PREMERA BLUE CROSS

PHARMACY / MEDICAL POLICY – 8.01.503

Immune Globulin Therapy

BCBSA Ref. Policy: 8.01.05

Effective Date:	Jan. 1, 2019	RELATED MEDICAL POLICIES:
Last Revised:	Dec. 19, 2018	5.01.550 Pharmacotherapy of Arthropathies
Replaces:	N/A	11.01.523 Site of Service: Infusion Drugs and Biologic Agents

Select a hyperlink below to be directed to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Immune globulins are proteins made by special cells that help the body fight infections. The proteins are in the blood stream, and are concentrated in plasma, the fluid that is left after removing red and white blood cells from whole blood. Advances in medical technology have made it possible to collect, store and infuse these proteins into other people who have immune system problems. This process is called immune globulin therapy. Some people lack some or all of the cells that make immune globulins. Providing them with intravenous immune globulin therapy can be life-saving. Other conditions also may improve with immune globulin therapy. This policy describes when the health plan covers the use of immune globulin therapy. For some diseases, the use of immune globulins is still under study. Generally, the use of immune globulin (IVIG) treatment requires pre-approval of the health plan.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Bivigam®
- Carmiune® NF
- Flebogamma® DIF
- GammaSTAN® S/D
- Gammagard
- Gammaked™
- Gammaplex®
- Gamunex®-C
- Hizentra®
- Octagam®
- Privigen®

Click on the links below to be directed to the related medical necessity criteria:

Alloimune Processes

Autoimmune / Inflammatory Conditions

Hematopoietic Cell Transplantation

Infections

Miscellaneous

Primary Immunodeficiency States

Prior to solid organ transplant

Site of Service

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective**

Site of Service Administration	Medical Necessity
infusion department • **Hospital-based outpatient clinical level of care**	**site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* ***Note:** This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.** **This site is considered medically necessary only when the patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:** • Known cardiac condition (eg, symptomatic cardiac arrhythmia) or pulmonary condition (eg, significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
Hospital-based outpatient	**These sites are considered not medically necessary for infusion**

Site of Service Administration	Medical Necessity
setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Intravenous Immune Globulin (IVIG) Therapy

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
Primary immunodeficiency states: • **Ataxia telangiectasia** • **Common variable immunodeficiency** • **Congenital agammaglobulinemia** • **Hypogammaglobulinemia** • **Severe combined immunodeficiency** • **Wiskott-Aldrich syndrome** • **X-linked agammaglobulinemia** • **X-linked hyperimmunoglobulinemia M syndrome**	**IVIG therapy may be considered medically necessary when items 1, 2, and 3 are present:** 1. Laboratory evidence of immunoglobulin deficiency indicated by: ○ Agammaglobulinemia (total immunoglobulin G [IgG] <200 mg/dl) **OR** ○ Persistent hypogammaglobulinemia (total IgG <400 mg/dl, or at least 2 standard deviations below normal, on at least 2 occasions) **OR** ○ Absence of B lymphocytes 2. Documented inability to mount an adequate immunologic response to inciting antigens as indicated by: ○ Lack of appropriate rise in antibody titer following a polysaccharide antigen **OR** ○ Lack of appropriate rise in antibody titer following a protein antigen 3. Persistent and severe infections, despite treatment with prophylactic antibiotics
Specific antibody deficiency (SAD)	**IVIG therapy may be considered medically necessary when ALL of the following criteria are met:** • Immunological evaluation with documented normal

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
	serum IgG, IgG subclass, IgA, and IgM • Normal responses to protein antigens (eg tetanus and diptheria toxoid) measured 4 weeks after immunization • Inadequate responsiveness to pneumococcal polysaccharide vaccine (eg, Pneumovax®23) 4-8 weeks after vaccination as demonstrated by either of the following: ○ Age <6 years, <50% of serotypes are protective (ie, ≥1.3 mcg/ml per serotype), **or** ○ Age ≥ 6years, <70% of serotypes are protective (ie, ≥ 1.3 mcg/ml per serotype) • Recurrent infections as demonstrated by the following: ○ History of recurrent, severe bacterial sinopulmonary infections despite treatment with: ▪ Prevnar 7 or Prevnar 13 vaccination, **and** ▪ Failure or inadequate response to prophylactic antibiotic therapy ○ Documented management of underlying asthma or allergic rhinitis (eg, treatment with nasal or inhaled glucocorticoids, bronchodilators, or antihistamines)
Individual who is undergoing/undergone hematopoietic cell transplantation or CAR T-cell therapy	**IVIG therapy may be considered medically necessary when IgG levels are less than 400 mg/dl.**
Prior to solid organ transplant	**IVIG therapy may be considered medically necessary when there is high risk of antibody-mediated rejection as indicated by either:** • Highly sensitized patients (PRA >20%) panel reactive antibody test **OR** • Transplant (ABO) incompatible organ
Infections	

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
Chronic lymphocytic leukemia (CLL) diagnosis and persistent bacterial infection	**IVIG therapy may be considered medically necessary when:** • The IgG level is less than 400 mg/dl **AND** • There are persistent bacterial infections
Children with HIV to prevent opportunistic infections	**IVIG therapy may be considered medically necessary when the IgG level is less than 400 mg/dl.**
Severe anemia due to human parvovirus B19	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Toxic Shock Syndrome (TSS)	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Autoimmune / Inflammatory Conditions	
Autoimmune mucocutaneous blistering diseases • **pemphigus, pemphigoid, pemphigus vulgaris, and pemphigus foliaceus**	**IVIG therapy may be considered medically necessary for severe progressive disease, and the patient has failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide**
Idiopathic thrombocytopenic purpura (ITP)- Adults	**IVIG therapy may be considered medically necessary when:** • Platelet count is <10,000/mm^3 and individual is considered at risk for severe bleeding or cerebral bleeding **OR** • Platelet count is <30,000/ mm^3 and **ONE** of the following medically necessary situations is present: o Need to rapidly increase platelets due to bleeding, major surgery planned, or risk of cerebral bleeding **OR** o Not a candidate for splenectomy, or experienced relapse post splenectomy **AND** o Failure, contraindication, or intolerance to corticosteroids* ***Note:** See **5.01.566- Pharmacotherapy of Thrombocytopenia**

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
	for more details
Idiopathic thrombocytopenic purpura (ITP)- Pediatric	**IVIG therapy may be considered medically necessary when:** • Platelet count is <30,000/mm^3 and **ONE** of the following medically necessary situations is present: ○ Need to rapidly increase platelets due to bleeding, major surgery planned, or risk of cerebral bleeding **OR** ○ Prevention of bleeding in first 12 months after diagnosis
Adults with Guillain-Barré syndrome	**IVIG therapy may be considered medically necessary as an equivalent alternative to plasma exchange.**
Kawasaki syndrome	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Wegener granulomatosis (GPA)	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Chronic inflammatory demyelinating polyneuropathy (CIDP) with progressive symptoms for at least 2 months	**IVIG therapy may be considered medically necessary with diagnosis based on:** • Progressive or relapsing motor and/or sensory symptoms of more than one limb **AND** hyporeflexia or areflexia in affected limbs present for at least 2 months • Electrophysiologic findings indicate demyelinating neuropathy (3 of the following 4 criteria are met per the American Academy of Neurology): ○ Partial conduction block of ≥ 1 motor nerve ○ Reduced conduction velocity of ≥ 2 motor nerves ○ Prolonged distal latency of ≥ 2 motor nerves ○ Prolonged F-wave latencies of ≥ 2 motor nerves or the absence of F waves • Other causes of demyelinating neuropathy have been excluded (Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure, hereditary demyelinating neuropathy. prominent

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
	sphincter disturbance, multifocal motor neuropathy (MMN), IgM monoclonal gammopathy, and others • **If available**, results of other testing to support diagnosis should be provided. Such as: o Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count <10/mm^3 o MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses o Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis
Multifocal motor neuropathy	**IVIG therapy may be considered medically necessary with this documented diagnosis, and symptoms have been present for one month or longer.**
Eaton-Lambert myasthenic syndrome	**IVIG therapy may be considered medically necessary when the patient fails to respond to anticholinesterase medications (Mestinon), corticosteroids, and/or azathioprine.**
Neuromyelitis optica	**IVIG therapy may be considered medically necessary when there is a contraindication to, or lack of response to first-line treatment, such as steroids or plasma exchange.**
Severe refractory myasthenia gravis	**IVIG therapy may be considered medically necessary when the patient has chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.**
Myasthenic exacerbation (ie, acute episode of respiratory muscle weakness)	**IVIG therapy may be considered medically necessary when plasma exchange is contraindicated or as an alternative.**
Dermatomyositis or polymyositis	**IVIG therapy may be considered medically necessary when:**

Condition	Medical Necessity
IVIg therapy is subject to review for site of service administration.	
	• The disease is refractory to treatment with corticosteroids **AND** • IVIG is used in combination with other immunosuppressive agents
Warm antibody hemolytic anemia	**IVIG therapy may be considered medically necessary when the disease is refractory to other therapies: azathioprine, cyclophosphamide, prednisone, plasmapheresis, or splenectomy.**
Antiphospholipid syndrome	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Multiple Sclerosis	**IVIG therapy is considered not medically necessary for patients with any type of multiple sclerosis**
Alloimune Processes	
Neonatal alloimmune thrombocytopenia	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Miscellaneous	
Stiff person syndrome	**IVIG therapy may be considered medically necessary when All of the following are present:** • The diagnosis is based on clinical findings and positive anti-GAD antibodies, or anti-amphiphysin antibodies, and EMG test **AND** • The patient has significant disability (uses walker or cane) **AND** • The patient has not improved with diazepam or baclofen

Condition	Investigational
Immunodeficiency states	**IVIG therapy is considered investigational for patients who have received a solid organ transplant for:**

Condition	Investigational
	• Prophylaxis or treatment of acute antibody mediated rejection
Infections	**IVIG therapy is considered investigational for:** • Patients with neonatal sepsis (prophylaxis or treatment) • Adult patients with sepsis
Autoimmune / inflammatory conditions	**IVIG therapy is considered investigational for:** • Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis • Patients with inclusion body myositis • Patients with systemic lupus erythematosus • Patients with immune optic neuritis • Patients with Crohn disease • Patients with hemophagocytic lymphohistiocytosis
Alloimmune processes	**IVIG therapy is considered investigational for:** • Patients with recurrent spontaneous abortion
Miscellaneous	**IVIG therapy is considered investigational for patients with:** • Acquired factor VIII inhibitors • Acute lymphoblastic leukemia • Acute myocarditis • Adrenoleukodystrophy • Alzheimer disease • Aplastic anemia • Asthma • Autism spectrum disorder • Behçet syndrome • Birdshot retinopathy • Chronic fatigue syndrome • Chronic sinusitis • Complex regional pain syndrome • Cystic fibrosis • Diabetes mellitus • Diamond-Blackfan anemia • Epidermolysis bullosa acquisita • Epilepsy • Fisher syndrome • Goodpasture syndrome • Hemolytic uremic syndrome • IGG subclass deficiency

Condition	Investigational
	• Immune-mediated neutropenia • Multiple myeloma • Necrotizing fasciitis • Nonimmune thrombocytopenia • Noninfectious uveitis • Opsoclonus-myoclonus • Organ transplant rejection • Other vasculitides besides Kawasaki disease, including polyarteritis nodosa • Otitis media, recurrent • Paraneoplastic syndromes • Paraproteinemic neuropathy • Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections (PANDAS) • Pericarditis, refractory recurrent • Polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy [CIDP]) • Post-polio syndrome • Red cell aplasia • Rheumatoid arthritis, refractory • Thrombotic thrombocytopenic purpura (TTP) • Vasculitis associated with other connective tissue diseases

Subcutaneous Immune Globulin (SCIG) Therapy

Condition	Medical Necessity
Conditions where SCIG is covered	**Subcutaneous immune globulin (SCIG) therapy may be considered medically necessary for any condition where IVIG would otherwise be covered.**

Condition	Investigational
All other diagnoses	**Other applications of SCIG therapy are considered investigational.**

Approval	Criteria
Initial authorization	**The initial authorization will be for 6 months unless otherwise indicated (eg, in bone marrow transplant).**
Re-authorization	**At the time of re-authorization for ongoing care, it is expected that there will be clinical documentation of objective measures of response (eg, reduction in the incidence of infections). Re-authorization will be provided for 12 months unless otherwise indicated.**

Documentation Requirements
The medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of: • Diagnosis/condition • History and physical examination documenting the severity of the condition, including frequency and severity of infections if applicable • Laboratory results or diagnostic evidence supporting the indication for immune globulin

Coding

Code	Description
CPT	
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
HCPCS	
J1459	Injection, immune globulin (Privigen), intravenous, nonlyophilized (eg, liquid), 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (eg, liquid), 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), non-lyophilized (eg, liquid), 500 mg

Code	Description
J1562	Injection, immune globulin (Vivaglobin), 100 mg
J1566	Injection, immune globulin, intravenous, lyophilized (eg, powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin (Octagam) intravenous, non-lyophilized (eg, liquid), 500 mg
J1569	Injection, immune globulin (Gammagard) intravenous, non-lyophilized (eg, liquid), 500 mg
J1572	Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (eg, liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immune globulin
J1599	Injection, immune globulin, intravenous, non-lyophilized (eg, liquid), not otherwise specified, 500 mg

Related Information

This policy only addresses nonspecific pooled preparations of immunoglobulin (IG); it does **not** address IG preparations that are specifically used as passive immunization to prevent or reduce infection that may occur with specific viral diseases that include but may not be limited to:

- Cytomegalovirus (CMV)
- Hepatitis A
- Hepatitis B
- Measles
- Respiratory syncytial virus (RSV)
- Rubella
- Varicella/chickenpox

Black Box Warnings and Precautions for IVIG:

- Thrombosis may occur with immunoglobulin products. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial

thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

- For individuals at risk of thrombosis, administer immunoglobulin products at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in individuals at risk for hyperviscosity.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of human IVIG products in predisposed individuals. Individuals predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes, age greater than 65, volume depletion, sepsis, paraproteinemia, or individuals receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in individuals receiving IVIG products that contain sucrose.
- For individuals at risk of renal dysfunction or renal failure, administer IVIG at the minimum infusion rate practicable.

Additional warnings and precautions include:

- Immunoglobulin A (IgA)-deficient individuals with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output, in individuals at risk of developing acute renal failure.
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in individuals receiving IVIG therapy.
- Thrombosis may occur. Monitor individuals with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic meningitis syndrome may occur in individuals receiving IVIG therapy, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IVIG treatment. Monitor individuals for signs and symptoms of hemolysis and hemolytic anemia.
- Monitor individuals for pulmonary adverse reactions (transfusion-related acute lung injury).

- Individuals receiving IVIG for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for developing fever, chills, nausea, and vomiting.
- IVIG is made from human plasma and may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent).
- Passive transfer of antibodies may confound serologic testing.

The subcutaneous immunoglobulin (SCIG) product information labels note that reactions similar to other immunoglobulin products may occur. The most common adverse events with subcutaneous injections include local reactions (ie, swelling, redness, heat, pain, and itching at the injection site).

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) should have an established diagnosis of CIDP such as criteria established by the American Academy of Neurology in 1991 or those described in a guideline from the European Federation of Neurological Societies and the Peripheral Nerve Society, published in 2006 and updated in 2010. There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

IVIG treatment in CIDP should be limited to patients who do not respond to initial therapy with prednisone and are experiencing serious clinical worsening. In patients treated for chronic diseases (eg, CIDP, multifocal motor neuropathy, dermatomyositis), the effect of IVIG is transitory and therefore periodic infusions of IVIG are needed to maintain treatment effect. The frequency of transfusions is titrated to the treatment response; typically, biweekly or monthly infusions are needed.

Consideration of Age

In relation to infusion place of service, the age described in this policy for medical necessity of select intravenous and injectable therapy services is 13 years of age or older. The age criteria are based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and

age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to patients above the age of 13.

The ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for this drug.

Benefit Application

Based on benefits or contract language, IVIG may be considered either a pharmacy or medical benefit.

Evidence Review

Description

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immune deficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G antibodies against a wide variety of bacterial and viral antigens. This policy addresses the use of human immunoglobulin therapy for preventing and/or treating disorders in the outpatient setting. Both intravenous immunoglobulin (IVIG) infusion and subcutaneous immunoglobulin (SCIG) infusion are addressed. However, the policy only considers nonspecific pooled preparations of IVIG; it does not consider other preparations used for passive immunization to specific antigens.

Background

Immunoglobulins are derived from human donor plasma and used to treat an array of disorders, including primary and secondary immunodeficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against a wide variety of bacterial and viral antigens. Two formulations of human IgG are available: intravenous

immunoglobulin (IVIG) and subcutaneous immunoglobulin. Intramuscular immunoglobulin depot injections have been largely abandoned.

IVIG is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIG has been used to correct immunodeficiencies in patients with 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. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (eg, Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

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

IVIG is considered a mainstay of treatment for immunodeficiency conditions and bullous skin disorders. It has been prescribed off-label to treat a wide variety of autoimmune and inflammatory neurologic conditions.

Summary of Evidence

Immunodeficiency States

Primary Humoral Immune Deficiencies

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.

For individuals who have primary humoral immunodeficiency who receive IVIG or SCIG therapy, the evidence includes multiple RCTs and noncomparative studies. Relevant outcomes are overall survival, symptoms, change in disease status, morbid events, functional outcomes, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG and SCIG therapy improved disease-related outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Hematopoietic Cell Transplantation (Prophylaxis)

Hematopoietic cell transplantation (HCT) 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.

For individuals who are undergoing HCT who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs, systematic reviews, and a meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for routine prophylaxis of infection in patients undergoing HCT was not associated with survival benefit or reduction in infection. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Acute Antibody-Mediated Rejection After Solid Organ Transplant

Acute rejection after transplant can be broadly divided into 2 categories: the more common acute cellular rejection related to activation of T cells, and the less common acute antibody-mediated rejection (ABMR) 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.

For individuals who are at risk of acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes multiple RCTs, noncomparative observational studies, systematic reviews, and meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for prophylaxis of infection in patients with high panel reactive antibody levels was not associated with a survival benefit or reduction in infection. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective

studies. Larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Infections

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) 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 (less than 400mg/dl) are likely to benefit from monthly infusions of IVIG.

For individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in CLL patients has shown reductions in minor and moderate infections without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

HIV-Infected Children

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

For individuals who are HIV-infected children with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes a single RCT. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prevention of opportunistic infections in HIV-infected children has shown reductions in minor and serious infections without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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.

For individuals who are preterm and low birth weight infants with sepsis who receive IVIG therapy (treatment), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Prophylaxis of Neonatal Sepsis

For individuals who are preterm and low birth weight infants and at risk for sepsis who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown 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. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Treatment of Sepsis in Adults

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for adult sepsis showed reductions in mortality in the meta-analysis. However, multiple factors preclude recommending routine use of IVIG to treat sepsis. They include the preponderance of small low-quality studies, use of heterogeneous dosing regimens, types of IVIG preparations used, and changes over time in the management of sepsis. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have severe anemia associated with human parvovirus B19 who receive IVIG therapy, the evidence includes case series. Relevant outcomes are change in disease status, treatment-related mortality, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Toxic Shock Syndrome

Toxic shock syndrome is also called 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.

For individuals who have toxic shock syndrome who receive IVIG therapy, the evidence includes a small RCT and multiple observational studies. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for toxic shock syndrome in adult women has shown reductions in mortality in the small RCT and in multiple observational studies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Autoimmune / Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), 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.

For individuals who have ITP who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, a meta-analysis, and noncomparative studies. Relevant outcomes are disease-specific survival, change in disease status, morbid events, and treatment-related mortality and

morbidity. Compared with corticosteroids, IVIG therapy improved platelet counts. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) 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.

For individuals who have Guillain-Barré syndrome who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 the disease has reduced the prevalence of coronary artery abnormalities.

For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown significant decreases in new coronary artery abnormalities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes systematic reviews and an RCT. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. The success of IVIG in Kawasaki disease has led to the investigation of IVIG therapy for other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial 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. The evidence is sufficient to determine that he technology results in a meaningful improvement in the net health outcome.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) 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. CIDP is difficult to diagnose due to its heterogeneous presentation (both clinical and electrophysiological).

For individuals who have CIDP who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (eg, 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIPD might be effective, with relatively low adverse events, but this trial also had a number of limitations (eg, small sample, 30% dropout rate). The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have MMN who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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.

For individuals who have Eaton-Lambert myasthenic syndrome who receive IVIG therapy, the evidence includes an RCT and multiple observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in outcomes assessing muscle strength and activity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Neuromyelitis Optica

Neuromyelitis optica (NMO) 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.

For individuals who have NMO who receive IVIG therapy, the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Studies have shown that IVIG treatment may

benefit patients who are refractory to first-line treatment with steroids or plasma exchange, particularly children. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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.

For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. Compared with plasma exchange, IVIG therapy did not show significantly improved outcomes but was better tolerated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Relapsing-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.

For individuals who have RRMS who receive IVIG therapy, the evidence includes multiple RCTs and technology assessments. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. According to technology assessments, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Hayes concluded, "Evidence regarding the efficacy of IVIG as a treatment for MS is conflicting. There is some evidence from published studies that IVIG may reduce the frequency of acute exacerbations and provide symptomatic relief in patients with relapsing-remitting forms of MS and may lessen the pregnancy-related exacerbations of MS. However, the evidence is relatively

weak, and the effects reported are variable, measured by subjective parameters, and of small magnitude. In addition, there is no information regarding the benefits of IVIG compared with other available therapies. Moreover, the largest placebo-controlled study found no treatment effect of IVIG in patients with secondary progressive disease, and there was no evidence of benefit in patients with MS-related syndromes, including muscle group weakness and optic neuritis. There were no randomized, placebo-controlled studies of IVIG in patients with primary progressive MS."[155]

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.

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes2 RCTs, a systematic review, and multiple uncontrolled studies. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. A systematic review found improvements in over 90% of patients. RCTs have reported benefit in disease activity in the population as a whole (1 trial) or subgroup of patients with severe disease (1 trial). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

For individuals who have TEN or SJS who receive IVIG therapy, the evidence includes systematic reviews of observational studies. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. No RCTs have evaluated IVIG for TEN or SJS; most trials that have, have been uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies are a group of disorders characterized by inflammation of skeletal muscles and include dermatomyositis, polymyositis and inclusion body myositis. 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.

Dermatomyositis and Polymyositis

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes 2 RCTs, multiple noncomparative observational studies, and a systematic review. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. In one of the RCTs, compared with placebo, IVIG therapy showed improvements in muscle strength. A large case series also noted improvements in most patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Inclusion Body Myositis

For individuals who have inclusion body myositis who receive IVIG therapy, the evidence includes multiple RCTs. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy failed to show improvements in muscle strength. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

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.

For individuals who have SLE who receive IVIG therapy, the evidence includes an RCT, multiple observational studies, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 with MS at some time during the course of their illness.

For individuals who have immune optic neuritis who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show improvements in vision-related outcomes. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

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.

For individuals who have Crohn disease who receive IVIG therapy, the evidence includes multiple case reports of single patients summarized in a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have hemophagocytic lymphohistiocytosis who receive IVIG therapy, the evidence includes multiple case reports summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Warm Antibody Autoimmune Hemolytic Anemia

Also known as autoimmune hemolytic anemia, warm antibody autoimmune hemolytic anemia occurs commonly due to IgG antibodies that react with protein antigens on the red blood cell surface at body temperature.

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data. Relevant outcomes are change in disease status, quality of life, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefit with IVIG therapy in select patients. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Antiphospholipid Syndrome

Antiphospholipid syndrome is an autoimmune disease that results from the development of antibodies against phospholipid proteins, which causes venous or arterial thromboses and/or pregnancy morbidity.

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential mortality benefit with IVIG therapy. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Alloimmune Processes

Neonatal Alloimmune Thrombocytopenia

Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet-antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage (ICH) is identified in 10% to 30% of affected neonates. Currently, screening for this condition is unavailable and, thus, thrombocytopenia is only identified at birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia and the severity of thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIG.

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple 2 RCTs and a systematic review. Relevant outcomes are disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Compared with combination use with corticosteroids, IVIG alone did not show any additional increases in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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. Women with recurrent spontaneous abortion frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss.

For individuals who have recurrent spontaneous abortion who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are disease-specific survival, treatment-related mortality, and treatment-related morbidity. In multiple RCTs, compared with placebo, IVIG therapy alone did not show any beneficial effects in preventing spontaneous abortions. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Miscellaneous

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 infections. This syndrome is not well-understood and diagnosis of PANDAS requires expert consultation.

For individuals who have PANDAS who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related mortality and morbidity. The trials had mixed findings and both had small sample sizes and short intervention duration. The evidence is insufficient to determine the effects of the technology on health outcomes.

Autism Spectrum Disorder

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

For individuals who have autism spectrum disorder who receive IVIG therapy, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. Although improvements were observed in 1 case series, the other two reported negative findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have CRPS who receive IVIG therapy, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown improvements in pain scores.

However, methodologic limitations restrict the conclusions drawn from data on 12 patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

Alzheimer Disease

For individuals who have Alzheimer disease who receive IVIG therapy, the evidence includes 3 RCTs. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. With the exception of a few subgroup analyses using MCI status, IVIG therapy was not significantly better than placebo for outcomes such as brain atrophy, level of plasma amyloid β 1–40, or cognition and function. Studies differed by treatment protocols, outcomes assessed, and two of the three had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have paraproteinemic neuropathy who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG showed mild and transitory improvements in 1 trial but failed to show any improvement in another. The evidence is insufficient to determine the effects of the technology on health outcomes.

Chronic Fatigue Syndrome

Chronic fatigue syndrome, aka systemic exertion intolerance disease, is a complex and controversial disease with multiple definitions.

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes an RCT and anecdotal reports. Relevant outcomes are symptoms, quality of life, and

treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown no therapeutic benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 post-infectious inflammatory reaction, or a combination of the two.

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes an RCT, a quasi-randomized trial, and multiple case reports. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy failed to show improvements in event-free survival in the RCT while it showed favorable effects on rates of event-free survival in a quasi-randomized study. However, both studies were rated as very low quality and at a high risk of bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

Refractory Recurrent Pericarditis

Refractory recurrent pericarditis is defined as recurrent pericarditis not responding to conventional anti-inflammatories such as aspirin, nonsteroidal inflammatory drugs, corticosteroids, and colchicine.

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes multiple case reports and case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Although improvements were observed in some patients, controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Stiff Person Syndrome

Stiff person syndrome is a 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.

For individuals who have stiff person syndrome who receive IVIG therapy, the evidence includes an RCT and multiple case reports. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown decreases in stiffness score and improvements in functional outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Noninfectious Uveitis

Noninfectious uveitis is the inflammation of eye that results from eye trauma, anomalous immune processes, or unknown etiology.

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. The case series (total N=28 patients) reported measurable improvements in visual acuity after IVIG therapy, but controlled studies are needed to draw conclusions about the efficacy of IVIG for this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

For individuals who have post-polio syndrome who receive IVIG therapy, the evidence includes multiple RCTs, prospective studies, and a meta-analysis. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Necrotizing Fasciitis

For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes an RCT. Relevant outcomes are overall survival, symptoms, functional outcomes, and treatment-related mortality and morbidity. The RCT found that, compared with placebo, IVIG therapy did not significantly improve functional outcomes, mortality rates, or other outcomes (eg, the use of life support in the intensive care unit). Additional controlled studies are needed to draw conclusions about the efficacy of IVIG for treating necrotizing fasciitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 3 physician specialty societies and 5 academic medical centers in March 2013 after this policy was under review in 2012. Input focused on intravenous immunoglobulin (IVIG) treatment for 7 rare conditions. There was consensus, or near-consensus, that IVIG is investigational for 6 of these conditions: birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, opsoclonus myoclonus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, and polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy). Clinical input was mixed overall on the seventh condition, IVIG for treating severe anemia associated with parvovirus B19.

Additional clinical input was obtained in June 2013, focusing on severe anemia due to parvovirus B19. Input was received from 3 reviewers (all hematologists), and there was consensus that IVIG is not investigational for this indication. There was a lack of consensus among the 3 reviewers on any specific clinical or patient characteristics that can be used to select patients with severe anemia due to parvovirus B19 for treatment with IVIG and on any treatments that should be used by these patients before IVIG.

Practice Guidelines and Position Statements

Immunodeficiency States

Primary Humoral Immune Deficiencies

National Advisory Committee on Blood and Blood Products and Canadian Blood Services

In 2010, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services (CBS) published guidelines on use of immunoglobulin therapy for patients with primary immune deficiency.[2] The guidelines reported that there was sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, lowers mortality, and improves quality of life. Treatment should be started at a dose of 400 to 600 mg/kg per 4 weeks for intravenous immunoglobulin (IVIG) or 100 to 150 mg/kg per week for subcutaneous immunoglobulin infusion.

American Academy of Allergy, Asthma, and Immunology

In 2015, the American Academy of Allergy, Asthma, and Immunology published practice parameters for the diagnosis and management of primary immunodeficiency.[139] The Academy advised that treatment of these conditions include antibiotic prophylaxis and immunoglobulin G (IgG) replacement.

Hematopoietic Cell Transplantation (Prophylaxis)

In 2007, NAC and CBS published guidelines on the use of IVIG for hematologic conditions.[40] The guidelines stated that evidence does not support the use of IVIG after hematopoietic cell transplantation.

Acute Antibody-Mediated Rejection After Solid Organ Transplant

In 2010, CBS and NAC developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation.[140] 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.

Chronic Lymphocytic Leukemia

The National Comprehensive Cancer Network guidelines (v.1.2019) on chronic lymphocytic leukemia recommend IVIG as supportive care for patients with chronic lymphocytic leukemia: for the treatment of autoimmune cytopenias and recurrent sinopulmonary infections (IgG levels <500 mg/dL).[141] The guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.3-0.5 g/kg) to maintain levels of 500 mg/dl.

Infections

Infections in HIV-Infected Children

In 2013, updated joint guidelines on prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published.[26] The guidelines, endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and other agencies and societies, included the following statement: "Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia."

Neonatal Sepsis

The American Academy of Pediatrics published guidelines in 2012 on the management of neonates with suspected or proven early-onset bacterial sepsis.[142] The guidelines did not address the use of IVIG to treat neonatal sepsis.

Autoimmune / Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

In 2007, NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including idiopathic thrombocytopenic purpura (ITP).[40] Recommendations for patients with ITP are as follows:

- Adult acute ITP with bleeding: IVIG strongly recommended as a part of multimodality therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.
- Adult acute ITP with severe thrombocytopenia but no bleeding: IVIG not recommended as first-line therapy alone, except for patients with contraindications to corticosteroids.
- Adult ITP with no or slow response to adequate dose corticosteroids: IVIG may be considered as a possible adjunctive therapy.
- Adult chronic ITP post splenectomy: IVIG may be considered as a possible adjunctive therapy as a corticosteroid-sparing measure. The minimal dose of IVIG should be used that maintains a safe platelet count. Patients should be reevaluated every 3 to 6 months, and alternative therapies to IVIG should be considered for patients who do not achieve a durable response for a minimum of 2 to 3 weeks.

Guillain-Barré Syndrome

The 2012 American Academy of Neurology (AAN) guidelines on the treatment of neuromuscular disorders concluded that IVIG is as efficacious as plasmapheresis and should be offered as a treatment option to adults with Guillain-Barré syndrome (Level A).[59] The guidelines indicated that there was insufficient evidence to support or refute the use of IVIG in children.

The European Federation of Neurological Societies (EFNS) issued guidelines in 2008 on the use of IVIG for the treatment of neurological disorders.[143] The guidelines stated that the efficacy of IVIG treatment of Guillain-Barré syndrome is proven (level A).

Kawasaki Syndrome and Other Vasculitides

The American Academy of Family Physicians (2015)[144] and the American Heart Association (2004)[145] have supported the use of IVIG in the treatment of Kawasaki syndrome.

Chronic Inflammatory Demyelinating Polyneuropathy

The 2012 AAN guidelines on the treatment of neuromuscular disorders stated that IVIG is effective and should be offered in the long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) (level A).[59] The guidelines indicated that data are insufficient to compare the efficacy of prednisone and IVIG in the treatment of CIDP.

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines indicated that the efficacy of IVIG for the treatment of CIDP has been established (level A).

Multifocal Motor Neuropathy

The 2012 AAN guidelines on the treatment of neuromuscular disorders have stated that IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (level B).[59] There were insufficient data to determine the optimal treatment interval, dosing, and duration.

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines indicated that the efficacy of IVIG for the treatment of multifocal motor neuropathy has been established (level A).

Eaton-Lambert Myasthenic Syndrome

The 2012 AAN guidelines on the treatment of neuromuscular disorders stated that IVIG is possibly effective and may be considered for treating Lambert-Eaton myasthenic syndrome (level C).[59]

Neuromyelitis Optica

According to the Neuromyelitis Optica's 2014 updated guidelines, high-dose IVIG is potentially beneficial in long-term treatment of neuromyelitis optica and may be used as an alternative for patients with a contraindication to one of the other treatments or, particularly, in children.[146]

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

The 2012 AAN guidelines on the treatment of neuromuscular disorders concluded that IVIG therapy is probably effective in treating patients with severe myasthenia gravis and should be considered in the treatment plan (level B).[59] There was insufficient evidence to compare IVIG and plasmapheresis in treatment of these patients.

EFNS issued guidelines in 2008 on the use of IVIG to treat neurologic disorders.[143] The guidelines indicated that the efficacy of IVIG for the treatment of acute exacerbations of myasthenia gravis and short-term treatment of severe myasthenia gravis has been established (level A).

Relapsing-Remitting Multiple Sclerosis

In 2002, AAN published a technology assessment on therapies for multiple sclerosis.[79] The assessment was reviewed and reaffirmed in 2018. The assessment offered the following recommendations on IVIG:

- Studies of IVIG to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI (magnetic resonance imaging) outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIG reduces the attack rate in relapsing-remitting multiple sclerosis (type C recommendation: possibly effective, ineffective, or harmful).
- Current evidence suggests that IVIG is of little benefit with regard to slowing disease progression (type C recommendation: possibly effective, ineffective, or harmful).

EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines recommended IVIG as second- or third-line therapy for relapsing-remitting multiple sclerosis, if conventional immunomodulatory therapies are not tolerated (level B).

Autoimmune Mucocutaneous Blistering Diseases

There are currently no guidelines specific to the treatment of autoimmune mucocutaneous blistering disease.

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

In 2016, the British Association of Dermatologists published guidelines on the management of toxic epidermal necrosis and Stevens-Johnson syndrome.[147] These guidelines are accredited by the National Institute for Health and Care Excellence. The guidelines indicated that evidence for the use of IVIG for the treatment of toxic epidermal necrosis and Stevens-Johnson syndrome is not of sufficient quality or consistency.

Idiopathic Inflammatory Myopathies

The 2012 AAN guidelines on IVIG for treating neuromuscular disorders have stated that IVIG is possibly effective and may be considered as a treatment for nonresponsive dermatomyositis (an idiopathic inflammatory condition) in adults (level C).[59]

EFNS issued guidelines in 2008 on the use of IVIG for treating neurologic disorders.[143] The guidelines recommended IVIG in combination with prednisone as a second-line treatment for dermatomyositis (level B).

Immune Optic Neuritis

Optic neuritis presents as a manifestation of multiple sclerosis (see the **Relapsing-Remitting Multiple Sclerosis** section above).

Alloiummune Processes

Neonatal Alloimmune Thrombocytopenia

In 2007, NAC and CBS published guidelines on the use of IVIG for hematologic conditions.[40]

- Treatment of fetus: Evidence is limited and weak but given that the condition is rare and the consequences are serious, IVIG was deemed an appropriate option and should be considered the standard of care.
- Treatment of newborn: First line therapy should be antigen-negative compatible platelets, with IVIG considered as adjunctive therapy.

Recurrent Spontaneous Abortion

In 2011, the Royal College of Obstetricians and Gynecologists issued guidelines on the treatment of recurrent first- and second-trimester miscarriages.[148] The guidelines, accredited by the National Institute for Health and Care Excellence, concluded that IVIG does not improve the live birth rate in women with recurrent miscarriages (level A).

Miscellaneous

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

In 2007, NAC and CBS convened a panel of national experts to develop evidence-based practice guidelines on the use of IVIG for neurologic conditions.[149] The panel recommended the use of IVIG for the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The optimal dose and duration of treatment is uncertain.

Autism Spectrum Disorder

The 2007 NAC and CBS guideline on neurologic conditions did not recommend IVIG for autism.[149]

In 2014, the American Academy of Child and Adolescent Psychiatry published practice parameters on the assessment and treatment of autism spectrum disorder.[150] The Academy parameters did not address the use of IVIG for the treatment of autism spectrum disorder.

Chronic Fatigue Syndrome

In 2007, the National Institute for Health and Care Excellence issued guidance on the diagnosis and management of chronic fatigue syndrome.[151] The guidance was reviewed in 2014, and no changes to the recommendations were made at that time. The guidance indicated that there is no cure for chronic fatigue syndrome and that symptoms (pain, sleep disturbances, physical limitations, and debilitating fatigue) should be managed under supervision of a specialist. The use of IVIG was not addressed.

Viral Myocarditis

In 2013, the American College of Cardiology Foundation and the American Heart Association issued joint guidelines on the management of heart failure.[152] The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

Stiff Person Syndrome

The EFNS issued guidelines in 2008 on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines indicated that IVIG seems to have a favorable effect in the treatment of stiff person syndrome (Level A).

Post-polio Syndrome

EFNS updated its guidelines on the definition and management of post-polio syndrome in 2011.[153] The guidelines indicated that IVIG could have a modest therapeutic effect on post-polio syndrome, though there were limitations to the study evidence (small sample size, inadequate comparators, appropriate dosage). Due to these limitations, EFNS concluded that IVIG cannot be recommended as a standard treatment.

Medicare National Coverage

In 2002, the Centers for Medicare & Medicaid Services published a national coverage determination on IVIG for treatment of autoimmune mucocutaneous blistering diseases.[154] IVIG is covered for patients with biopsy-proven disease who have failed conventional therapy or for

whom conventional therapy is contraindicated, and to supplement conventional therapy in patients with rapidly progressive disease.

No national coverage determinations on other uses of IVIG or subcutaneous immune globulin were identified.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00892112[a]	Intravenous Immunoglobulin (IVIg) for Parvovirus B19(PVB19) Mediated Cardiomyopathy	50	Jan 2019
NCT03065244	KIDCARE (Kawasaki Disease Comparative Effectiveness Trial) (KIDCARE)	250	Sep 2020
NCT02176863[a]	Study of the Efficacy and Safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in Patients With Post-polio Syndrome (FORCE)	210	Jun 2021
NCT03194815	IVIG and Rituximab in Antibody-associated Psychosis - SINAPPS2 (SINAPPS2)	80	Dec 2021
NCT02899702	Effectiveness of Intravenous Immunoglobulins (IVIG) in Toxic Shock Syndromes in Children (IGHN2)	156	Apr 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Regulatory Status

Several IVIG products have been approved by the U.S. Food and Drug Administration (FDA). They include Bivigam® (Biotest) Carimune® (CSL Behring AG), Flebogamma DIF® (Instituto Grifols), GammaSTAN S/D® (Grifols Therapeutics), Gammagard Liquid® (Baxter), Gammagard

S/D® (Baxter), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), and Privigen® (CSL Behring).[1]

Several subcutaneous immunoglobulin products have been approved by FDA. They include Gammagard Liquid® (Baxter), Gamunex-C® (Grifols Therapeutics), Cuvitru® (Baxalta), Hizentra® CSL (Behring AG), Hyqvia® (Baxter), and Vivaglobin® CSL (Behring GmbH).[1]

At least 1 IVIG product is FDA-approved to treat the following conditions[1]:

- Primary humoral immunodeficiency
- Multifocal motor neuropathy
- B-cell chronic lymphocytic leukemia
- Immune (aka idiopathic) thrombocytopenic purpura
- Kawasaki syndrome
- Chronic inflammatory demyelinating polyneuropathy

References

1. Food and Drug Administration (FDA). Vaccines, Blood & Biologics: Immune Globulins. 2018; **https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm127589.htm** . Accessed December 2018.
2. Shehata N, Palda V, Bowen T, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev. Jan 2010;24(Suppl 1):S28-50. PMID 19962579
3. Ochs HD, Gupta S, Kiessling P, et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol. May 2006;26(3):265-273. PMID 16783465
4. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. J Clin Immunol. Mar 2006;26(2):177-185. PMID 16758340
5. Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs. Aug 2013;73(12):1307-1319. PMID 23861187
6. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol. Feb 10 2009;27(5):770-781. PMID 19114702
7. Sullivan KM, Kopecky KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. N Engl J Med. Sep 13 1990;323(11):705-712. PMID 2167452
8. Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol. Dec 2004;15(12):3256-3262. PMID 15579530

9. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. Jul 17 2008;359(3):242-251. PMID 18635429

10. Alachkar N, Lonze BE, Zachary AA, et al. Infusion of high-dose intravenous immunoglobulin fails to lower the strength of human leukocyte antigen antibodies in highly sensitized patients. Transplantation. Jul 27 2012;94(2):165-171. PMID 22735712

11. Kozlowski T, Andreoni K. Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time? Ann Transplant. Apr-Jun 2011;16(2):19-25. PMID 21716181

12. Marfo K, Ling M, Bao Y, et al. Lack of effect in desensitization with intravenous immunoglobulin and rituximab in highly sensitized patients. Transplantation. Aug 27 2012;94(4):345-351. PMID 22820699

13. Stegall MD, Gloor J, Winters JL, et al. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. Am J Transplant. Feb 2006;6(2):346-351. PMID 16426319

14. Mohan S, Palanisamy A, Tsapepas D, et al. Donor-specific antibodies adversely affect kidney allograft outcomes. J Am Soc Nephrol. Dec 2012;23(12):2061-2071. PMID 23160511

15. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. Jul 28 2011;365(4):318-326. PMID 21793744

16. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. Transplantation. Oct 27 2012;94(8):775-783. PMID 23032865

17. Casadei DH, del CRM, Opelz G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation. Jan 15 2001;71(1):53-58. PMID 11211195

18. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Engl J Med. Oct 6 1988;319(14):902-907. PMID 2901668

19. Boughton BJ, Jackson N, Lim S, et al. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol. Mar 1995;17(1):75-80. PMID 7621634

20. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica. Mar-Apr 1996;81(2):121-126. PMID 8641639

21. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol. Sep 1994;88(1):209-212. PMID 7803248

22. Griffiths H, Brennan V, Lea J, et al. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood. Feb 1989;73(2):366-368. PMID 2492832

23. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma. May 2009;50(5):764-772. PMID 19330654

24. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. N Engl J Med. Jul 11 1991;325(2):73-80. PMID 1675763

25. Siberry GK, Abzug MJ, Nachman S, et al. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Pediatr Infect Dis J. Nov 2013;32(Suppl 2):i-KK4. PMID 24569199

26. Centers for Disease Control (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: bacterial infections. 2013; **https://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and-treatment-guidelines/0**. Accessed December 2018.

27. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database Syst Rev. Jul 02 2013;7(7):CD000361. PMID 23821390

28. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database Syst Rev. Mar 27 2015;3(3):CD001239. PMID 25815707

29. Inis Collaborative Group, Brocklehurst P, Farrell B, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. Sep 29 2011;365(13):1201-1211. PMID 21962214

30. Busani S, Damiani E, Cavazzuti I, et al. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. Minerva Anestesiol. May 2016;82(5):559-572. PMID 26474267

31. Ito S, Oyake T, Uchiyama T, et al. Successful treatment with cyclosporine and high-dose gamma immunoglobulin for persistent parvovirus B19 infection in a patient with refractory autoimmune hemolytic anemia. Int J Hematol. Oct 2004;80(3):250-253. PMID 15540900

32. Koduri PR, Kumapley R, Khokha ND, et al. Red cell aplasia caused by parvovirus B19 in AIDS: use of i.v. immunoglobulin. Ann Hematol. Jul-Aug 1997;75(1-2):67-68. PMID 9322687

33. Chuhjo T, Nakao S, Matsuda T. Successful treatment of persistent erythroid aplasia caused by parvovirus B19 infection in a patient with common variable immunodeficiency with low-dose immunoglobulin. Am J Hematol. Mar 1999;60(3):222-224. PMID 10072114

34. Crabol Y, Terrier B, Rozenberg F, et al. Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus b19 infection: a retrospective study of 10 patients and review of the literature. Clin Infect Dis. Apr 2013;56(7):968-977. PMID 23243178

35. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. Aug 01 2003;37(3):333-340. PMID 12884156

36. Linner A, Darenberg J, Sjolin J, et al. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis. Sep 15 2014;59(6):851-857. PMID 24928291

37. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis. Apr 1999;28(4):800-807. PMID 10825042

38. Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. Scand J Infect Dis. Apr 2005;37(3):166-172. PMID 15849047

39. Shah SS, Hall M, Srivastava R, et al. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. Clin Infect Dis. Nov 01 2009;49(9):1369-1376. PMID 19788359

40. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev. Apr 2007;21(2 Suppl 1):S9-56. PMID 17397769

41. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomized, multicenter trial. Lancet. Jan 5 2002;359(9300):23-29. PMID 11809183

42. von dem Borne AE, Vos JJ, Pegels JG, et al. High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. Br Med J (Clin Res Ed). Jan 23 1988;296(6617):249-250. PMID 2449258

43. Jacobs P, Wood L. The comparison of gammaglobulin to steroids in treating adult immune thrombocytopenia. An interim analysis. Blut. Jul 1989;59(1):92-95. PMID 2752179

44. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev. Sep 19 2014;9(9):CD002063. PMID 25238327

45. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Lancet. Jan 25 1997;349(9047):225-230. PMID 9014908

46. Overell JR, Hsieh ST, Odaka M, et al. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. Cochrane Database Syst Rev. Jan 24 2007(1):CD004761. PMID 17253522

47. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. Oct 2003(4):CD004000. PMID 14584002

48. Fortin PM, Tejani AM, Bassett K, et al. Intravenous immunoglobulin as adjuvant therapy for Wegener's granulomatosis. Cochrane Database Syst Rev. Jan 31 2013;1(1):CD007057. PMID 23440811

49. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM. Jul 2000;93(7):433-439. PMID 10874052

50. Eftimov F, Winer JB, Vermeulen M, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. Dec 30 2013;12(12):CD001797. PMID 24379104

51. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. Dec 1994;36(6):838-845. PMID 7998769

52. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. Aug 2001;50(2):195-201. PMID 11506402

53. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomized controlled trial. Lancet Neurol. Jun 2012;11(6):493-502. PMID 22578914

54. Vermeulen M, van Doorn PA, Brand A, et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo-controlled study. J Neurol Neurosurg Psychiatry. Jan 1993;56(1):36-39. PMID 8429321

55. Hahn AF, Bolton CF, Zochodne D, et al. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. Brain. Aug 1996;119 (Pt 4):1067-1077. PMID 8813271

56. Thompson N, Choudhary P, Hughes RA, et al. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol. Mar 1996;243(3):280-285. PMID 8936360

57. Mendell JR, Barohn RJ, Freimer ML, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. Feb 27 2001;56(4):445-449. PMID 11222785

58. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. Lancet Neurol. Feb 2008;7(2):136-144. PMID 18178525

59. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. Mar 27 2012;78(13):1009-1015. PMID 22454268

60. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. Jan 2018;17(1):35-46. PMID 29122523

61. Markvardsen LH, Sindrup SH, Christiansen I, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. Eur J Neurol. Feb 2017;24(2):412-418. PMID 28000311

62. van Schaik IN, van den Berg LH, de Haan R, et al. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst Rev. Apr 18 2005(2):CD004429. PMID 15846714

63. Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology. Mar 1994;44(3 Pt 1):429-432. PMID 8145910

64. Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. Neurology. Nov 14 2000;55(9):1256-1262. PMID 11087764

65. Leger JM, Chassande B, Musset L, et al. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain. Jan 2001;124(Pt 1):145-153. PMID 11133794

66. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo-controlled study. J Neurol Neurosurg Psychiatry. Sep 1995;59(3):248-252. PMID 7673950

67. Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology. Sep 1996;47(3):678-683. PMID 8797464

68. Muchnik S, Losavio AS, Vidal A, et al. Long-term follow-up of Lambert-Eaton syndrome treated with intravenous immunoglobulin. Muscle Nerve. Jun 1997;20(6):674-678. PMID 9149073

69. Rich MM, Teener JW, Bird SJ. Treatment of Lambert-Eaton syndrome with intravenous immunoglobulin. Muscle Nerve. May 1997;20(5):614-615. PMID 9140371

70. Takano H, Tanaka M, Koike R, et al. Effect of intravenous immunoglobulin in Lambert-Eaton myasthenic syndrome with small-cell lung cancer: correlation with the titer of anti-voltage-gated calcium channel antibody. Muscle Nerve. Sep 1994;17(9):1073-1075. PMID 8065398

71. Bird SJ. Clinical and electrophysiologic improvement in Lambert-Eaton syndrome with intravenous immunoglobulin therapy. Neurology. Jul 1992;42(7):1422-1423. PMID 1620360

72. Elsone L, Panicker J, Mutch K, et al. Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients. Mult Scler. Apr 2014;20(4):501-504. PMID 23986097

73. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia. Mar 2013;28(2):65-72. PMID 22841880

74. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. Dec 12 2012;12:CD002277. PMID 23235588

75. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology. Mar 13 2007;68(11):837-841. PMID 17353471

76. Barth D, Nabavi Nouri M, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. Jun 7 2011;76(23):2017-2023. PMID 21562253

77. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. Arch Neurol. Nov 2005;62(11):1689-1693. PMID 16286541

78. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol. Jun 1997;41(6):789-796. PMID 9189040

79. Goodin DS, Frohman EM, Garmany GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. Jan 22 2002;58(2):169-178. PMID 11805241

80. Gurcan HM, Jeph S, Ahmed AR. Intravenous immunoglobulin therapy in autoimmune mucocutaneous blistering diseases: a review of the evidence for its efficacy and safety. Am J Clin Dermatol. Jul 2010;11(5):315-326. PMID 20642294

81. Amagai M, Ikeda S, Hashimoto T, et al. A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid. J Dermatol Sci. Feb 2017;85(2):77-84. PMID 27876358

82. Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol. Apr 2009;60(4):595-603. PMID 19293008

83. Huang YC, Chien YN, Chen YT, et al. Intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. G Ital Dermatol Venereol. Oct 2016;151(5):515-524. PMID 27248150

84. Barron SJ, Del Vecchio MT, Aronoff SC. Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. Int J Dermatol. Jan 2015;54(1):108-115. PMID 24697283

85. Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol. May 2012;31(5):801-806. PMID 22274797

86. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. Dec 30 1993;329(27):1993-2000. PMID 8247075

87. Miyasaka N, Hara M, Koike T, et al. Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial. Mod Rheumatol. Jun 2012;22(3):382-393. PMID 21971943

88. Cherin P, Pelletier S, Teixeira A, et al. Results and long-term follow-up of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis Rheum. Feb 2002;46(2):467-474. PMID 11840450

89. Dalakas MC, Sonies B, Dambrosia J, et al. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology. Mar 1997;48(3):712-716. PMID 9065553

90. Walter MC, Lochmuller H, Toepfer M, et al. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol. Jan 2000;247(1):22-28. PMID 10701893

91. Dalakas MC, Koffman B, Fujii M, et al. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. Feb 13 2001;56(3):323-327. PMID 11171896

92. Sakthiswary R, D'Cruz D. Intravenous immunoglobulin in the therapeutic armamentarium of systemic lupus erythematosus: a systematic review and meta-analysis. Medicine (Baltimore). Oct 2014;93(16):e86. PMID 25310743

93. Boletis JN, Ioannidis JP, Boki KA, et al. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. Lancet. Aug 14 1999;354(9178):569-570. PMID 10470708

94. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. Apr 2006;117(4 Suppl):S525-553. PMID 16580469

95. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology. Mar 8 2005;64(5):804-810. PMID 15753413

96. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. Neurology. Jun 12 2001;56(11):1514-1522. PMID 11402108

97. Rogosnitzky M, Danks R, Holt D. Intravenous immunoglobulin for the treatment of Crohn's disease. Autoimmun Rev. Dec 2012;12(2):275-280. PMID 22579561

98. Rajagopala S, Singh N. Diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics: systematic review from the Indian subcontinent. Acta Med Acad. Jan 2012;41(2):161-174. PMID 23331391

99. Hot A, Madoux MH, Viard JP, et al. Successful treatment of cytomegalovirus-associated hemophagocytic syndrome by intravenous immunoglobulins. Am J Hematol. Feb 2008;83(2):159-162. PMID 17849465

100. Ostronoff M, Ostronoff F, Coutinho M, et al. Hemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin. Bone Marrow Transplant. Apr 2006;37(8):797-798. PMID 16518425

101. Arlet JB, Le TH, Marinho A, et al. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis. Dec 2006;65(12):1596-1601. PMID 16540551

102. Flores G, Cunningham-Rundles C, Newland AC, et al. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. Am J Hematol. Dec 1993;44(4):237-242. PMID 8237993

103. Macintyre EA, Linch DC, Macey MG, et al. Successful response to intravenous immunoglobulin in autoimmune haemolytic anaemia. Br J Haematol. Jun 1985;60(2):387-388. PMID 4005186

104. Bucciarelli S, Espinosa G, Cervera R, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. Aug 2006;54(8):2568-2576. PMID 16868979

105. Rayment R, Brunskill SJ, Soothill PW, et al. Antenatal interventions for feto-maternal alloimmune thrombocytopenia. Cochrane Database Syst Rev. May 11 2011(5):CD004226. PMID 21563140

106. Paridaans NP, Kamphuis MM, Taune Wikman A, et al. Low-dose versus standard-dose intravenous immunoglobulin to prevent fetal intracranial hemorrhage in fetal and neonatal alloimmune thrombocytopenia: a randomized trial. Fetal Diagn Ther. Apr 2015;38(2):147-153. PMID 25896635

107. Berkowitz RL, Lesser ML, McFarland JG, et al. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomized controlled trial. Obstet Gynecol. Aug 2007;110(2 Pt 1):249-255. PMID 17666597

108. Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol. Jan 2006;107(1):91-96. PMID 16394045

109. Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol. May 1996;174(5):1414-1423. PMID 9065105

110. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev. Apr 19 2006(2):CD000112. PMID 16625529

111. Egerup P, Lindschou J, Gluud C, et al. The effects of intravenous immunoglobulins in women with recurrent miscarriages: a systematic review of randomized trials with meta-analyses and trial sequential analyses including individual patient data. PLoS One. Oct 2015;10(10):e0141588. PMID 26517123

112. Wang SW, Zhong SY, Lou LJ, et al. The effect of intravenous immunoglobulin passive immunotherapy on unexplained recurrent spontaneous abortion: a meta-analysis. Reprod Biomed Online. Dec 2016;33(6):720-736. PMID 27720163

113. Christiansen OB, Pedersen B, Rosgaard A, et al. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. Hum Reprod. Mar 2002;17(3):809-816. PMID 11870141

114. Branch DW, Peaceman AM, Druzin M, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. Am J Obstet Gynecol. Jan 2000;182(1 Pt 1):122-127. PMID 10649166

115. Jablonowska B, Selbing A, Palfi M, et al. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. Hum Reprod. Mar 1999;14(3):838-841. PMID 10221723

116. Williams KA, Swedo SE, Farmer CA, et al. Randomized, controlled trial of intravenous immunoglobulin for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. J Am Acad Child Adolesc Psychiatry. Oct 2016;55(10):860-867.e862. PMID 27663941

117. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. Oct 2 1999;354(9185):1153-1158. PMID 10513708

118. Gupta S, Aggarwal S, Heads C. Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. J Autism Dev Disord. Aug 1996;26(4):439-452. PMID 8863094

119. Plioplys AV. Intravenous immunoglobulin treatment of children with autism. J Child Neurol. Feb 1998;13(2):79-82. PMID 9512308

120. DelGiudice-Asch G, Simon L, Schmeidler J, et al. Brief report: a pilot open clinical trial of intravenous immunoglobulin in childhood autism. J Autism Dev Disord. Apr 1999;29(2):157-160. PMID 10382136

121. Goebel A, Bisla J, Carganillo R, et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: a randomized trial. Ann Intern Med. Oct 3 2017;167(7):476-483. PMID 28973211

122. Goebel A, Baranowski A, Maurer K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med. Feb 2 2010;152(3):152-158. PMID 20124231

123. Relkin NR, Thomas RG, Rissman RA, et al. A phase 3 trial of IV immunoglobulin for Alzheimer disease. Neurology. May 02 2017;88(18):1768-1775. PMID 28381506

124. Kile S, Au W, Parise C. IVIG treatment of mild cognitive impairment due to Alzheimer's disease: a randomized double-blinded exploratory study of the effect on brain atrophy, cognition and conversion to dementia. Feb 2017;88(2):106-112. PMID 26420886

125. Dodel R, Rominger A, Bartenstein P, et al. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomized, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol. Mar 2013;12(3):233-243. PMID 23375965

126. Comi G, Roveri L, Swan A, et al. A randomized controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. J Neurol. Oct 2002;249(10):1370-1377. PMID 12382151

127. Dalakas MC, Quarles RH, Farrer RG, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. Ann Neurol. Nov 1996;40(5):792-795. PMID 8957021

128. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. Am J Med. Jul 1997;103(1):38-43. PMID 9236484

129. Robinson J, Hartling L, Vandermeer B, et al. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. Cochrane Database Syst Rev. May 20 2015(5):CD004370. PMID 25992494

130. McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation. May 8 2001;103(18):2254-2259. PMID 11342473

131. Bhatt GC, Sankar J, Kushwaha KP. Use of intravenous immunoglobulin compared with standard therapy is associated with improved clinical outcomes in children with acute encephalitis syndrome complicated by myocarditis. Pediatr Cardiol. Dec 2012;33(8):1370-1376. PMID 22588459

132. Heidendael JF, Den Boer SL, Wildenbeest JG, et al. Intravenous immunoglobulins in children with new onset dilated cardiomyopathy. Cardiol Young. Jan 2018;28(1):46-54. PMID 28797313

133. Imazio M, Lazaros G, Picardi E, et al. Intravenous human immunoglobulins for refractory recurrent pericarditis: a systematic review of all published cases. J Cardiovasc Med (Hagerstown). Apr 2016;17(4):263-269. PMID 26090917

134. Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med. Dec 27 2001;345(26):1870-1876. PMID 11756577

135. LeHoang P, Cassoux N, George F, et al. Intravenous immunoglobulin (IVIg) for the treatment of birdshot retinochoroidopathy. Ocul Immunol Inflamm. Mar 2000;8(1):49-57. PMID 10806434

136. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. Am J Ophthalmol. May 1999;127(5):545-549. PMID 10334347

137. Huang YH, Chen HC, Huang KW, et al. Intravenous immunoglobulin for postpolio syndrome: a systematic review and meta-analysis. BMC Neurol. Mar 22 2015;15:39. PMID 25886512

138. Madsen MB, Hjortrup PB, Hansen MB, et al. Immunoglobulin G for patients with necrotizing soft tissue infection (INSTINCT): a randomized, blinded, placebo-controlled trial. Intensive Care Med. Nov 2017;43(11):1585-1593. PMID 28421246

139. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. Nov 2015;136(5):1186-1205 e1181-1178. PMID 26371839

140. Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med Rev. Jan 2010;24(Suppl 1):S7-S27. PMID 19962580

141. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 1.2019. **https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf** Accessed December 2018.

142. Polin RA, Committee on Fetus Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. May 2012;129(5):1006-1015. PMID 22547779

143. Elovaara I, Apostolski S, van Doorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol. Sep 2008;15(9):893-908. PMID 18796075

144. Saguil A, Fargo M, Grogan S. Diagnosis and management of Kawasaki disease. Am Fam Physician. Mar 15 2015;91(6):365-371. PMID 25822554

145. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. Oct 26 2004;110(17):2747-2771. PMID 15505111

146. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. Jan 2014;261(1):1-16. PMID 24272588

147. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. Jun 2016;174(6):1194-1227. PMID 27317286

148. Royal College of Obstetricians and Gynecologists. The Investigation and Treatment of Couples with Recurrent Firsttrimester and Second-trimester Miscarriage. Royal Colleg of Obstetricians and Gynecologists Green-Top Guidelines No. 17. 2011; **https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf** Accessed December 2018.

149. Feasby T, Banwell B, Benstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev. Apr 2007;21(2 Suppl 1):S57-107. PMID 17397768

150. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. Feb 2014;53(2):237-257. PMID 24472258

151. National Institute for Health and Care Excellence (NICE). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management [CG53]. 2007; **https://www.nice.org.uk/guidance/cg53** Accessed December 2018.

152. Writing Committee Members, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. Oct 15 2013;128(16):e240-327. PMID 23741058

153. Farbu E, Gilhus NE, Barnes MP, et al. Chapter 18: Post-polio syndrome. In: Gilhus NE, Barnes MP, Brainin M, eds. European Handbook of Neurological Management: Volume 1, 2nd Edition. Hoboken, NJ: Blackwell Publishing; 2011.

154. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination for intravenous immune globulin for the treatment of autoimmune mucocutaneous blistering diseases (250.3). 2002; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=158&ncdver=1&CoverageSelection=National&KeyWord=globulin&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAA& Accessed December, 2018

155. Hayes, Inc. Hayes Medical Technology Directory. Intravenous Immunoglobulin for Multiple Sclerosis. Lansdale, PA: Hayes, Inc.; October 2005

156. Perez, E, Bonilla, F, et.al. Specific Antibody Deficiency: Controversies in Diagnosis and Management. Front Immunol 2017;May 22, 8: 586. PMID 28588580.

157. Sorense, R, Paris, K. Specific antibody deficiency. UpToDate (online serial). Waltham, MA: UpToDate; updated July 2018.

History

Date	Comments
09/01/98	Add to Therapy Section - New Policy
03/22/99	Replace Policy - Added myasthenia gravis to medically necessary indications
02/12/02	Replace Policy - Updated policy approved by P&T committee January 2002. No change to policy statement, added reference.
02/11/03	Replace Policy - Updated policy approved by P&T committee February 2003. No change to policy statement.
07/08/03	Replace Policy - Policy replaces CP.MP.PR.8.01.103. Policy updated; added 2 medically necessary myasthenia gravis indications and additional information in the rationale section on autoimmune mucocutaneous blistering diseases, stiff person syndrome, organ transplant rejection, non-infectious uveitis, and demyelinating optic neuritis.
05/11/04	Replace Policy - Policy replaces CP.MP.BC.8.01.05. Policy reviewed and updated by P&T committee 3/24/04; policy statements concerning medically necessary and investigational conditions significantly revised. Policy guidelines, rationale, and references updated.
09/01/04	Replace Policy - Policy renumbered from PR.8.01.103. No changes to dates.
05/10/05	Replace Policy - Scheduled review; policy reviewed and approved by P&T 3/22/05; policy statement changed to remove autoimmune hemolytic anemia from investigational and add B-cell malignancy as medically necessary.
04/11/06	Replace Policy - Scheduled review; minor clarification changes to the policy statement; policy reviewed and approved by P&T 3/28/06.
06/02/06	Disclaimer and Scope update - No other changes.
12/21/06	Codes Updated - No other changes.
05/08/07	Replace Policy - Policy updated with literature review; references added. Policy statement updated to include pure red cell aplasia as a medically necessary off-label indication for IVIg. Reviewed by P&T on March 27, 2007.
08/23/07	Codes Updated - No other changes.
03/11/08	Cross Reference Updated - No other changes.
05/13/08	Replace Policy - Policy updated with literature search; no change to the policy statement. Reviewed by P&T committee on March 25, 2008. Code Q4097 added.
01/13/09	Code Updates - Code added, J1459; effective 1/1/09.
06/09/09	Replace Policy - Policy updated with literature search. Policy updated to include b cell

Date	Comments
	diagnosis under the medically necessary statement. Reviewed by P&T committee March 2009.
03/09/10	Replace Policy - Policy updated with literature search. Multiple Myeloma deleted from the Investigational criteria list in the policy statement. Reviewed by Pharmacy in January 2010.
08/10/10	Replace Policy - Policy updated to include treatment of antibody-mediated rejection or high risk of antibody-mediated rejection of solid organ transplants is considered medically necessary. Codes added: 90284, 96365, 96366, 96369, 96370, 96371; J1567, J1572.
05/10/11	Replace Policy - PANDAS added to the list of investigational applications within the Policy section; Rationale updated in support of this addition. References added.
07/12/11	Replace Policy - Policy updated policy statements for Hizentra: considered medically necessary for FDA-approved indication for txt of PIDD; considered medically necessary for subcutaneous administration as equal to any other IVIG drug as listed as medically necessary in this policy; and considered investigational for any other indication. Description and Rationale sections updated; reference added. Reviewed by P&T in May 2011. Title changed; "Intravenous" removed, to leave the title as "Immune Globulin Therapy".
01/27/12	Codes updated; HCPCS codes J1557 and J7183 added.
02/21/12	Code update; HCPCS code J1559 added to the policy.
04/10/12	Replace policy. Policy rewritten and reorganized, merging content from 8.01.05 (not an active policy). Policy Guidelines updated to support new policy statements. Reviewed by P&T on March 27, 2012. Codes added: J1599 and 90284; code J1567 removed. This policy was approved with a 90-day hold for provider notification and is effective September 1, 2012.
11/26/12	Update Related Policies. Add 5.01.526.
12/09/13	Replace policy. Policy updated with literature search through February 12, 2013. Clinical input added. References 30, 44, 83-86, 97 and 98 added; other references renumbered or removed. PANDAs moved to investigational from medically necessary; birdshot retinopathy added as investigational; laboratory testing section removed from policy. Rationale updated.
03/10/14	Annual Review. Organ transplant rejection deleted from investigational list because it has been considered medically necessary since 2010.
08/11/15	Interim Review. Policy tabled at August MPC meeting for further revisions and formatting changes.
09/08/15	Annual Review. Diagnoses added to Medically Necessary statement: Hemolytic disease of the fetus and newborn (aka erythoblastosis fetalis), Stevens-Johnson syndrome, toxic epidermal necrolysis. Clarified B-Cell-like pathology indications under hematologic subheading. Postpolio syndrome added to Investigational policy

Date	Comments
	statement. Policy statement for treatment of relapsing/remitting multiple sclerosis changed from medically necessary to not medically necessary. Diagnostic criteria for CIDP and MMN moved from the Appendix to the Policy Guidelines section. Subheading for Initial and Ongoing Authorization of Coverage added to Policy Guidelines. All lists put in alphabetical order. Policy updated with literature review through April 20, 2015. References 26, 27, 53, 73-74, 80, 91 added. Policy statements revised as noted. Removed CPT codes 96360, 96361, 96365, 96366, 96399, 95370, 96371; all PX/DX ICD9/ICD10 codes; and HCPCS code J7183 – these are not reviewed in relationship to this policy.
12/11/15	Interim update. Minor formatting change to Policy Guidelines for clarity.
01/20/16	Coding update. New HCPCS code J1575, effective 1/1/16, added to policy.
01/27/16	Minor edit. Reordered codes in coding table for numeric order.
02/01/16	Coding update. HCPCS code J1556 added to policy.
05/01/16	Annual Review, approved April 12, 2016. Policy updated with criteria for site of service for IV infusion of IVIG – considered medically necessary in hospital-based outpatient center only when criteria are met. Policy section reformatted for purposes of clarity and understandability.
05/17/16	Minor edit. Corrected typo related to INCAT sensory sum score.
07/01/16	Interim Review, approved June 14, 2016. Correction made to site of service administration criteria.
10/01/16	Interim update, approved September 13, 2016. Coding updated. Policy moved into new policy format.
11/01/16	Interim Review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages.
02/01/17	Annual Review, approved January 10, 2017. Content adopted from BCBSA most recent update, with literature review through October 2016. New covered indications include stiff-person syndrome, polymyositis, and Wegener's granulomatosis, patients with CLL who meet criteria, and neuromyelitis optica. The following were changed from medically necessary to investigational: treatment of antibody mediated rejection following solid organ transplantation, patients with neonatal sepsis (prophylaxis or treatment), patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. Coding update; removed 90281, 96365, 96366, 96369, 96370 and 96371.
04/01/17	Interim Review, approved March 14, 2017. Five indications, intended for inclusion in the January 2017 update, unintentionally omitted. These 5 indications: toxic shock syndrome (references 36-39 added), warm antibody autoimmune hemolytic anemia (reference 106 and 107 added), antiphospholipid syndrome (references 108 added), X-linked hyper-IgM syndrome, and ataxia telangiectasia. Section on dosing related to rituximab was deleted because it was a typographical error.

Date	Comments
07/01/17	Formatting update; added hyperlinks to Medical Necessity sections.
09/12/17	Formatting updated for clarity in Policy Guidelines section.
11/01/17	Interim Review, approved October 10, 2017. Policy updated to address different therapy approach for ITP for Pediatrics versus Adults based on specialty input. Additional detail for alternative treatments added to policy. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.
01/01/18	Coding update; added HCPCS code J1555 (new code effective 1/1/18).
02/14/18	Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.
02/20/18	Coding update; removed HCPCS code J1460.
05/01/18	Annual Review, approved April 18, 2018. Clarified initial and ongoing authorization criteria. Policy updated with literature search. Medically necessary statement for neuromyelitis optica changed to state when there is contraindication to, or lack of response to, "first-line treatment (particularly in children)". Removed references 95, 96, 122, and 159 as well as duplicate references. Added references 84, 118, 126, and 138. Policy statements otherwise unchanged.
06/01/18	Minor update. Removed IVIG bullet from adult ITP criteria that had been added incorrectly from a related pharmacy policy.
07/01/18	Interim Review, approved June 22, 2018. Reference 155 added. Policy statement updated to read "IVIG therapy is considered not medically necessary for patients with any type of multiple sclerosis." The words relapsing-remitting were removed.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Interim Review, approved December 13, 2018.References 156, 157 added. Medically necessary indications added for those undergoing/undergone CAR-T cell therapy and for specific antibody deficiency (SAD) and ITP in an adult with a platelet count less than 10,000/mm^3.Additional edit approved December 19, 2018. Multiple myeloma is considered investigational; this was inadvertently not reflected in previous policy history.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በእከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).