LOUISIANA BLUE

# Immune Globulin Therapy

**Policy # 00170**
Original Effective Date: 08/24/2005
Current Effective Date: 01/01/2025

*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 of the following criteria for treatment with immune globulin:
    - Laboratory evidence of immunoglobulin deficiency; AND
    - Documented inability to mount an adequate immunologic response to inciting antigens; AND
    - Persistent and severe infections despite treatment with prophylactic antibiotics

**Acute Humoral Rejection**

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

- Pemphigus
- Pemphigoid
- Pemphigus vulgaris
- Pemphigus foliaceus
- Stevens-Johnson syndrome (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; i.e., MGFA class IV, see Policy Guidelines) 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

**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

# 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

# When Services Are 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.*

**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), X-linked agammaglobulinemia (XLA), and CIDP to be **eligible for coverage.****

- Note that patients with primary immunodeficiency (PID) syndromes should meet ALL of the following criteria for treatment with immune globulin:
  - Laboratory evidence of immunoglobulin deficiency; AND
  - Documented inability to mount an adequate immunologic response to inciting antigens; AND
  - 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.***

# Policy Guidelines

**Myasthenia Gravis Foundation of America (MGFA) Clinical Classification**

| ***Class*** | ***Description*** |
|---|---|
| I | Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal |
| IIa | Mild weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles |
| IIb | Mild weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both. |
| IIIa | Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles. |
| IIIb | Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both. |
| IVa | Severe weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles. |
| IVb | Severe weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both. |
| V | Intubation with or without mechanical ventilation except when employed during routine postoperative management. |

**Quantitative Myasthenia Gravis (QMG) Score**

| ***Test Item*** | ***None*** | ***Mild*** | ***Moderate*** | ***Severe*** | ***Score*** |
|---|---|---|---|---|---|
| ***Grade*** | ***0*** | ***1*** | ***2*** | ***3*** | |
| Double vision on lateral gaze (secs) | 61 | 11-60 | 1-10 | Spontaneous | |
| Ptosis (upward gaze) | 61 | 11-60 | 1-10 | Spontaneous | |
| Facial muscles | Normal lid closure | Complete, weak, some resistance | Complete without resistance | Incomplete | |
| Swallowing 4 oz water | Normal | Minimal coughing or throat clearing | Severe coughing/choking or nasal congestion | Cannot swallow (test not attempted) | |

| | | | | | |
|---|---|---|---|---|---|
| Speech after counting aloud from 1 to 50 (onset of dysarthria) | None at 50 | Dysarthria at 30-49 | Dysarthria at 10-29 | Dysarthria at 9 | |
| Right arm outstretched (90 degrees sitting), seconds | 240 | 90-239 | 10-89 | 0-9 | |
| Left arm outstretched (90 degrees sitting), seconds | 240 | 90-239 | 10-89 | 0-9 | |
| Forced Vital Capacity | ≥80 | 65-79 | 50-64 | ≤50 | |
| Rt-hand grip, kg<br>Men<br>Women | <br>≥45<br>≥30 | <br>15-44<br>10-29 | <br>5-14<br>5-9 | <br>0-4<br>0-4 | |
| Lt-hand grip, kg<br>Men<br>Women | <br>≥35<br>≥25 | <br>15-34<br>10-24 | <br>5-14<br>5-9 | <br>0-4<br>0-4 | |
| Head lifted (45 degrees supine), seconds | 120 | 30-119 | 1-29 | 0 | |
| Right leg outstretched (45 degrees supine), seconds | 100 | 31-99 | 1-30 | 0 | |
| Left leg outstretched (45 degrees supine), seconds | 100 | 31-99 | 1-30 | 0 | |
| | | | | **Total QMG Score:** | |

Immune Globulin Therapy

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# 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.

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)**

Several IVIG have been approved by the FDA. These include, Flebogamma®‡ (Instituto Grifols), Gammagard®‡ (Takeda), Gamunex-C®‡ (Griffols), Gammaplex®‡ (Bio Products Lab), Gammaked®‡ (Kedrion Biopharma), Octagam®‡ (Octapharma), Privigen®‡ (CSL Behring LLC), Bivigam®‡ (ADMA Biologics), Panzyga®‡ (Pfizer), Asceniv®‡ (ADMA Biologics), Alyglo®‡ (GC Biopharma), and Yimmugo®‡ (Biotest AG).

Several SCIG products have received FDA marketing approval for PID. These include Vivaglobin®‡ (ZLB Behring LLC, discontinued by the company in 2013), Gammagard Liquid (Takeda), Hizentra®‡ (CSL Behring AG), Gamunex-C®‡ (Grifols), Gammaked®‡ (Kedrion Biopharma), Cuvitru®‡ (Takeda), Hyqvia®‡ (Takeda), Cutaquig®‡ (Octopharma), 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, 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 subcutaneously or intravenously 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 has 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.

A 2010 systematic review by Gurcan et al identified 23 studies evaluating IVIG for autoimmune mucocutaneous blistering diseases (1 RCT, 22 case series). The studies included 260 patients treated with IVIG: 191 patients had pemphigus, and 69 patients had pemphigoid. Of the 260 patients, 245 (94%) improved after IVIG treatment.

Amagai et al (2017) evaluated IVIG for bullous pemphigoid in a multicenter, double-blind and placebo-controlled randomized trial that included 56 patients. The IVIG group received 400 mg/kg/d for 5 days and the placebo group received saline for 5 days. The primary endpoint was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant (p=0.089). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15 (p=0.041). In patients with severe disease, there were significantly lower DAS scores in the IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.

Another RCT by the same research group was published by Amagai et al (2009); this study was multicenter, placebo-controlled, and double-blind in design and included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥ 20 mg/d). Patients were randomized 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 endpoint 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.

**Idiopathic Inflammatory Myopathies**
Polymyositis and dermatomyositis involve weakness of the proximal muscles such as the muscles of the hips and thighs, upper arms, and neck. Dermatomyositis is associated with various characteristic skin manifestations. In inclusion body myositis, the muscles most affected are those of the wrists and fingers and the front of the thigh.

In 2022, Xiong et al conducted a systematic review of 17 studies (3 RCTS, 14 observational) evaluating IVIG safety and efficacy in 411 patients with dermatomyositis or polymyositis. Creatinine kinase, Manual Muscle Test scores, the Medical Research Council scale, and the Activities of Daily Living scale all significantly improved with IVIG treatment. Intravenous immune globulin also provided a corticosteroid-sparing effect in 72 of 88 patients evaluated. Meta-analysis of the 3 RCTS found significantly improved efficacy with IVIG compared with control/placebo (standard mean difference. 0.63; 95% CI, 0.22 to 1.03). Intravenous immune globulin was well-tolerated.

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.

In 1997, Dalakas et al reported on a double-blind, placebo-controlled, crossover study that compared IVIG with placebo in 19 patients with inclusion body myositis. There was no statistically significant improvement in overall muscle strength in the IVIG group compared with the placebo group. Two more RCTs published in 2000 and 2001 (58 IVIG patients) also found no significant functional improvement when IVIG treatment was compared with placebo.

**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 2023 Cochrane review of RCTs by Broderick et al identified 31 trials for meta-analysis. Comparator therapies included aspirin, prednisolone, or infliximab. Results showed a significant decrease in new coronary artery abnormalities in favor of IVIG compared with aspirin at 30 days (OR, 0.60; 95% CI, 0.41 to 0.87). Adverse effects were similar between groups. There was low certainty evidence comparing aspirin and IVIG for acute coronary syndrome and need for additional treatment. Comparisons between IVIG and prednisolone had low certainty. Reviewers concluded that high dose IVIG probably reduces coronary artery abnormalities compared to aspirin or medium or low dose IVIG regimens.

**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.

**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 were 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 were 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**
Chronic inflammatory demyelinating polyneuropathy is an acquired neurologic disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder is caused by damage to the myelin sheath of the peripheral nerves. The disease is difficult to diagnose due to its heterogeneous presentation (both clinical and electrophysiological).

*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.

In 2024, Bus et al published an updated Cochrane review of RCTs on IVIG for treating CIDP. Nine RCTs were included (N=372 patients). Only one new trial was included; however, it did not contribute any data to the meta-analysis.

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.

In 2021, the European Academy of Neurology and the Peripheral Nerve Society published updated guidelines on the management of CIDP and recommend IVIG as a first line treatment option for CIPD.

*SubQ*
In 2024, Ramzi et al published a systematic review and meta-analysis of SCIG therapy for CIDP. The systematic review included 50 studies whereas the meta-analysis evaluated 20 studies. The meta-analysis results showed that SCIG had fewer, milder side effects, decreased relapse rates, greatly increased muscle strength, and was highly preferred by patients compared to IVIG therapy.

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. The PATH open-label extension trial (2019) evaluated the long-term safety and efficacy of SCIG in patients with CIDP. Eighty-two patients were enrolled in the trial and 66 patients completed the 48-week study duration. Patients treated with 0.4 g/kg had an overall relapse rate of 10%, whereas those treated with 0.2 g/kg had a rate of 48%. After dose reduction, 19 of 28 who finished the PATH study without experiencing a relapse continued to be relapse-free on the 0.2 g/kg dose. Adverse events were reported in sixty-two patients (76%), the majority of which were mild or moderate and had no associated significant adverse events.

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.

A randomized, placebo-controlled study was evaluated for the FDA approval of Hyqvia to treat CIDP. The study included participants ≥ 18 years of age with definite or probable CIDP (n=122). The analysis of the primary endpoint revealed a statistically significant difference in relapse rates between the Hyqvia group (n=57, 14.0%) and the placebo group (n=65, 32.3%) (p=0.0314). The treatment difference of -18.3% ( -3.1%; two-sided 95% CI: -32.1%) demonstrated that Hyqvia was superior to placebo in preventing relapse of CIDP.

**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.

In 2022, Keddie et al updated a 2005 Cochrane review identifying a total of 6 crossover RCTs (N=90 patients). Studies included patients with definite or probable MMN treated with IVIG or SCIG. Outcomes included muscle strength, disability, or electrophysiological conduction block. In 3 trials (N=18) of induction treatment, IVIG improved disability in 39% of patients compared with 11% of placebo-treated patients (risk ratio, 3.00; 95% CI, 0.89 to 10.12). In the 3 trials (N=27) evaluating

strength, 78% of IVIG-treated patients improved compared with 4% of placebo-treated patients (risk ratio, 11.00; 95% CI, 2.86 to 42.25). Conduction block results non significantly favored IVIG to placebo in 4 trials of 28 patients (risk ratio, 7.00; 95% CI, 0.95 to 51.70). Adverse effects were increased in patients with IVIG; however, only 1 serious event (a pulmonary embolism) was documented. Most patients who responded to IVIG deteriorated with treatment withdrawal.

**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. 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. In a cohort of patients (N=36) treated long-term, monthly IVIG maintained efficacy in 67% of patients for a median of 3.3 years.

**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.

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.

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 $81\times10^9$/L in the 0.5-g/kg group versus $110\times10^9$/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 shown 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 HIV-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 $0.2\times10^9$/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 $0.2\times10^9$/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 known 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.

**Acute Antibody-Mediated Rejection After 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 ABMR reaction related to the presence of anti-donor antibodies. Acute ABMR is an entity now better defined and often detected earlier in the clinical course, based on the recognition of characteristic histologic findings, positive C4d staining, and the detection of donor-specific antibodies. The risk of ABMR 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. Recipients of ABO mismatched donor organs are also at risk of ABMR.

In 2019, Bourasssa-Blanchette and colleagues published a systematic review involving 18 trials (with 8 RCTs) investigating the impact of IVIG prophylaxis on infection, rejection, graft loss, and death following kidney transplantation. Results revealed that IVIG administration did not reduce cytomegalovirus infection (odds ratio [OR], 0.68; 95% CI , 0.39 to 1.21; 6 studies, n=295), rejection (OR, 0.96; 95% CI , 0.50 to 1.82; 4 studies, n=187), or graft loss (OR, 1.03; 95% CI , 0.46 to 2.30; 6 studies, n=265) in the RCTs. Among the included nonrandomized studies, IVIG administration was associated with a reduction in rejection and graft loss but not cytomegalovirus infection or death. The authors noted that the quality of included studies was variable with a high to very high risk of bias and that additional adequately powered RCTs are needed in order to determine if IVIG is an effective intervention.

In the National Institutes of Health (NIH)-sponsored IG02 study, 101 adults with a PRA screen of 50% or higher were randomized to IVIG 2 g/kg monthly for 4 months or placebo. If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reductions in PRA levels compared with placebo (35% vs. 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80%

IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than placebo in reducing anti-human leukocyte antigen antibody levels and improving transplantation rates in highly sensitized patients with end-stage renal disease. In a follow-up study, the combination of high-dose IVIG and B-cell depletion therapy reduced PRA from 77% to 44% at the time of transplantation.

More recent studies have failed to show a reduction in PRA levels, specifically in patients with a PRA greater than 80%. Nonrandomized clinical observations have suggested that a combination of plasmapheresis plus low-dose IVIG and interleukin-2 blockade or rabbit anti-thymocyte globulin for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients.

Most studies of IVIG treatment for ABMR are retrospective case series from single institutions. A systematic review by Roberts et al (2012) of treatments for acute ABMR in renal allografts identified 10,388 citations but only 5 small RCTs, none of which addressed the use of IVIG in the treatment of ABMR.20, A RCT by Casadei et al (2011) demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection; however, IVIG was ineligible for inclusion in the Roberts review because 83% of the patients had Banff 1 (pure cellular) rejection on biopsy. According to Roberts et al (2012), the evidence to support the use of IVIG to treat ABMR is very low (GRADE criteria).

In 2010, the Canadian Blood Services (CBS) and National Advisory Committee on Blood and Blood Products of Canada (NAC) developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation. The following conclusions were issued on non-kidney solid organ transplantation:

- For patients undergoing heart transplantation, to improve graft/overall survival or to treat rejection: insufficient evidence to recommend for or against the routine use of IVIG (however, other factors may influence decision-making)
- For desensitization for patients undergoing lung transplantation or for the treatment of rejection: insufficient evidence to make a recommendation for or against the routine use of IVIG (however, other factors may influence decision-making)
- For patients undergoing liver transplantation or for the treatment of rejection/ABO-incompatible liver transplantation: insufficient evidence to make a recommendation for or against the routine use of IVIG
- For the use of IVIG for solid organ transplantation: limited methodologically rigorous evidence
- Future studies are needed to delineate the effect of IVIG on desensitization using standardized methods for desensitization; the effect of IVIG on acute rejection rates, graft survival, and overall survival; the use of the combined modality IVIG and plasmapheresis compared either to plasmapheresis or IVIG alone; and the optimum dosage of IVIG.

**Neonatal Sepsis**
Preterm and low birth weight infants are prone to infection because of an immature immune system as well as increased exposure to nosocomial pathogens.

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.

A Cochrane review by Ohlsson and Lacy (2020) identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or confirmed 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 rates with IVIG versus the control therapy (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.

A 2023 meta-analysis by Pan et al pooled 31 RCTS of IVIG use in patients (adults and neonates) with sepsis. Evidence from the pooled results found that IVIG was highly effective in lowering mortality in patients (RR 0.86, 95% CI: 0.77 to 0.95; p = 0.02, I2 = 37%). In subgroup analyses, IVIG was shown to have an effect in reducing adult sepsis mortality specifically (RR 0.70; 95% CI, 0.57 to 0.86; p =.15, I2 = 27%). Authors did note the limitation of inclusion of marginally representative data and potential confounders that may have affected the results of the meta-analysis.

**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.

Based on a technology assessment by Goodin et al (2002), the American Academy of Neurology (AAN) recommended the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation) for the treatment of RRMS. 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.

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. In 2022, Cajamarca-Barón et al published a systematic review on IVIG in patients with lupus nephritis. A total of 28 articles were included with case reports or series comprising the vast majority of the evidence. Only 1 RCT (N=14) was identified. In the

RCT, 11 patients remained in remission after 1.5 years of follow-up. In compiled data from the case reports and case series, a complete response occurred in 30.4% of patients with 33.9% of patients having a partial response. Although IVIG appears effective for lupus nephritis based on this analysis, there is a lack of RCTs to support the use of IVIG in this setting. 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. 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.

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.

A 1999 RCT by Perlmutter et al included 30 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections. Patients were randomized to IVIG, plasma exchange, or placebo (10 per group). At the 1-month follow-up, IVIG and plasma exchange showed statistically significant improvements in obsessive-compulsive symptoms, anxiety, and overall functioning.

In 2016, Williams et al randomized 35 children who met diagnostic criteria for PANDAS and had moderate-to-severe obsessive-compulsive disorder symptoms to treatment with 2 treatment sessions of IVIG or placebo. After a 6-week, double-blind treatment phase, nonresponders could continue treatment on an open-label basis. The primary outcome at 6 weeks, the Children’s Yale-Brown Obsessive Compulsive Scale total score, did not differ significantly between groups. There was a mean decrease in the Children’s Yale-Brown Obsessive Compulsive Scale of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvements in other outcomes (eg, mean Clinical Global Impressions improvement scores) also did not differ

significantly between groups. A total of 24 participants met the criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the Children's Yale-Brown Obsessive Compulsive Scale improved significantly compared with 6 weeks; however, the 12-week analysis did not include a placebo comparison.

**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; $p < 0.001$).

**Alzheimer Disease**
Three placebo-controlled, double-blind, randomized trials in patients with AD were identified. Two included patients with mild-to-moderate AD. Relkin et al (2017) reported on 390 patients treated with 1 of 2 doses of IVIG (0.2 or 0.4 g/kg every 2 weeks for 18 months) or placebo. The primary outcomes were a change from baseline to 18 months on the cognitive subscale of the Alzheimer

Disease Assessment scale and on the Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory. Neither outcome was significantly improved in either IVIG group compared with the placebo group.

Kile et al (2017) assessed 50 patients with mild cognitive impairment (MCI) related to AD. Patients were stratified into early and late MCI stages based on scores on the Clinical Dementia Rating, Sum of Boxes test (≤1 for the early MCI group and >1 for the late MCI group). Patients received a total IVIG dose of 2 g/kg over 5 sessions, or placebo. The primary outcome was brain atrophy, defined as annualized percent change in the ventricular volume measured by MRI. In unadjusted analyses, annualized percent change in the ventricular volume did not differ significantly between groups at 12 or 24 months. In a subgroup analysis, the annualized percent change in the ventricular volume was significantly lower in the IVIG compared with the placebo group in patients with early MCI but not late MCI at 12 months, and there was no significant difference at 12 months in either the early or late MCI groups. Secondary outcomes, cognition scores, and conversion to AD dementia did not differ between the IVIG and placebo groups at 12 or 24 months. As with the primary outcome, for several secondary outcomes, IVIG showed a significant benefit in the early MCI group at 12 months but not 24 months.

In a trial by Dodel et al (2013) with 56 patients, the primary outcome (area under the curve of plasma amyloid β 1-40) did not differ between the IVIG and the placebo groups. Secondary outcomes, including cognitive and functional scales, also did not differ between groups.

**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 2002 RCT of 22 patients focused on short-term outcomes at 2 weeks. 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.

The literature has been summarized in a Cochrane review by Robinson et al (2015) updated in 2020, that included a 2001 placebo-controlled, randomized trial of 62 adults with recent-onset dilated cardiomyopathy, a randomized, multicenter trial in Japan of 41 adults with a clinical diagnosis compatible with acute myocarditis, and a randomized, placebo-controlled study from Egypt in 86 children with acute onset dilated cardiomyopathy. The overall certainty of the included evidence was very low, with an unclear risk of bias in the 2 adult studies and a low risk of bias in the pediatric study. In adults, the evidence regarding the effect of IVIG on event-free survival and OS is uncertain (event-free survival: risk ratio , 1.76; 95% CI, 0.48 to 6.40 and overall survival: pooled risk ratio , 0.91; 95% CI, 0.23 to 3.62). For the pediatric study, the evidence for OS was also uncertain (risk ratio of death , 0.48; 95% CI, 0.20 to 1.15).

Huang et al (2019) published a meta-analysis assessing IVIG for patients with acute myocarditis. Thirteen studies (1534 participants), published between 1994 and 2017, were included. In-hospital mortality rates (pooled results: OR, 0.44; 95% CI, 0.17 to 0.71; $p < 0.001$) were significantly reduced for the IVIG group compared with patients who did not receive IVIG, and left ventricular ejection fraction (OR, 1.73; 95% CI, 1.34 to 2.13; $p < 0.001$) was significantly increased for IVIG. The study was limited by the IVIG doses not being uniformly predefined and by the limited follow-up durations (mainly between 6 and 12 months) across the included studies.

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.

**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.

**Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome**
Several systematic reviews have evaluated the literature on TEN and SJS. More recently, Huang et al (2016) identified 11 studies evaluating IVIG for TEN or SJS, none of which were RCTs. Three of the studies had control groups and 2 of these included historical controls. Intravenous immunoglobulin was not found to reduce mortality in TEN or SJS. The pooled standardized mortality ratio in the 10 studies was 1.00 (95% CI, 0.76 to 1.32; p = 0.67). A meta-analysis by Barron et al (2015) also did not demonstrate a survival advantage of IVIG for TEN and/or SJS.

**Necrotizing Fasciitis**
In 2017, Madsen et al published a placebo-controlled, randomized trial evaluating IVIG for patients with necrotizing soft tissue infection (eg, necrotizing fasciitis). The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admission to the intensive care unit. The primary outcome was patient-reported physical function at 6 months, assessed using the Physical Component Summary score of the 36-Item Short-Form Health Survey. The mean Physical Component Summary score adjusted for the site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant (p =0 .81). Other outcomes (ie, mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

**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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169. Hyqvia [package insert]. Takeda Pharmaceuticals. Lexington, Massachusetts. Updated January 2024.
170. Yimmugo [package insert]. Biotest AG. Dreieich, Germany. Updated June 2024.

# Policy History

Original Effective Date: 08/24/2005
Current Effective Date: 01/01/2025

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|---|---|
| 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. |

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| 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. |
| 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. |
| 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. |
| 04/07/2022 | Medical Policy Committee review |
| 04/13/2022 | Medical Policy Implementation Committee approval. No change to coverage. |
| 06/08/2022 | Coding update |
| 04/06/2023 | Medical Policy Committee review |
| 04/12/2023 | Medical Policy Implementation Committee approval. Added definition for severe refractory Myasthenia Gravis. Updated literature review. |
| 06/06/2023 | Coding update |
| 04/04/2024 | Medical Policy Committee review |
| 04/10/2024 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged |
| 11/07/2024 | Medical Policy Committee review |
| 11/13/2024 | Medical Policy Implementation Committee approval. Added two new drugs to policy, Alyglo and Yimmugo. Removed discontinued products, Carimune®‡ , Gamastan S/D®‡, and Polygam S/D®‡, from policy. Updated literature review. |
| 12/10/2024 | Coding update |

Next Scheduled Review Date: 11/2025

# Coding

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 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.*

*The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines.*

Immune Globulin Therapy

Policy # 00170
Original Effective Date: 08/24/2005
Current Effective Date: 01/01/2025

*Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

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, J1460, J1551, J1554, J1555, J1556, J1557, J1558, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1575, J1576, J1599, J3490, J3590<br>Add code effective 01/01/2025: J1552 |
| ICD-10 Diagnosis | All related diagnoses |

*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 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.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.