg may be given prior to transplant to reduce the numbers of allo-antibodies and the risk of AMR, thus reducing the wait time for a compatible organ. IVIg may be one component of therapy after transplant if AMR develops.

One RCT of 30 patients published in 2001 suggested that IVIg is at least as good as anti-CD3 in combating corticosteroid-resistant rejection of kidney transplants. Later, in 2003-4, 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 four monthly infusions of IVIg or placebo prior to transplant. If transplanted, additional infusions were given monthly for four 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 eight 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 seven 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 three 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 two 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 three 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.

**Stiff Person Syndrome**

Dalakas et al randomized 16 patients with disease and anti-BAD65 autoantibodies to IVIg or placebo for three months. After a one-month washout period, patients were crossed over to three 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 six weeks to one year without additional treatment. Thus, results suggest benefit, but no other comparative trials or series data with at least ten patients are available for confirmation.

**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 one 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. Thus, IVIg for systemic lupus erythematosus is considered investigational.

**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 four months. Most (78%) had CVID, 22% had or X-linked agammaglobulinemia. One week after the last IVIg dose administered during a three to four baseline period, once-weekly SCIg therapy was administered for at least three 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, two serious bacterial infections (pneumonias) were reported in two 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 two 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). 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. The authors identified 20 studies; two 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 three 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 four 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.

**Chronic Inflammatory Demyelinating Polyneuropathy (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. Patients were randomized to SCIg at a dose comparable with their prestudy IVIg dose or to placebo (subcutaneous saline), two to three 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 two 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 one small trial comparing SCIg with placebo following IVIg for CIDP, SCIg for treatment of CIDP is considered investigational.

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

In 2013, a updated joint guideline on prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children was published. 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. Specific recommendations are discussed in appropriate sections of the Key Points.

**Key Words:**
Immune Globulin, Intravenous Therapy, IVIG, vivaglobin, subcutaneous immunoglobulin, SCIg

**Approved by Governing Bodies:**
Several IVIg products have been approved by the U.S. Food and Drug Administration (FDA). These include Carimune® (ZLB Bioplasma), Flebogamma® (Grifols), Gammagard® (Baxter), Gamunex-C® (Grifols), Octagam® (Octapharma), Polygam® S/D (Baxter) Privigen® (CSL Behring LLC) and BIVIGAM™ (Biotest Pharmaceuticals).

Several SCIg products have received FDA marketing approval for primary immunodeficiencies. These include Vivaglobin® (ZLB Behring LLC, Kankakee, IL), Hizentra® (ZLB Behring LLC, Kankakee, IL), Gamunex-C® (Grifols), and Gammaked® (Kedrion Biopharma, Cambridge, MA).

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member’s benefit plan.
Lowe’s Precertification Requirement—**Effective for dates of service on or after February 1, 2010** please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama’s medical policy does not apply for Lowe’s members for dates of service on or after February 1, 2010. This policy was in effect for Lowe’s prior to February 1, 2010).

**Current Codes:**
**CPT Codes:**
- 90281 Immune globulin (Ig), human, for intramuscular use
- 90283 Immune globulin (IgIV), human, for intravenous use
- 90284 Immune globulin (SCIG), human, for use in subcutaneous infusions, 100 mg, each
96365  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366   ;each additional 1 hour (List separately in addition to code for primary procedure)
96367   ;additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368   ;concurrent infusion (List separately in addition to code for primary procedure)
96369  Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
96370   ;each additional hour (List separately in addition to code for primary procedure
96371   ;additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure

HCPCS Codes:

J1459  Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1556  Injection, immune globulin (bivigam), 500 mg (effective 01/01/2014)
J1557  Injection, immune globulin, (GammaPlex), intravenous, non-lyophilized (e.g. liquid), 500 mg (effective 01/01/2012)
J1559  Injection, immune globulin (Hizentra), 100 mg
J1561  Injection, immune globulin, (Gamunex-C-Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562  Injection, immune globulin, (Vivaglobulin), 100 mg
J1566  Injection, immune globulin, intravenous, lyophilized (e.g. powder) not otherwise specified, 500 mg
J1568  Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1569  Injection, immune globulin, (Gammagard liquid), non-lyophilized, (e.g. liquid), 500 mg
J1572  Injection, immune globulin, (flebogamma/flebogamma DIF), intravenous, non-lyophilized (e.g. liquid), 500 mg
J1599  Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg (effective 01/01/2012)

Previous Codes:
CPT Codes

90765  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour (deleted 01/01/2009)
90766  ;each additional hour, up to 8 hours (list separately in addition to code for primary procedure) (deleted 01/01/2009)
90768  ;concurrent infusion (list separately in addition to code for primary procedure) (deleted 01/01/2009)
90769  Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump set-up and establishment of subcutaneous infusion site(s) (deleted 01/01/2009)
90770  ;each additional hour (list separately in addition to code for primary procedure) (deleted 01/01/2009)
90771  ;additional pump set-up with establishment of new subcutaneous infusion site(s) (list separately in addition to code for primary procedure) (deleted 01/01/2009)

References:
37. Department of Health & Human Services (DHHS) and Centers for Medicare & Medicaid Services (CMS), Program Memorandum: Intermediaries/Carriers, May 1, 2002.
47. Gaddipati, Sreedhar, Berkowitz, Richard L., Lembet, A. Arda, et al. Initial fetal platelet counts predict the response to intravenous gammaglobulin therapy in fetuses that are


Policy History:
Medical Policy Group, May 2002
Available for Comment May 31-July 15, 2002
Medical Policy Group, May 2005 (3)
Medical Policy Administration Committee, August 2005
Available for comment August 27-October 10, 2005
Medical Policy Group, September 2005 (1)
Medical Policy Administration Committee, October 2005
Available for comment October 12-November 28, 2005
Medical Policy Group, December 2005 (2)
Medical Policy Administration Committee, December 2005
Medical Policy Group, August 2006 (1)
Medical Policy Administration Committee, August 2006
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Medical Policy #043

Available for comment August 17-October 2, 2006
Medical Policy Group, November 2006 (1)
Medical Policy Administration Committee, November 2006
Available for comment November 7-December 21, 2006
Medical Policy Group, July 2007 (1)
Medical Policy Administration Committee, July 2007
Available for comment July 27-September 10, 2007
Medical Policy Group, February 2008 (1)
Medical Policy Administration Committee, February 2008
Available for comment February 29-April 14, 2008
Medical Policy Group, September 2009 (1)
Medical Policy Administration Committee, October 2009
Available for comment October 3-November 17, 2009
Medical Policy Group, June 2010 (1): Information added regarding Hizentra
Medical Policy Administration Committee, July 2010
Available for comment July 2-August 16, 2010
Medical Policy Group, August 2010, (1): Organized FDA labeled indications and off-label indications, added one new indication
Medical Policy Group, November 2010 (1): Coding update, added new code for Hizentra and unspecified code to policy.
Medical Policy Group, March 2012 (1): Update to Description, Policy, Key Points and References related to coverage and non-coverage effective 05/01/2012; Total policy reformatted
Medical Policy Administration Committee, March 2012
Available for comment March 15 – April 30, 2012
Medical Policy Group, April 2012 (1): Update to References related to article published in Neurology 2012 and authored by H.S. Patwa et al concerning IVIg and neuromuscular disorders
Medical Policy Group, May 2012 (1): Placed effective date of 5/1/2012 for specific lab values related to primary immunodeficiencies
Medical Policy Group, November 2012: 2013 Code Updates; verbiage change to #J1561, (removed gamunex) & J1569, (removed intravenous)
Medical Policy Group, January 2013 (2): Policy statement updated to documented serum IgG below the lower limits of normal on at least two occasions from <400 mg/dl or 2 standard deviationa below normal on two occasions.
Medical Policy Administration Committee, February 2013
Available for comments February 19 through April 5, 2013
Medical Policy Panel, June 2013
Medical Policy Group, September 2013 (1): Policy statement updated to add coverage for severe anemia due to parvovirus B19; update to Key Points, Governing Bodies and References
Medical Policy Administration Committee, September 2013
Available for comment September 4 through October 29, 2013
Medical Policy Group, January 2014 (1): 2014 Coding Update: added new HCPCS code, J1556 to coding section, effective 01/01/2014
Medical Policy Panel, May 2014
Medical Policy Group June 2014 (1): Policy statement, Key Points and References updated related to addition of coverage for prevention of infection in preterm and/or low birth weight neonates effective 05/01/2014, also added clarification statements in the investigational/non-covered conditions related to hemophagocytic syndrome and that SCIg would not be covered for other conditions except for what is listed

Medical Policy Administration Committee, July 2014
Available for comment July 11 through August 25, 2014

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.