Immune Globulin Therapy

Policy # 00170
Original Effective Date: 08/24/2005
Current Effective Date: 05/10/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Intravenous Immune globulin (IVIG) Therapy

Based on review of available data, the Company may consider intravenous immune globulin (IVIG) therapy to be **eligible for coverage**** for the following indications:

Primary Immunodeficiencies, including:

- Congenital agammaglobulinemia;
- Hypogammaglobulinemia;
- Common variable immunodeficiency;
- X-linked agammaglobulinemia (Bruton's);
- X-linked hyperimmunoglobulinemia M Syndrome;
- Severe combined immunodeficiency (SCID);
- Wiskott-Aldrich syndrome (WAS);
- Ataxia telangiectasia;
- IgG subclass deficiency: [IgG1, IgG2, or IgG3 > 2 standard deviations below the mean age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/ low IgA levels];
- Patients with primary immunodeficiency (PID) syndromes should meet all the following criteria for treatment with immune globulin:
    - Laboratory evidence of immunoglobulin deficiency;
    - Documented inability to mount an adequate immunologic response to inciting antigens;
    - Persistent and severe infections despite treatment with prophylactic antibiotics.

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Acute Humoral Rejection

Autoimmune Mucocutaneous Blistering Diseases, in patients with severe, progressive disease despite treatment with conventional agents (corticosteroids, azathioprine, cyclophosphamide, etc.)

- Pemphigus
- Pemphigoid
- Pemphigus vulgaris
- Pemphigus foliaceus
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Autoimmune and Inflammatory Disorders

- Dermatomyositis or polymyositis refractory to treatment with corticosteroids; in combination with other immunosuppressive agents
- Kawasaki syndrome

Neuroimmunological

- Severe refractory myasthenia gravis (MG) in patients with chronic debilitating disease in spite of treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine
- Myasthenic exacerbation (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange (PE)
- Guillain-Barre syndrome (GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP); in patients with progressive symptoms for at least two months
- Multifocal motor neuropathy (MMN)
- Eaton-Lambert myasthenic syndrome; in patients who have failed to respond to anticholinesterase medications and/or corticosteroids
- Stiff person syndrome not controlled by other therapies
- Patients with neuromyelitis optica as an alternative for patients with contraindication or lack or response to steroids or plasma exchange

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Hematologic

- Idiopathic thrombocytopenic purpura (ITP)
  - Treatment of acute, severe idiopathic thrombocytopenic purpura (ITP)
  - Treatment of chronic idiopathic thrombocytopenic purpura (ITP) in patients with at least 6 months' duration of disease, and with persistent thrombocytopenia (platelets <20,000 per microliter [adult] or 30,000 per microliter [child] despite treatment with corticosteroids and splenectomy
- Neonatal alloimmune thrombocytopenia
- Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)
- Patients undergoing/undergone hematopoietic cell transplantation who have immunoglobulin G (IgG) levels less than 400 mg/dL
- Chronic lymphocytic leukemia (CLL); in patients with IgG levels less than 400 mg/dL and persistent bacterial infections
- Warm antibody autoimmune hemolytic anemia, refractory to corticosteroids and immunosuppressive agents
- Anti-phospholipid syndrome
- Severe anemia due to human parvovirus B19
- Wegener Granulomatosis

Infectious Diseases

- HIV [human immunodeficiency virus]-infected children who have IgG levels less than 400 mg/dL to prevent opportunistic infections
- Toxic shock syndrome
- Patients with primary defective antibody synthesis

Transplantation

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

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When Services Are Considered Not Medically Necessary

The use of intravenous immune globulin (IVIG) therapy as a treatment of relapsing/remitting multiple sclerosis (MS) is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers other applications of intravenous immune globulin (IVIG) therapy including, but not limited to, the following conditions to be **investigational:***

- Chronic progressive multiple sclerosis (MS);
- Refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus;
- Recurrent spontaneous abortion (RSA)
- Inclusion-body myositis;
- Immune optic neuritis
- Myasthenia gravis (MG) in patients responsive to immunosuppressive treatment;
- Other vasculitides besides Kawasaki disease, including polyarteritis nodosa, Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases;
- Thrombotic thrombocytopenic purpura;
- Hemolytic uremic syndrome;
- Paraneoplastic syndromes, other than Eaton-Lambert myasthenic syndrome;
- Paraproteinemic neuropathy;
- Epilepsy;
- Chronic sinusitis;
- Asthma;
- Chronic fatigue syndrome;
- Acute myocarditis
- Refractory recurrent pericarditis;
- Aplastic anemia;

- Diamond-Blackfan anemia;
- Red cell aplasia;
- Acquired factor VIII inhibitors;
- Hemophagocytic syndrome (e.g. hemophagocytic lymphohistiocytosis);
- Acute lymphoblastic leukemia;
- Multiple myeloma;
- Immune-mediated neutropenia;
- Nonimmune thrombocytopenia;
- Cystic fibrosis;
- Recurrent otitis media;
- Diabetes mellitus;
- Behcet's syndrome;
- Adrenoleukodystrophy;
- Uveitis;
- Recent-onset dilated cardiomyopathy;
- Fisher syndrome;
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS);
- Autism spectrum disorder;
- Complex regional pain syndrome (CRPS);
- Alzheimer's disease (AD);
- IGG sub-class deficiency;
- Crohn's disease;
- Opsoclonus-myoclonus;
- Birdshot retinopathy;
- Epidermolysis bullosa acquisita;
- Necrotizing fasciitis;
- Polyradiculoneuropathy (other than CIDP);
- Postpolio syndrome;
- Neonatal sepsis (prophylaxis or treatment);
- Adult sepsis

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When Services Are Eligible for Coverage

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- *Medical necessity criteria and guidelines are met.*

Subcutaneous Immune Globulin (SCIG) Therapy

Based on review of available data, the Company considers SCIG for the treatment of primary immunodeficiencies (PID), including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency (CVID), severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS), and X-linked agammaglobulinemia (XLA) to be **eligible for coverage.****

- Note that patients with primary immunodeficiency (PID) syndromes should meet all the following criteria for treatment with immune globulin:
  - Laboratory evidence of immunoglobulin deficiency;
  - Documented inability to mount an adequate immunologic response to inciting antigens;
  - Persistent and severe infections despite treatment with prophylactic antibiotics.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of subcutaneous immune globulin (SCIG) for indications that are NOT listed in the SCIG patient selection criteria to be **investigational.***

Background/Overview

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

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

Intravenous infusion immune globulin is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. Intravenous immune globulin therapy 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 FDA for IVIG are listed in the coverage section. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., GBS), MG, MS, and solid organ transplantation.

This policy only addresses nonspecific pooled preparations of IVIG; it does not address other immunoglobulin preparations that are specifically used for passive immunization to prevent or attenuate infection with specific viral diseases such as respiratory syncytial virus, cytomegalovirus, or hepatitis B.

Subcutaneous infusion immune globulin is used for treating patients with 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. In recent years, other SCIG products have also received FDA-marketing approval.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Immune Globulin Therapy

Policy # 00170
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Several IVIG have been approved by the FDA. These include Carimune®‡ (ZLB Bioplasma), Flebogamma®‡ (Grifols), Gammagard®‡ (Baxter), Gamunex-C®‡ (Griffols), Gamastan S/D®‡ (Griffols), Gammaplex®‡ (Bio Products Lab), Octagam®‡ (Octapharma), Polygam S/D®‡ (Baxter), Privigen®‡ (CSL Behring LLC), Bivigam®‡ (Biotest Pharmaceuticals), Panzyga®‡ (Octapharma), and Asceniv®‡ (Adma Biologics).

Several SCIG products have received FDA marketing approval for PID. These include Vivaglobin®‡ (ZLB Behring LLC, discontinued by the company in 2013), Gammagard Liquid (Baxter), Hizentra®‡ (ZLB Behring), Gamunex-C®‡ (Talecris Biotherapeutics, Inc), Gammaked®‡ (Kedrion Biopharma), Cuvitru®‡ (Baxalta), Hyqvia®‡ (Baxter), Cutaquig®‡ (Octapharam), and Xembify®‡ (Griffols).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Intravenous Immune Globulin Therapy

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

Primary Immune Deficiency

Primary humoral immunodeficiency deficiencies refer to diseases resulting from impaired antibody production because of a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Antibody deficiency characteristically leads to recurrent, often severe upper and lower respiratory tract infections. Findings associated with severe primary humoral immunodeficiencies

include failure to thrive, chronic diarrhea, recurrent fever, nodular lymphoid hyperplasia in the gut, and hepatosplenomegaly.

In 2010, the National Advisory Committee on Blood and Blood Products (NAC) and Canadian Blood Services (CBS) published a guideline on use of immunoglobulin therapy for patients with primary immune deficiency; recommendations were based on a systematic review of evidence by a panel of experts. The search identified 3 RCTs, several cohort studies, and numerous case series.

For individuals with immunodeficiencies, both IVIG and SCIG are effective. Use of SCIG for the treatment of primary immunodeficiencies was approved by the FDA based on an open-label, nonrandomized, prospective, multicenter study. Generally, many 10% IVIG solutions can be administered subcutaneous or intravenous but more concentrated products (eg, 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse effects and provides more stable serum IgG levels. In contrast, SCIG have not been studied as extensively in autoimmune/inflammatory disorders.

Autoimmune Mucocutaneous Blistering Diseases
Autoimmune mucocutaneous blistering diseases are a group of conditions that manifest with blisters on the skin or mucous membranes and include pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, and linear IgA dermatosis.

The evidence base to support IVIG treatment for refractory pemphigus include several uncontrolled studies and case series, 1 RCT, and a 2010 systematic review. The multicenter, placebo-controlled, double-blind trial randomized adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥20 mg/d) to a single cycle of IVIG 400 mg/kg/d for 5 days, IVIG 200 mg/kg/d for 5 days, or a placebo infusion for 5 days. The primary end point was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (ie, time to escape protocol). Time to escape protocol was significantly longer for patients in the IVIG 400-mg group than for patients in the placebo group but not between the IVIG 200-mg group and the placebo group. Furthermore, a significant decrease in a pemphigus activity score was detected at all study observation points for patients in the IVIG 400-mg group and at all study observation points after day 15 in the IVIG 200-mg group. The pemphigus activity score did not decrease significantly at any time point in the placebo group. The 2010 systematic review

identified 23 studies evaluating IVIG for autoimmune mucocutaneous blistering diseases (22 case series, 1 RCT). The studies included a total of 260 patients treated with IVIG: 191 patients had pemphigus and 69 patients had pemphigoid. Of the 260 patients, 245 (94%) improved after IVIG treatment.

Several systematic reviews focused on IVIG for TEN and/or SJS. Most recently, in 2015, Barron et al identified 13 studies of patients who met diagnostic criteria for TEN or SJS and received IVIG alone or in combination with other medications. Eight studies included a control group, but none were RCTs. All control patients received corticosteroids and, in 4 of the studies, patients in the IVIG group received concomitant corticosteroid therapy. A meta-analysis of all included studies did not find a statistically significant benefit of IVIg therapy for mortality (standardized mortality ratio [SMR], -0.32; 95% CI, -0.77 to 0.12). Logistic regression analyses found that there were reductions in SMR as dosage of IVIG increased. A sensitivity analysis with the 2 studies that used the lowest doses of IVIg excluded found a statistically significant reduction in SMR in IVIG-treated groups (SMR=0.70; 95% CI, 0.51 to 0.96).

Previously in 2012, Huang and colleagues focused on IVIG for treating TEN. The authors identified 17 studies with a total of 221 with TEN treated with IVIG; 5 studies were retrospective, non-randomized controlled studies, and the remaining 11 studies were case series. Twelve out of the 17 studies supported use of IVIG. Overall, the mean time from initiation of IVIG to response was 2.4 days, and the mean time from initiation of IVIG to remission was 10.9 days. The mean length of hospital stay was 17.4 days, and the mortality rate was 19.9%. In summary, the literature available to date has shown that IVIG can be efficacious in the treatment of AMBDs and can be a corticosteroid-sparing agent.

Dermatomyositis and Polymyositis

In 2012, Wang et al published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis. Reviewers identified 14 studies including 2 RCTs, 9 prospective case series, and 3 retrospective case series. Eleven of 14 studies included patients with refractory disease. For example, a 1993 trial by Dalakas et al compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis. At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified MRC scale and the Neuromuscular Symptom Scale (NSS) (mean modified MRC scale score, 84.6 IVIG

vs 78.6 placebo; mean NSS score, 51.4 IVIG vs 45.7 placebo). Repeated transfusions every 6 to 8 weeks can be required to maintain a benefit.

Miyasaka et al (2012) in Japan conducted an RCT of 26 patients with corticosteroid-resistant polymyositis or dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month. Patients were randomly assigned to treatment with IVIG (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary end point was change from baseline mean manual muscle test (MMT) scores at 8 weeks. Change in mean MMT was 11.8 points in the IVIG group versus 9.9 points in the placebo group. This difference was not statistically significant (1.9 points; 95% CI, -4.8 to 8.5). Other outcomes also did not differ significantly between groups.

A case series of 35 patients with polymyositis, all of whom had disease that required ongoing glucocorticoid therapy and none could be weaned from glucocorticoids despite trials of 1 or more additional therapies, showed some clinical benefit; 33 patients with initially elevated serum creatine kinase levels showed biochemical improvement; 25 of 35 showed improvement in muscle strength, which returned to near-normal in 10 of the 25 responders; 8 of 11 patients with esophageal dysfunction showed resolution of dysphagia; 12 of the 25 responders had complete clinical responses (absence of myositis activity) while receiving not more than prednisone 6 mg/d. Mean follow-up for these patients was 39 months. Five patients discontinued all other medical treatments for myositis.

Kawasaki Disease
Kawasaki disease is among the most common vasculitides of childhood; it is characterized by fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. It is typically self-limiting but may cause cardiovascular complications, particularly coronary artery aneurysms, which can lead to coronary occlusion and cardiac ischemia ultimately leading to significant morbidity and even death. Therefore, early treatment is essential. Although the mechanism of action of IVIG is not understood, its use early in the course of disease has reduced the prevalence of coronary artery abnormalities.

Multiple RCTs and meta-analysis have demonstrated efficacy of IVIG in preventing cardiac consequences of Kawasaki disease in children. A 2003 systematic review of RCTs identified 59 trials in the initial search and included 16 trials for meta-analysis using relative risk for dichotomous data or weighted mean difference for continuous data. Results showed a significant decrease in new

coronary artery abnormalities in favor of IVIG compared to placebo at 30 days (RR=0.74; 95% CI, 0.61 to 0.90). Reviewers concluded that children fulfilling the diagnostic criteria for Kawasaki disease should be treated with IVIG (2 gm/kg single dose) within 10 days of onset of symptoms.

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation
Myasthenia gravis (MG) is a relatively rare autoimmune disorder in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction of skeletal muscles resulting in characteristic patterns of progressively reduced muscle strength with repeated use and recovery of muscle strength after a period of rest.

In 2012, a Cochrane systematic review was published on IVIG for treating acute exacerbations or for chronic long-term MG. Reviewers identified 7 RCTs including 1 unpublished trial, all of which investigated short-term benefit. The trials varied in inclusion criteria, comparator interventions, and outcome measures and, thus, study findings were not pooled. Five trials evaluated IVIG for treating MG worsening or exacerbation, and 2 evaluated IVIG for treatment of moderate or severe MG. Several trials were small, with insufficient statistical power. Reviewers concluded that there was some evidence for efficacy in exacerbations of MG, and that evidence for treating chronic MG was insufficient to form conclusions about efficacy.

Zinman et al (2007) is the only RCT that compared IVIG to placebo in 51 patients with MG with progressive weakness. The primary outcome measure was the difference between arms in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity from baseline to days 14 and 28. In IVIG-treated patients, a clinically meaningful improvement in QMG Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a QMG Score for Disease Severity greater than 10.5. Remaining RCTs either compared IVIG with plasma exchange or compared 2 doses of IVIG. Gajdos et al (1997) compared IVIG with plasma exchange in 87 patients with MG exacerbations. The study did not find a statistically significant difference in the efficacy between the 2 treatments, but found that IVIG was better tolerated. Nine patients experienced adverse events (8 in the plasma exchange group, 1 in the IVIG group). Barth et al (2011) compared IVIG with plasma exchange in 84 patients with moderate-to-severe MG. The study also did not find a statistically significant difference in the efficacy between both treatments. Gajdos et al (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of MG. Mean improvement in the myasthenic muscular scores

did not differ significantly between doses after 2 weeks. The trial by Schuchardt (2002) was not published and therefore not summarized here.

Guillain-Barré Syndrome
Guillain-Barré syndrome is a heterogeneous condition with several variant forms and encapsulates many acute immune-mediated polyneuropathies. It is characterized by a rapid-onset of muscle weakness caused by the immune system damaging the peripheral nervous system.

A Cochrane review by Hughes et al, updated in 2014, reviewed the results of randomized trials of immunotherapy for GBS. Reviewers identified 12 randomized trials; none was placebo-controlled. Seven trials compared IVIG with plasma exchange, 3 trials compared IVIG with supportive treatment only, 2 trials compared plasma exchange, and 2 compared IVIG with immunoabsorption (1 compared of IVIG plus immunoabsorption to immunoabsorption only). Four trials included adults only, 5 included children only, 1 included both, and 2 included adults and possibly children. The primary outcome of the review was change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIG with plasma exchange did not find significant differences between groups in change in the number of disability grades at 4 weeks (MD = -0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIG versus plasma exchange (eg, number of patients who improved by ≥1 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. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR=0.14; 95% CI, 0.05 to 0.36).

Most trials had small sample sizes. The largest was a 1997 multicenter, randomized trial of 383 adults that compared IVIG, plasma exchange, and combination IVIG plus plasma exchange. The objectives of the trial were to establish that IVIG is equivalent or superior to plasma exchange and to establish that plasma exchange followed by IVIG is superior to a single treatment. Noninferiority was defined as no more than a 0.5-grade difference in change in disability grade at 4 weeks. At 4 weeks, the difference in improvement between the IVIG group and plasma exchange group was 0.09 grade (95% CI, -0.23 to 0.42); this met the predefined criterion for equivalence of these treatments. Differences were 0.29 grade (95% CI, -0.04 to 0.63) between the IVIG plus plasma exchange group and the IVIG only group, and 0.20 grade (95% CI, -0.14 to 0.54) between the IVIG plus plasma

exchange group and the plasma exchange only group. Thus, neither combined treatment groups was superior to either treatment alone.

Miller Fisher syndrome is a variant of GBS characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). A 2007 Cochrane systematic review evaluated acute immunomodulatory therapies in Fisher syndrome or its variants. No RCTs were identified.

Chronic Inflammatory Demyelinating Polyneuropathy

Intravenous

In 2013, Eftimov et al published a Cochrane review of RCTs on IVIG for treating CIDP. Reviewers identified 8 RCTs that enrolled 332 patients with definite or probable CIDP and that compared IVIG with placebo, corticosteroid, or plasma exchange. Three trials compared IVIG with another active treatment, and the other 5 were placebo-controlled (n=235). The primary trial outcome was the proportion of participants with a significant improvement in disability within 6 weeks of starting treatment. Studies used a variety of disability measures. When possible, Cochrane reviewers transformed the data on disability to a modified 6-point Rankin Scale for disability. Data from the 5 placebo-controlled RCTs were pooled. The pooled relative risk for improvement in the IVIG group compared with the placebo group was 2.40 (95% CI, 1.72 to 3.36; $p<0.001$). When data were pooled from 3 studies on IVIG versus placebo in which the disability measures could be converted to the Rankin Scale, the relative risk was similar (2.40) but not statistically significant (95% CI, 0.98 to 5.83; $p=0.054$). Pooled analyses of data from these 3 placebo-controlled studies found a statistically higher rate of any adverse event with IVIG, but not serious adverse events. Data from studies comparing IVIG with an active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

ICE, the largest study included in the meta-analysis, was a double-blind multicenter trial that randomized 117 patients to IVIG or placebo. The primary outcome measure was proportion of patients showing clinically meaningful improvement in disability at week 24. Results showed that the proportion of patients meeting the primary end point was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase

were rerandomized to IVIG or placebo. Relapse rates were significantly lower for patients treated with IVIG (13% vs 45%; hazard ratio, 0.19; 95% CI, 0.05 to 0.70). Benefits of IVIG treatment extended to as long as 48 weeks with maintenance treatments of 1 g/kg every 3 weeks.

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

SubQ
In the randomized, double-blind, placebo-controlled, phase 3 PATH trial, van Schaik et al (2018) studied the relapse rates in 172 patients with CIDP given SCIG and placebo. Patients were randomized in a 1:1:1 ratio to a placebo group (n=57 [33%]), a low-dose group (n=57 [33%]), and a high-dose group (n=57 [33%]). The trial found that both SCIG doses were effective and well-tolerated, suggesting that either can be used as maintenance treatment for CIDP. Seventy-seven patients withdrew from the trial due to relapse- or other reasons: 36 (63%; 95% CI, 50% to 74%) placebo patients, 22 (39%; 95% CI, 27% to 52) low-dose SCIG patients, and 19 (33%; 95% CI, [22% to 46) high-dose patients ($p<0.001$). The trial was limited by missing patient data and inadequate follow-up of those who withdrew.

One crossover RCT comparing IVIG and SCIG for CIDP was identified; this trial by Markvardsen et al (2017) included 20 patients. Patients underwent 10 weeks of treatment with SCIG and IVIG, in random order, for a total intervention duration of 20 weeks. The primary efficacy outcome was change in isokinetic muscle strength. Fourteen (20%) of 20 patients completed the trial. Isokinetic muscle strength increased by 7.4% with SCIG and 14% with IVIG; the difference between groups was not statistically significant. Conclusions about the relative efficacy of SCIG and IVIG cannot be drawn from this trial due to the small sample size, high dropout rate, short-term follow-up, and the crossover design without a washout period.

Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (eg, 45% of patients withdrew from the trial). Another RCT demonstrated that the use of SCIG for the maintenance of CIPD might be effective, with relatively low adverse events, but this trial also had a

number of limitations (eg, small sample, 30% dropout rate). Additional direct comparisons, particularly in parallel-group RCTs, are needed.

Multifocal Motor Neuropathy
Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities, a presentation similar to that of motor neuron disease. The benefit of IVIG for MMN has been demonstrated in 4 RCTs (total N=53 patients).63-66 The largest of the 4 RCTs randomized 19 patients with MMN with persistent conduction block to IVIG or placebo. Response to treatment was assessed by measuring Medical Research Council (MRC) score in 28 muscles; a responder was defined as at least 1 more MRC point in 2 affected muscles plus 1 point less in 2 activities of daily life compared with baseline. At 4 months, 7 of 9 patients who received IVIG responded compared with 2 of 9 patients treated with placebo. Von Schaik et al (2005) included 4 RCTs (total N=34 patients) in a meta-analysis to assess the efficacy and safety of IVIG in MMN. Strength improved in 78% of patients treated with IVIG versus 4% in placebo-treated patients. Disability improved in 39% and 11%, respectively (p=NS). Mild, transient side effects were reported in 71% of IVIG-treated patients. Serious side effects were not encountered.

Eaton-Lambert Myasthenic Syndrome
Eaton-Lambert myasthenic syndrome 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 most commonly with small-cell lung cancer.

One crossover RCT of 9 patients treated with IVIG therapy (1 g/kg/d for 2 days) or placebo showed statistically significant improvements in serial measurements of limb, respiratory, and bulbar muscle strength associated with IVIG treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude.68 A number of noncomparative studies have substantiated clinical benefits.

Stiff Person Syndrome
Stiff person syndrome is rare acquired neurologic disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, resulting in severely impaired ambulation. It is caused by increased muscle activity due to decreased inhibition of the central nervous system.

If left untreated, it can progress to cause difficulty walking and significantly impact a person's ability to perform routine, daily tasks.

Multiple case reports have suggested that patients with stiff person syndrome may benefit from IVIG. The benefit was confirmed in a small crossover randomized comparing IVIG with placebo in 16 patients with stiff person syndrome and anti-GAD65 autoantibodies. After a 1-month washout period, patients were crossed over to 3 months of the alternative treatment. Stiffness scores decreased significantly on IVIG, but not on placebo, regardless of order. Eleven (69%) patients were able to walk more easily or without assistance; the frequency of falls decreased, and patients were able to perform work-related or household tasks. The duration of benefit lasted 6 weeks to 1 year without additional treatment.

Neuromyelitis Optica
Neuromyelitis optica is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Previously considered a variant of multiple sclerosis, it is now recognized as a distinct clinical entity.

There are no published clinical trials demonstrating efficacy of IVIG treatment in NMO. Published literature consists of case reports and case series. A retrospective review of 10 patients treated with IVIG for acute relapses after lack of response to steroids with or without plasma exchange showed improvement in about 50% of patients. A case series of 9 Spanish NMO patients showed positive results using bimonthly IVIG treatment (0.7 g/kg body weight per day for 3 days) for up to 2 years.

Idiopathic Thrombocytopenic Purpura
Idiopathic thrombocytopenic purpura, also known as primary immune thrombocytopenia, is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. It is a more common cause of thrombocytopenia in otherwise asymptomatic adults.

In 2007, NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including ITP, based on 6 RCTs and 1 nonrandomized trial of IVIG for adult ITP. Three of the trials compared IVIG with corticosteroids, and 4 trials evaluated different doses of IVIG. None 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 $x10^9$/L at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG vs corticosteroids) and 1 randomized (IVIG alone vs oral prednisone alone vs IVIG plus oral prednisone) found no difference in platelet counts greater than $50x10^9$/L at 48 hours or in response rates between groups, respectively.

Neonatal 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 (ICH) is identified in 10% to 30% of affected neonates. Currently, screening for this condition is unavailable and, thus, thrombocytopenia is only identified at birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia and the severity of thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIG.

There are no RCTs evaluating the efficacy of IVIG or steroids alone versus placebo in alloimmune thrombocytopenia. Trials of this nature would be unethical because of the known risk of ICH with this condition. Rayment et al (2011), in a Cochrane systematic review, summarized the results of 4 RCTs on the maternal administration of corticosteroids and IVIG in pregnancies with neonatal alloimmune thrombocytopenia in 206 patients. Reviewers concluded that the optimal management of fetomaternal alloimmune thrombocytopenia remains unclear. Lack of complete data sets for 2 trials and differences in interventions precluded the pooling of data from these trials. Bussel et al did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids. Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because 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 platelet count of 69,000/mL. There were no instances of ICHs, although hemorrhage had occurred previously in 10 untreated siblings. Berkowitz et al did not demonstrate a difference in standard risk pregnancies but did demonstrate that IVIG and prednisone was more effective in raising the fetal platelet count in high-risk pregnancies. The Berkowitz et al trial in 2007 showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies. Paridaans et al (2015) evaluated the effectiveness of a lower dose of IVIG (0.5 g/kg/wk vs 1 g/kg/wk)

in a RCT of 23 women. The primary outcome was fetal or neonatal ICH. The median newborn platelet count was 81×10^9/L in the 0.5-g/kg group versus 110×10^9/L in the 1-g/kg group (p=0.644).

Hematopoietic Stem Cell Transplantation
Hematopoietic cell transplantation is the intravenous infusion of hematopoietic stem and progenitor cells designed to establish marrow and immune function in patients with various acquired and inherited malignant and nonmalignant disorders.

The initial use of immunoglobulin for prophylaxis in HCT was based on the 1990 RCT by Sullivan et al in 369 patients undergoing HCT. The trial showed that neither survival nor risk of relapse was altered by IVIG. However, IVIG treatment was associated with a reduction in the incidence of acute graft-versus-host disease compared to controls (51% vs 34%) and deaths due to transplant-related causes after transplantation of human leukocyte antigen (HLA)-identical marrow (46% vs 30%). There were many methodologic flaws in the trial, including lack of control for type 1 error for multiple comparisons, inclusion of a heterogeneous group of patients, and lack of a placebo control. Subsequent to this pivotal trial, multiple trials have been conducted and systematic reviews have assessed the efficacy of immunoglobulin prophylaxis in HCT to prevent infection and prolong survival. The most recent systematic review and meta-analysis (2009) included 30 trials with 4223 patients undergoing HCT. There was no difference in all-cause mortality between IVIG and cytomegalovirus-IVIG compared to controls (relative risk [RR], 0.99; 95% confidence interval [CI], 0.88 to 1.12; RR=0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections with IVIG compared to control (RR=1.00; 95% CI, 0.90 to 1.10). Reviewers concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection and therefore routine use of IVIG prophylaxis in patients undergoing HCT is not recommended.

Chronic Lymphocytic Leukemia
Chronic lymphocytic leukemia is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes and most patients develop hypogammaglobulinemia at some point in the course of their disease. Patients experiencing recurrent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of IVIG.

Multiple trials and a meta-analysis comparing IVIG to placebo have shown decreased bacterial infections but not decreased mortality. IVIG has not been directly compared with the use of prophylactic antimicrobials. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. Treatment with IVIG has not been show to increase quality of life or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both. Although minor or moderate bacterial infections were significantly less common in patients receiving IVIG, there was no impact on the incidence of major infections, mortality, or nonbacterial infections.

Warm Antibody Autoimmune Hemolytic Anemia
Also known as autoimmune hemolytic anemia, antibody autoimmune hemolytic anemia occurs commonly due to IgG antibodies that react with protein antigens on the red blood cell surface at body temperature. Published literature on the use of IVIG in warm antibody autoimmune hemolytic anemia is limited to observational data for 37 patients pooled from 3 institutions and a case report. Overall, 29 (39.7%) of 73 patients responded to IVIG therapy. Because of limited therapeutic value, it is used in patients refractory to conventional therapy with prednisone and splenectomy or as a conjunctive therapy in patients with very severe disease. Further, the effect is usually transient, unless repeated courses are given every 3 weeks.

Antiphospholipid Syndrome
Antiphospholipid syndrome is an autoimmune disease that results from the development of antibody against phospholipids protein, which causes venous or arterial thromboses and/or pregnancy morbidity.

Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry. Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received triple therapy of anticoagulants, corticosteroids, plasma exchange, and/or IVIGs compared to combinations that did not use plasma exchange, IVIG, or both.

Severe Anemia Associated With Human Parvovirus B19
Human parvovirus B19 is a common single-stranded DNA virus. Infections are usually mild or asymptomatic, and do not require treatment. In some cases, infection can lead to sufficiently severe complications such as transient aplastic crisis in which case treatment is indicated and may be lifesaving.

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 et al, retrospectively reported on 10 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 9 of 10 patients. Four patients had adverse effects associated with IVIG (2 cases of acute reversible renal failure, 2 cases of pulmonary edema). In the same article, Crabol et al reported on findings of a literature search in which they identified 123 cases of pure red cell aplasia treated with IVIG (other than the 10 patients in their series). Among 86 (70%) of 123 patients available at 12-month follow-up, hemoglobin was corrected in 36 (42%) patients, and the remaining 50 (58%) patients had persistent anemia.

Granulomatosis With Polyangiitis (Wegener Granulomatosis)
The success of IVIG therapy for Kawasaki disease led to investigation of IVIG therapy in other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This trial, published by Jayne et al, compared single course IVIG (n=17) with placebo (n=17) and found significantly more responders in the IVIG treatment group at 3 months but no significant differences after 3 months or in the frequency of relapse or use of other medications.

HIV-Infected Children
Prevention of opportunistic infections remains a critical component of care for HIV-infected children even though availability of combination antiretroviral therapies have substantially and dramatically decreased AIDS-related opportunistic infections and deaths.

A double-blind RCT published in 1991 allocated 372 HIV-infected children to IVIG or placebo every 28 days. Median length of follow-up was 17 months. Results were stratified by CD4+ counts ($\geq 0.2\times10^9$/L or $<0.2\times10^9$/L). After 24 months, for children with CD4+ counts of 0.2×10^9/L or

greater, IVIG treatment compared to placebo significantly increased infection-free rates (67% vs 48% respectively; p<0.05); reduced overall the number of serious and minor bacterial infections (RR=0.68; p<0.05); and reduced the number of hospitalizations for acute care (RR=0.65; p<0.05). The effect was less marked in children with CD4+ counts of less than 0.2×10^9/L. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children have recommended IVIG to prevent serious bacterial infections in HIV-infected children who have IgG levels less than 400 mg/dL. The guidelines for the prevention and treatment of serious opportunistic infections in HIV-infected adults and adolescents do not give such recommendations.

Toxic Shock Syndrome
Toxic shock syndrome is also called as Streptococcal toxic shock syndrome. Streptococcal toxins induce the release of inflammatory cytokines, which cause capillary leakage and tissue damage resulting in shock, multiorgan failure, and death.

The evidence for use of IVIG treatment for toxic shock syndrome is limited and includes 1 small RCT and multiple observational studies. IVIG is used for treatment of septic shock syndrome to boost antibody levels via passive immunity. The 2003 RCT allocated 21 adults with toxic shock syndrome to IVIG or to placebo. Mortality rates were 10% and 36%, respectively, but the difference in mortality rates was not statistically significant. However, the study was originally planned to enroll 120 patients, so was likely underpowered to detect any significant differences. In a 2014 prospective observational study, 23 patients receiving IVIG therapy were compared 44 patients who received placebo. The odds ratio for survival was 5.6 for IVIG versus placebo (p=0.03). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls. While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups pose difficulties when interpreting the results. A 2009 retrospective study including 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG.

Solid Organ Transplantation
Acute rejection after transplant can be broadly divided into two categories, the more common acute cellular rejection (ACR) related to activation of T cells and the less common AMR reaction 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 PE. 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. Intravenous immune globulin therapy 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 National Institutes of Health (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. Intravenous immune globulin therapy significantly reduced PRA levels in study subjects compared to placebo, resulting in a higher transplant rate. For example, a total of 24 patients subsequently underwent transplant, 16 in the IVIG group and 8 in the placebo group. There was acceptable graft survival in both groups. Desensitization protocols varied among transplant centers; certain protocols commonly used are referred to as the Cedars-Sinai protocol and the Johns Hopkins protocol. The Cedars-Sinai protocol consisted of high-dose IVIG (2 g/kg) and was offered to patients awaiting either a deceased or live donor. The Johns Hopkins protocol consisted of low-dose IVIG (100 mg/kg) in combination with plasmapheresis with or without treatment with anti-CD-20 (i.e., Rituxan).

A retrospective cohort study published in 2009 compared outcomes in pediatric liver transplant patients entered into a multicenter Registry who did (n = 336) and did not (n = 1,612) receive IVIG within 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 AMR, IVIG is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. Intravenous immune globulin therapy 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 AMR. 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.

Prophylaxis of Neonatal Sepsis
A 2013 Cochrane review addressed IVIG for the prevention of infection in preterm and/or low birth weight infants. Investigators identified 19 RCTs that compared IVIG to placebo or no intervention for approximately 5000 preterm (<37 weeks of gestational age) and/or low birth weight (<2500 g) infants. Five of the 19 studies were considered to be high quality; the remaining studies had potential biases (eg, lack of caregiver blinding in 10 studies). In meta-analysis of 10 studies, IVIG was associated with a statistically significant reduction in sepsis (≥1 episodes; RR=0.85; 95% CI, 0.75 to 0.98). Moreover, meta-analysis of 16 studies showed a significant reduction in serious infection (≥1 episodes) with IVIG (RR=0.82; 95% CI, 0.74 to 0.92). However, IVIG was not associated with a significant reduction in mortality. Meta-analysis of 15 studies that reported all-cause mortality found a relative risk of 0.89 (95% CI, 0.75 to 1.05), and meta-analysis of 10 studies that reported mortality due to infection found a relative risk of 0.83 (95% CI, 0.56 to 1.22). Reviewers noted that a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without reduction in other clinically important outcomes, including mortality, were of marginal clinical importance. No major adverse effects related to IVIG administration were reported.

Treatment of Neonatal Sepsis
A 2015 Cochrane review identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or proven infection. Studies included a total of 3973 infants; the largest trial had a sample size of 3493 and contributed 90% of the data. Meta-analysis of all 9 trials found no statistically significant difference in mortality rate with IVIG versus control (RR=0.95; 95% CI, 0.80 to 1.13). Meta-analysis of 3 trials found that IVIG significantly reduced the length of the hospital stay compared with a control intervention (mean difference [MD], -4.08; 95% CI, -6.47 to -1.69). Results were not pooled for other outcomes.

The trial with the large sample size was published by the International Neonatal Immunotherapy Study group in 2011; it was conducted in 9 countries. Infants receiving antibiotics for suspected or confirmed serious infection were randomly assigned to receive 2 infusions of IVIG at a dose of 500 mg/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 (according to

predefined criteria) at age 2 years. By age 2, 686 (39%) of 1759 children in the IVIG group had died or had major disability compared with 677 (39%) of 1734 children in the placebo group (RR=1.00; 95% CI, 0.92 to 1.08). There were also no statistically significant differences in the primary outcome when prespecified subgroups (eg, birthweight, gestational age at birth, sex) were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIG group (including 2 deaths) versus 10 in the placebo group (including 4 deaths).

Sepsis in Adults
A 2016 published meta-analysis that pooled 18 RCTs showed that use of IVIG reduced the mortality risk of septic patients by half (odds ratio [OR], 0.50; 95% CI, 0.34 to 0.71) However, there was a preponderance of small low quality studies in the evidence base, which was further complicated by heterogeneous dosing regimens and types of IVIG preparations used across studies that were conducted over a long time horizon. Reviewers concluded that the evidence did not support widespread use of IVIG as adjunctive therapy for sepsis in adults.

Relapse-Remitting Multiple Sclerosis
Relapsing-remitting multiple sclerosis (RRMS) is an immune-mediated inflammatory disease that attacks and destroys myelinated axons in the central nervous system, resulting in variable degrees of physical disability characterized by symptomatic episodes that occur months or years apart and affect different anatomic locations.

A 1998 TEC Assessment concluded that IVIG therapy for RRMS met TEC criteria.82 However, by 2002, AAN was recommending the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation). AAN suggested that IVIG was no longer considered a drug of choice for RRMS.

Systemic Lupus Erythematosus
Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has protean manifestations and follows a relapsing and remitting course. It is characterized by an autoantibody response to nuclear and cytoplasmic antigens. SLE can affect any organ system, but it mainly attacks the skin, joints, kidneys, blood cells, and nervous system.

IVIG therapy is proposed for SLE because of its immunomodulatory properties and also because it prevents infection in patients taking immunosuppressive drugs. A 2014 systematic review by Sakthiswary et al identified 13 studies on IVIG for treatment of SLE. Three studies had control groups, and only 1 was an RCT. Most studies had small sample sizes; only 3 had more than 50 patients, and the single RCT included only 14 patients. In a meta-analysis of 6 studies (n=216 patients), there was a statistically significant difference in SLE disease activity in IVIG-treated groups (SMD=0.58; 95% CI, 0.22 to 0.95). This analysis was limited because there were few data in non-IVIG treated patients. A meta-analysis of data from 8 studies on the effect of IVIG on complement levels found a pooled response rate of 30.9% (95% CI, 22.1% to 41.3%). Findings on other outcomes were not pooled. However, there has been limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE.

Immune Optic Neuritis
Optic neuritis is an inflammatory demyelinating condition that causes acute, usually monocular, visual loss. It is associated with multiple sclerosis, occurring in 50% of individuals at some time during the course of their illness.

Two RCTs have studied the potential benefit of IVIG in this disease. Noseworthy et al (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo.99 The trial was terminated early after 55 patients were enrolled because investigators did not find a difference in the logMAR visual scores at 6 months (p=0.766). Roed et al (2005) randomized 68 in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34). They found no differences in the visual outcome measure and disease activity as measured by magnetic resonance imaging after 6 months.

Crohn Disease
Crohn disease is an inflammatory condition of unknown etiology that can affect any portion of the gastrointestinal tract, from the mouth to the perianal area, with a wide spectrum of clinical presentations. A 2012 systematic review of IVIG therapy for Crohn disease did not identify any randomized or nonrandomized controlled trials. Reviewers found 5 case reports of IVIG used for single patients with Crohn disease, and the remaining literature identified included conference papers, abstracts only, or a nonsystematic review.

Hemophagocytic Lymphohistiocytosis
Hemophagocytic lymphohistiocytosis is an uncommon but potentially fatal syndrome of excessive immune activation resulting from overactive histiocytes and lymphocytes. It may be inherited or acquired. Published literature on the use of IVIG in hemophagocytic syndrome is limited to small case series. A 2012 systematic review on diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics identified 156 cases; a portion of these patients were treated with IVIG. Steroids were the most common treatment. IVIG was used in 30% of children and in 4% of adults. Hemophagocytic syndrome-related mortality occurred in 32% of children and in 28% of adults.

Recurrent Spontaneous Abortion
Recurrent spontaneous abortion (RSA) is defined as 3 or more pregnancies resulting in a spontaneous abortion before 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.

A 2006 Cochrane review of various immunotherapies for treating recurrent miscarriage concluded that IVIG therapy provides no significant beneficial effect over placebo in preventing further miscarriages. Recently published meta-analyses that included 11 RCTs also found no significant difference in the frequency of the number of live birth with IVIG versus placebo or treatment as usual. A 1999 blinded RCT of 41 women treated with IVIG or saline placebo also found no differences in live birth rates. Likewise, a 2000 multicenter RCT comparing heparin plus low-dose aspirin with or without IVIG in women with lupus anticoagulant, anticardiolipin antibody, or both, found no significant differences. In addition, a 2002 RCT of 58 women with at least 4 unexplained miscarriages compared IVIG to placebo and analyzed results by intention to treat. The live birth rate was similar for both groups; also, there were no differences in neonatal data (eg, birth weight, gestational age at delivery). Other nonrandomized but controlled trials have also reported no benefit for IVIG treatment.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a term used to describe a subset of children whose symptoms of obsessive-compulsive disorder or tic disorders are exacerbated by group A streptococcal infection. This syndrome is not

well-understood and diagnosis of PANDAS requires expert consultation. Immune modulating therapies such as IVIG might be beneficial for severely ill patients who have not responded to standard therapies. Children who meet criteria for PANDAS with immune-modulating therapies should not be treated outside of the research setting.

In a single RCT, 29 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections were randomized to IVIG, plasma exchange, or placebo. At 1-month follow-up, IVIG and plasma exchange showed improvements in obsessive-compulsive symptoms, anxiety, and overall functioning. Improvement in symptoms was maintained at 1 year, with 14 (82%) of 17 children "much" or "very much" improved over baseline (7 of 8 for plasma exchange, 7 of 9 for IVIG).

Autism Spectrum Disorder
Autism spectrum disorder is neurodevelopmental disorder characterized by deficits in social communication and social interaction and restricted repetitive patterns of behavior, interests, and activities.

The evidence base supporting the use of IVIG in autism includes 3 case series. The first included 10 patients with abnormal immune parameters who received IVIG therapy monthly. After 6 months, 5 of 10 patients showed marked improvement in several autistic characteristics. Remaining 2 case series failed to replicate these findings. In the second, 1 of 10 patients showed improvements in autistic symptoms after receiving IVIG. No improvements were observed in the third series. There are no randomized comparative trials evaluating IVIG therapy in autism.

Complex Regional Pain Syndrome
Complex regional pain syndrome (CRPS) is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion.

Goebel et al (2017) conducted a 1:1 parallel, randomized, placebo-controlled, multicenter trial to confirm the efficacy of low-dose IVIG compared with placebo in reducing pain in adults who had CRPS of 1 to 5 years in duration. IVIG 0.5 g/kg of body weight or saline placebo on days 1 and 22 were administered after 111 patients were randomized. An 11-point (0- to 10-point) rating scale was

used to measure the primary outcome of 24-hour average pain intensity. Mean pain scores were 6.9 points for placebo and 7.2 points for IVIG at 6 weeks demonstrating that low-dose immunoglobulin treatment was not effective in relieving pain in moderate-to-severe CRPS patients.

Goebel et al (2010) reported on the use of IVIG treatment for CRPS in a crossover double-blinded RCT conducted at an academic pain management center in the U.K. The trial randomized 13 patients refractory to standard treatment to IVIG or normal saline. Median daily pain intensity score for each 14-day period was 6.21 after IVIG infusion vs 7.35 after saline infusion, a difference of 1.14 points. Trialists reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; $p<0.001$).

The evidence for IVIG treatment of CRPS consists of a small crossover RCT that showed reductions in pain scores compared with placebo. However, the evidence is insufficient to draw conclusions about the impact of IVIG on health outcomes in those who suffer with CRPS.

Alzheimer Disease
Two small studies have suggested that IVIG therapy may be benefit those with Alzheimer disease based on the effect of IVIG on biomarkers and symptoms of mild-to-moderate Alzheimer disease. In a more recent (2013) phase 2 double-blind, placebo-controlled dose-finding trial in 56 Alzheimer patients failed to show reductions in the biomarker or cognitive/functional scales compared to placebo.

Paraproteinemic Neuropathy
Paraproteinemic neuropathy is a heterogeneous set of neuropathies characterized by the presence of paraproteins, which are immunoglobulins produced in excess by an abnormal clonal proliferation of B lymphocytes or plasma cells. Paraproteinemic neuropathy may be caused by the interaction of antibodies with specific antigenic targets on peripheral nerves or by deposition of immunoglobulins or amyloid.

Results of a double-blind, placebo-controlled, randomized crossover trial of IVIG versus placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients. A subsequent 2012 RCT of 22 patients focused on short-term outcomes at 2 weeks.129 No significant differences were found between the treatment and placebo groups.

Chronic Fatigue Syndrome
Chronic fatigue syndrome, also called as systemic exertion intolerance disease, it is a complex and controversial disease with multiple definitions.

Numerous non-comparative studies have shown subjective benefits of IVIG therapy on chronic fatigue syndrome but a double-blind, randomized, placebo-controlled trial in 99 patients with chronic fatigue syndrome reported no therapeutic benefit of IVIG.

Acute Myocarditis
Acute myocarditis is a sudden inflammation of myocardium that can occurs in individuals of all ages. It is presumed to start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear whether the primary problem is most commonly ongoing damage from virus, a postinfectious inflammatory reaction or a combination of the two.

Multiple case reports have suggested that patients with acute myocarditis may benefit from high-dose IVIG. Spontaneous rapid or gradual improvement is common with acute myocarditis, and improvement noted in these case series may have been part of the natural history of the disease. The literature has been summarized in a Cochrane systematic review that included 1 placebo-controlled randomized trial of 62 adult patients with recent-onset dilated cardiomyopathy and a quasi-randomized study of 83 children with suspected viral encephalitis and associated myocarditis with a left ventricular ejection fraction less than 0.40. Both trials were rated as very low quality and had high risk of bias. In the RCT of adults, event-free survival did not differ significantly but favored the control group (OR=0.52; 95% CI, 0.12 to 2.30). The major limitation was that some patients did not have viral myocarditis because only 10 of 62 patients showed inflammation on cardiac biopsy. In the quasi-randomized trial in children, the incidence of event-free survival was 25 (96%) of 26 in the treated group and 44 (77%) of 57 in the control group (OR=7.39; 95% CI, 0.91 to 59.86).

Heidendael et al (2017) reported on 94 children with new-onset dilated cardiomyopathy in a retrospective cohort study with a median follow-up of 33 months. After viral tests were performed, 18 (19%) children met diagnostic criteria for “probably or definite viral myocarditis,” and IVIG was administered to 21 (22%) patients. Treatment was associated with a higher recovery rate within 5 years, compared with nontreated children (70 vs 43%; p=0.045), however the HR for recovery with IVIG was not significant (HR=2.1; 95% CI, 1.0 to 4.6; p=0.056) after correction for possible

cofounders. The authors concluded that IVIG treatment was associated with better improvement of systolic left ventricular function and better recovery, but did not influence transplant-free survival.

Multiple case reports have suggested that patients with acute myocarditis may benefit from high-dose IVIG. Spontaneous rapid or gradual improvement is common with acute myocarditis, and improvement noted in these case series might have been part of the natural history of the disease.

The evidence for IVIG treatment of dilated cardiomyopathy syndrome consists of multiple noncomparative studies, a quasi-randomized trial, and an RCT. All studies had a high risk of bias. High-quality RCTs are needed to demonstrate benefit of IVIG for viral myocarditis.

Refractory Recurrent Pericarditis
Refractory recurrent pericarditis is defined as recurrent pericarditis not responding to conventional anti-inflammatory such as aspirin, nonsteroidal inflammatory drugs, corticosteroids, and colchicine. Imazio et al conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports). Approximately 47% of patients had idiopathic recurrent pericarditis, 10% had an infective cause, and the remainder had systemic inflammatory disease. IVIGs were generally administered at a dose of 400 to 500 mg/kg/d for 5 consecutive days, with repeated cycles according to the clinical response. Overall, recurrences occurred in 26.6% of cases after the first IVIG cycle, and 22 (73.3%) of the 30 patients were recurrence-free after a mean follow-up of approximately 33 months.

Non-Infectious Uveitis
Noninfectious uveitis is the inflammation of eye that results from noninfectious causes such as eye trauma, anomalous immune processes, or unknown etiology. Two small case series of 18 and 10 patients, respectively, reported measurable improvements in visual acuity after IVIG therapy. Collectively, these 2 studies represent insufficient evidence to draw conclusions about efficacy.

Post polio Syndrome
Although polio no longer poses a major public health threat in the United States, many patients live with the sequelae of paralytic polio. Many polio survivors experience a modest decline in function and muscle strength over many years that may reflect the natural history of polio.

In 2015, Huang et al published a systematic review and meta-analysis of RCTs and nonrandomized prospective studies on IVIG treatment of post polio syndrome. Reviewers identified 3 RCTs (n=241 patients) and 5 prospective studies (n=267 patients). The primary outcomes of interest were severity of pain, fatigue, and change in muscle strength 2 to 3 months after IVIG administration. Meta-analyses of RCT data found no statistically significant differences between IVIG- and placebo-treated groups for any of these outcomes. For example, the pooled mean difference in pain scores (0-to-10 visual analog scale) from the 3 RCTs was -1.02 (95% CI, -2.51 to 0.47). Meta-analysis of the 2 RCTs that reported change in fatigue scores found a WMD of 0.28 (95% CI, -1.56 to 1.12). The small number of RCTs and the negative findings of this systematic review represent insufficient evidence of the efficacy of IVIG for post polio syndrome.

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

Subcutaneous Immune Globulin Therapy
Subcutaneous immune globulin replacement therapy for PID has been available outside the United States for decades and was cleared for use in the United States in 2006. Clinical data on the first SCIG product (Vivaglobin) available in the U.S. were published the same year as the FDA approval. An open-label, nonrandomized, prospective, multicenter study reported outcomes of SCIG replacement therapy in adults and children (older than 2 years with bodyweight 10 kg or more) with CVID or XLA that had been treated with IVIG for at least 4 months. A total of 65 patients (mean age: 34 +/- 15 years, range: 2 to older than 65 years, 57% male) were enrolled. Most (78%) had CVID, 22% had XLA. The study included 3 phases: baseline (3–4 weeks), wash-in/wash-out (12 weeks), and efficacy (52 weeks). During the baseline period, each patient received usual IVIG treatment, during and after which vital signs were collected, baseline biochemical and viral tests were performed, and serum IgG trough levels were measured. One week following the last IVIG dose, once-weekly SCIG therapy was administered for at least 3 months (wash-in/out phase), using a dose equivalent to 137% of the IVIG dose. The 12-month efficacy phase began after the wash-in/out phase, using a mean weekly dose of 158 mg/kg (range, 155–165 mg/kg). The mean pre-infusion IgG level increased from 7.9 g/L at baseline to 10.4 g/L during SCIG treatment, representing a 39% increase. Trough levels remained relatively stable throughout the study. During the efficacy phase, 2 serious bacterial infections (pneumonias) were reported in two patients, resulting in an

annual rate of 0.04 episodes per patient-year (upper 99% confidence limit: 0.14). Thirty-two patients (63%) missed a total of 192 days of school or work due to infections during the efficacy phase, resulting in an overall rate of 3.7 days per patient-year. Four patients were hospitalized due to infection (including the 2 with pneumonia), for a total of 12 days or 0.23 hospital days per patient-year. Of a total of 3,656 infusions, 2,584 treatment-emergent adverse events were reported (0.71 per infusion), with 1,901 considered to be treatment-related (0.52 per infusion). The most frequent type of adverse event, infusion-site reaction, was observed at least once in 60 cases (91%); the vast majority (96%) were of mild or moderate intensity and short duration (1 or 2 days). Importantly, the incidence of infusion-related adverse events declined by 50% over time, from 85% after the first infusion session to 41% after the 33rd session, after which the rate remained relatively stable. Three subjects withdrew from treatment due to infusion-site reactions. No deaths or notable changes in hematologic or other laboratory parameters were noted, nor were any virus-related safety issues reported.

A parallel study by Gardulf and colleagues of the same product (Vivaglobin) in Europe and Brazil among 60 patients (16 children, 44 adults, age range, 2–75 years) with a diagnosis of PID produced almost identical annualized rates of mild-to-moderate overall infections and serious bacterial infections (0.04 episodes per patient). However, Gardulf used a SCIG dose equivalent to 100% of the previous IVIG dose, compared to 137% in the North American study. The rates, intensity, and types of adverse events in the Gardulf report were similar to the North American study and also showed a similar decline in incidence with subsequent infusions. Among children in the Gardulf study, serum IgG trough levels increased from a mean 7.8 g/L to a mean 9.2 g/L during the efficacy phase; adult levels rose from a mean 8.6 g/L to 8.9 g/L. Six of the children and 10 adults missed days from school (range, 1–9 days) or work (range, 1–36 days). No deaths or notable changes in hematologic or other laboratory parameters were noted, nor were any virus-related safety issues reported.

In 2013, Lingman-Framme and Fasth published a systematic review of the literature on SCIG compared with IVIG for treatment of primary and secondary immunodeficiencies. The authors identified 20 studies; 2 were RCTs and 19 of the studies included patients with primary immunodeficiencies. The primary outcome of interest was the number of serious bacterial infections, defined as bacterial pneumonia, meningitis, osteomyelitis, septicemia, and peritonitis. Only 3 studies reported on serious bacterial infections during both SCIG and IVIG administration, and no serious

bacterial infections identified. Five studies reported the annual number of infections (bacterial and/or viral) and no significant difference was found in the infection rate associated with SCIG and IVIG. Four studies compared health related quality of life in patients who changed the route of administration from IV to subcutaneous. All 4 of these studies found that patients reported a better quality of life with home-based SCIG compared with hospital-based IVIG. Moreover, all 11 studies that reported IgG trough levels found higher levels with SCIG compared with IVIG.

Thus, taken together, the similar clinical efficacy of SCIG replacement therapy versus IVIG, in the context of a simpler delivery method for chronic therapy and some evidence of improved quality of life, suggests SCIG treatment may be considered medically necessary in lieu of IVIG to prevent recurrent infections in patients with primary immunodeficiency who require lifelong immunoglobulin replacement therapy. Viviglobin was discontinued by the manufacturer in 2013; it is likely that findings of the studies conducted with Viviglobin generalize to other SCIG products.

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158. Cutaquig [package insert]. Octapharma. Hoboken, New Jersey. Updated December 2018.
159. Xembify [package insert]. Griffols. Triangle Park, North Carolina. Updated July 2019.

160. Asceniv [package insert]. ADMA Biologics. Boca Raton, Florida. Updated April 2019.

Policy History

Original Effective Date: 08/24/2005
Current Effective Date: 05/10/2021

08/03/2005	Medical Director review
08/17/2005	Medical Policy Committee review
08/24/2005	Managed Care Advisory Council approval
01/04/2006	Medical Director review
01/17/2006	Medical Policy Committee review. Format revision. Changes to guideline. New criteria added.
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee review. Vivaglobin was added to be eligible for coverage for patients with primary immunodeficiency.
10/10/2007	Medical Director review
10/17/2007	Medical Policy Committee approval. Coverage eligibility unchanged. IVIG in the setting of Solid Organ Transplant added.
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
11/12/2009	Medical Policy Committee approval.
11/18/2009	Medical Policy Implementation Committee approval. Policy revised and updated.
11/04/2010	Medical Policy Committee approval.
11/16/2010	Medical Policy Implementation Committee approval. New drug Hizentra added.
12/08/2011	Medical Policy Committee approval.
12/21/2011	Medical Policy Implementation Committee approval. Policy revised and updated.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2013	Coding update
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Added that severe anemia due to parvovirus B19 as a new hematologic indication that is eligible for coverage for IVIG therapy. Deleted Kawasaki disease as an infectious disease indication for

	coverage of IVIG therapy. Added Crohn's disease, opsoclonus myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis and polyradiculoneuropathy (other than CIPD) as investigational applications of IVIG therapy.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. Added a new indication for the prevention of sepsis in certain young populations to track BCBS. Also updated background info. Included name of newest SQIG product, Hyqvia.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. HCPCS codes added also.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. Added new indication of hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis). Also added an additional investigational indication: Postpolio syndrome. Added the background info on each. Updated background/rationale sections with updates from BCBSA.
10/01/2016	Coding update
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Removed prevention of infection in preterm and/or low birth weight neonates. Clarified various indications in terms of defining thrombocytopenia, hypogammaglobulinemia, etc. Added new indications: Stiff person syndrome, Wegener Granulomatosis, neuromyelitis optica. Updated background information.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Added a new product, Panzyga, to the policy. Also added a new indication for coverage (IgG subclass deficiency) of IVIG.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Added two new SCIG formulations (Cutaquig, Xembify) to the policy.

Immune Globulin Therapy

Policy # 00170
Original Effective Date: 08/24/2005
Current Effective Date: 05/10/2021

12/10/2019	Coding update
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Added a new IV product (Asceniv) to the policy.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Added a clarifying statement that SC IG requests for PID meet the following: Laboratory evidence of immunoglobulin deficiency, documented inability to mount an adequate immunologic response to inciting antigens, and persistent and severe infections despite treatment with prophylactic antibiotics. This is currently operational and does not reflect a coverage change.
10/1/2021	Coding update

Next Scheduled Review Date: 04/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Immune Globulin Therapy

Policy # 00170
Original Effective Date: 08/24/2005
Current Effective Date: 05/10/2021

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	90283, 90284, 90399
HCPCS	J1459, J1555, J1556, J1557, J1558, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1575, J1599, J3490, J3590 Add code eff 1/1/2021: C9072 Add code eff 4/1/2021: J1554
ICD-10 Diagnosis	A40.0-A41.9, A48.3, A49.1-A49.9, B20, B34.3, B95.0-B95.8, B96.0-B96.29, B96.3-B96.89, B97.6, C79.82, C90.00-C90.01, C90.10-C90.11, C91.10-C91.12, D59.0-D59.1, D60.0-D60.9, D61.9, D68.61, D69.3, D69.49, D69.59-D69.6, D70.0-D70.9, D75.A, D75.9, D76.1-D76.3, D80.0-D80.7, D81.0-D81.9, D82.0-D82.9, D83.0-D83.9, D89.1-D89.2, E08.3211-E13.9, E71.50, E71.510-E71.518, E71.520-E71.529, E71.53, E71.540-E71.548, E84.0, F84.0-F84.9, G11.10-G11.19, G11.3. G25.3, G25.82, G35-G36, G40.42, G40.833-G40.834, G40.901-G40.909, G40.911-G40.919, G60.0-G60.9, G61.0, G61.81-G61.82. G70.00-G70.01, G73.3, H20.9, H35.101-H35.109, H46.9, H66.90-H66.93, I30.0-I30.1, I40.0-I40.9, I42.0-I42.9, I44.0-I44.7, I45.0-I45.9, J20.0-J20.2, J32.9, J44.0-J44.9, J45.20-J45.9, K50.10-K50.119, L10.0-L10.9, L51.3, L93.0-L93.2, M00.10-M00.49, M05.40-M05.9, M30.0-M30.8, M31.0, M31.30-M31.31, M31.7, M32.0-M32.9, M33.00-M33.99, M35.00-M35.09, M35.2, M36.0, M60.9, M79.11-M79.18, M79.7, N18.30-N18.32, N18.9, O03.9, P07.00-P07.39, P36.0-P36.9, P53, P55.8-P55.9, P61.0, T86.00-T86.9, Z48.21-Z48.24, Z48.280-Z48.288, Z48.290, Z48.298, Z94.0-Z94.9, Z95.3-Z95.4 Codes added eff 10/1/2021: M35.05-M35.0C Code deleted eff 10/1/2021: M31.1

Immune Globulin Therapy

Policy # 00170
Original Effective Date: 08/24/2005
Current Effective Date: 05/10/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally

recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.