LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 8.01.503

Immune Globulin Therapy

BCBSA Ref. Policy: 8.01.05

Effective Date:	**Nov. 6, 2026***	RELATED MEDICAL POLICIES:
Last Revised:	Jul. 14, 2026	5.01.550 Pharmacotherapy of Arthropathies
Replaces:	N/A	11.01.523 Site of Service: Infusion Drugs and Biologic Agents
*View the current policy here.		

The Site of Service Medical Necessity criteria within this policy DO NOT apply to Alaska fully insured members; refer to the infusion and injection drug Medical Necessity criteria only.

Site of Service *and* the infusion and injection drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ 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 lifesaving. 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

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only. Please contact Customer Service for more information.

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

For those aged 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:

- Alyglo
- Asceniv
- Bivigam
- Cutaquig
- Cuvitru
- Flebogamma DIF
- Gammagard
- Gammaked
- Gammaplex
- Gamunex-C
- Hizentra
- Hyqvia
- Octagam
- Panzyga
- Privigen
- Qivigy
- Xembify
- Yimmugo

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 and injection 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 infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe, and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion or injection 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 or injections is 6 months or longer. **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual'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 or injections of this drug.** **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at**

Site of Service Administration	Medical Necessity

	increased risk of complications for infusions or injections, including any 1 of the following:
	• Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, % FVC less than or equal to 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 or injection therapy
	• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
	
	This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:
	• CRS is grade 3 or 4 as evidenced by ALL the following:
	  ○ Temperature at least 38 °C
	  ○ Hypotension that requires 1 or more vasopressors
	  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)
	AND
	• The individual will be admitted into an inpatient setting as soon as possible

Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion 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.	
Immunodeficiency States	
Humoral immunodeficiency states	**IVIG therapy may be considered medically necessary for therapeutic use in humoral immunodeficiency states such as acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), lymphoma, or multiple myeloma on anti-B cell immunotherapy (e.g., rituximab, CAR-T, or hematopoietic stem cell transplant [HCT]) when:** • IgG level is less than 500 mg/dl
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 ALL the following criteria are met:** • Laboratory evidence of immunoglobulin deficiency indicated by: ○ Agammaglobulinemia (total immunoglobulin G [IgG] less than 200 mg/dl) **OR** ○ Persistent hypogammaglobulinemia (total IgG less than 500 mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions) **OR** ○ Absence of B lymphocytes **AND** • Documented inability to mount an adequate immunologic response to inciting antigens as indicated by: ○ Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen **OR** ○ Lack of appropriate rise in antibody titer following provocation with a protein antigen **AND** • Persistent and severe infections, despite treatment with prophylactic antibiotics

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
Specific antibody deficiency (SAD)	**IVIG therapy may be considered medically necessary for individuals with specific antibody deficiency (SAD) when ALL the following criteria are met:** • Immunological evaluation with documented normal serum IgG, IgG subclass, IgA, and IgM **AND** • Normal responses to protein antigens (e.g., tetanus and diphtheria toxoid) measured 4 weeks after immunization **AND** • Inadequate responsiveness to pneumococcal polysaccharide vaccine (e.g., Pneumovax23) 4-8 weeks after vaccination as demonstrated by either of the following: ○ The individual is aged less than 6 years, less than 50% of serotypes are protective (i.e., equal to or greater than 1.3 mcg/ml per serotype) **OR** ○ The individual is aged 6 years and older, less than 70% of serotypes are protective (i.e., equal to or greater than 1.3 mcg/ml per serotype) **AND** • Recurrent infections as demonstrated by the following: ○ History of recurrent, severe bacterial sinopulmonary infections despite treatment with: ▪ Pneumococcal vaccination, **AND** ▪ Failure or inadequate response to prophylactic antibiotic therapy **AND** ○ Documented management of underlying asthma or allergic rhinitis (e.g., treatment with nasal or inhaled glucocorticoids, bronchodilators, or antihistamines)
Infections	
Children with HIV to prevent opportunistic infections	**IVIG therapy may be considered medically necessary when:** • IgG level is less than 500 mg/dl

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
Measles post-exposure prophylaxis	**IVIG therapy may be considered medically necessary for measles post-exposure prophylaxis.**
Severe anemia associated with 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 and Inflammatory Conditions	

Autoimmune mucocutaneous blistering diseases:
• **Pemphigoid:**
  ○ **Bullous pemphigoid**
  ○ **Mucous membrane pemphigoid**
• **Pemphigus:**
  ○ **Pemphigus vulgaris**
  ○ **Pemphigus foliaceus**
  ○ **Immunoglobulin A (IgA) pemphigus**
  ○ **Paraneoplastic pemphigus**
	IVIG therapy may be considered medically necessary when:
	• The individual has severe progressive disease
	AND
	• Has tried and had an inadequate response to conventional agents such as corticosteroids, and immunosuppressive agents (e.g., azathioprine, cyclophosphamide, mycophenolate)

Immune thrombocytopenia (formerly known as idiopathic thrombocytopenic purpura) (ITP)-<u>Adults</u>	**IVIG therapy may be considered medically necessary for adult individuals with immune thrombocytopenia when:**
	• The individual is aged 18 years or older
	AND
	• Platelet count is less than 10,000/mm^3 and individual is considered at risk for severe bleeding or intracranial bleeding
	OR
	• Platelet count is less than 30,000/ mm^3 and **1** of the following medically necessary situations is present:
	  ○ Need to rapidly increase platelets due to bleeding, major surgery planned, or risk of intracranial bleeding
	  OR
	  ○ Not a candidate for splenectomy, or experienced relapse post splenectomy
	  AND

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
	○ Has had an inadequate response, contraindication, or intolerance to corticosteroids **Note:** See **5.01.566- Pharmacotherapy of Thrombocytopenia** for more details
Immune thrombocytopenia (formerly known as idiopathic thrombocytopenic purpura) (ITP)-Pediatric	**IVIG therapy may be considered medically necessary for pediatric individuals with immune thrombocytopenia when:** • The individual is aged less than 18 years **AND** • Platelet count is less than 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 intracranial bleeding **OR** ○ Prevention of bleeding in first 12 months after diagnosis
Adults with Guillain-Barré syndrome	**IVIG therapy may be considered medically necessary for adult individuals with Guillain-Barré syndrome when:** • The individual is aged 18 years or older **AND** • Has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness) **AND** • Initial treatment is within 4 weeks of symptom onset
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)	**IVIG therapy may be considered medically necessary for individuals with chronic inflammatory demyelinating polyneuropathy (CIDP) when ALL the following criteria are met:** • The individual has progressive or relapsing motor and/or sensory symptoms of more than 1 limb **AND** hyporeflexia or areflexia in affected limbs is present for at least 2 months **AND** • Has electrophysiologic findings that meet 1 of the following:

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
	○ Prolonged motor distal latency in at least 2 motor nerves ○ Reduced motor conduction velocity in at least 2 motor nerves ○ Prolonged F-wave latency in at least 2 motor nerves ○ Absent F-wave in at least 2 motor nerves plus one other demyelination criterion listed here in at least 1 other nerve ○ Partial motor conduction block in at least 2 motor nerves or in 1 nerve plus one other demyelination criterion listed here ○ Abnormal temporal dispersion conduction in at least 2 motor nerves ○ Distal CMAP duration increase in at least 1 nerve plus 1 other demyelination criterion listed here in at least 1 other nerve **AND** • Other causes of demyelinating neuropathy have been excluded (e.g., Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure, hereditary demyelinating neuropathy, prominent sphincter disturbance, multifocal motor neuropathy (MMN), IgM monoclonal gammopathy, and others) **AND** • **If available**, results of other testing to support diagnosis should be provided. Such as: ○ Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count less than $10/mm^3$ ○ MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses ○ Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis
Myelin oligodendrocyte glycoprotein antibody-	**IVIG therapy may be considered medically necessary for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) when:**

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
associated disease (MOGAD)	• The individual fails to respond to one previous therapy (e.g., glucocorticoids or plasma exchange)
Multifocal motor neuropathy	**IVIG therapy may be considered medically necessary for multifocal motor neuropathy when:** • The individual has stepwise or slowly progressive asymmetric limb weakness for at least 1 month **AND** • Motor involvement of at least 2 nerves on nerve conduction studies **AND** • Sensory nerve conduction studies are normal except for minor vibration loss in the lower limbs
Lambert Eaton myasthenic syndrome	**IVIG therapy may be considered medically necessary for Lambert Eaton myasthenic syndrome when:** • The individual has had an inadequate response to amifampridine (i.e., Firdapse), anticholinesterase medications (e.g., Mestinon, Regonol), corticosteroids, and/or azathioprine.

Neuromyelitis optica spectrum disorder (NMOSD) (previously known as Devic disease or neuromyelitis optica)	**IVIG therapy may be considered medically necessary for neuromyelitis optica spectrum disorder (NMOSD) when:**
	• Diagnosis is confirmed by one of the following clinical characteristics:
	  ○ Optic neuritis
	  ○ Acute myelitis
	  ○ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
	  ○ Acute brainstem syndrome
	  ○ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
	  ○ Symptomatic cerebral syndrome with NMOSD-typical brain lesions
	AND
	• Exclusion of alternative diagnoses (e.g., multiple sclerosis)
	AND
	• The individual has had an inadequate response or contraindication to first-line treatment (e.g., steroids or plasma exchange.

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
Severe refractory myasthenia gravis	**IVIG therapy may be considered medically necessary for severe refractory myasthenia gravis when:** • The individual has chronic debilitating disease despite treatment with cholinesterase inhibitors (e.g., Mestinon, Regonol), or an inadequate response or complications from corticosteroids and/or azathioprine.
Myasthenic exacerbation (i.e., acute episode of respiratory muscle weakness)	**IVIG therapy may be considered medically necessary for myasthenic exacerbation (i.e., acute episode of respiratory muscle weakness) when:** • Plasma exchange is contraindicated
Dermatomyositis or polymyositis	**IVIG therapy may be considered medically necessary for dermatomyositis or polymyositis when:** • Disease is refractory to treatment with corticosteroids **AND** • IVIG is used in combination with other immunosuppressive agents (e.g., azathioprine)
Warm antibody hemolytic anemia	**IVIG therapy may be considered medically necessary for warm antibody hemolytic anemia when:** • The disease is refractory to other therapies: corticosteroids with/without rituximab, azathioprine, cyclophosphamide, plasmapheresis, or splenectomy.
Catastrophic antiphospholipid syndrome	**IVIG therapy may be considered medically necessary for catastrophic antiphospholipid syndrome when:** • Plasma exchange is not an option **AND** • IVIG treatment is not being used as chronic or prophylactic therapy
Multiple sclerosis	**IVIG therapy is considered NOT medically necessary for individuals with any type of multiple sclerosis.**
Acute antibody-mediated transplant rejection (AMTR)	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Alloimmune Processes	
Neonatal alloimmune thrombocytopenia	**IVIG therapy may be considered medically necessary with this documented diagnosis.**

Condition	Medical Necessity
IVIG therapy is subject to review for site of service administration.	
Hemolytic disease of the fetus and newborn (erythroblastosis fetalis)	**IVIG therapy may be considered medically necessary with this documented diagnosis.**
Miscellaneous	
Stiff person syndrome	**IVIG therapy may be considered medically necessary for stiff person syndrome when All of the following criteria are met:** • Diagnosis is based on clinical findings and positive anti-GAD antibodies, or anti-amphiphysin antibodies, and abnormal EMG test **AND** • Activities of daily living are severely limited (e.g., uses walker or cane due to difficulty ambulating) **AND** • The individual has not improved with benzodiazepines (e.g., diazepam) or baclofen

Condition	Investigational
Impaired immunity states	**IVIG therapy is considered investigational for the following:** • Prophylactic use post hematopoietic stem cell transplant or in chronic lymphocytic leukemia, lymphoma, multiple myeloma or solid organ transplant • The individuals who have received a solid organ transplant for prophylaxis of acute antibody-mediated transplant rejection • Treatment for individuals at high risk of antibody-mediated transplant rejection including highly sensitized individuals and those receiving an ABO-incompatible organ prior to solid organ transplant
Infections	**IVIG therapy is considered investigational for the following:** • The individuals with neonatal sepsis (prophylaxis or treatment) • Individuals aged 18 years or older with sepsis
Autoimmune and inflammatory conditions	**IVIG therapy is considered investigational for the following:** • The individuals with Stevens-Johnson syndrome and toxic epidermal necrolysis • With inclusion body myositis

Condition	Investigational
	• With systemic lupus erythematosus • With immune optic neuritis • With Crohn disease • With hemophagocytic lymphohistiocytosis
Alloimmune processes	**IVIG therapy is considered investigational for the following:** • The individuals with recurrent spontaneous abortion
Miscellaneous	**IVIG therapy is considered investigational for individuals with:** • Acquired factor VIII inhibitors • 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 • Encephalitis • Epidermolysis bullosa acquisita • Epilepsy • Fisher syndrome • Goodpasture syndrome • Hemolytic uremic syndrome • IgG subclass deficiency • Immune-mediated neutropenia • Multiple myeloma • Necrotizing fasciitis • Nonimmune thrombocytopenia • Noninfectious uveitis • Opsoclonus-myoclonus • Organ transplant rejection

Condition	Investigational
	• 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
All diagnoses	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

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 diagnoses	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**
All other diagnoses	**Other applications of SCIG therapy are considered investigational.**

Approval	Criteria
Initial authorization	**All drugs listed in the policy may be approved up to 6 months unless otherwise indicated (e.g., in bone marrow transplant).**
Re-authorization	**All drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy with documentation of objective measures of response (e.g., reduction in the incidence of infections) and an IgG of at least 300 mg/dL.**

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 (e.g., liquid), 500 mg
J1551	Injection, immune globulin (Cutaquig), 100 mg
J1552	Injection, immune globulin (Alyglo), 500 mg
J1553	Injection, immune globulin (Yimmugo), 100 mg (new code effective 04/01/2026)
J1554	Injection, immune globulin (Asceniv), 500 mg

Code	Description
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (Xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg (Gammagard SD)
J1568	Injection, immune globulin (Octagam) intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin (Gammagard liquid) non-lyophilized (e.g., liquid), 500 mg
J1572	Injection, immune globulin (Flebogamma/Flebogamma DIF), intravenous, non-lyophilized (e.g., liquid), 500 mg (code termed 01/01/26)
J1575	Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immune globulin
J1576	Intravenous, non-lyophilized (e.g., liquid), 500 mg (Panzyga)
J1577	Injection, immune globulin (Qivigy), 100 mg (new code effective 07/01/26)
J3590	Unclassified biologics (used to report Yimmugo)

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 individuals 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 dose and infusion rate practicable. Ensure adequate hydration in individuals before administration.

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 (e.g., 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 (i.e., swelling, redness, heat, pain, and itching at the injection site).

Primary Immunodeficiency Syndromes

The diagnosis of immunodeficiency and postimmunization titers must be taken in context with the clinical presentation of the individuals and may vary depending on the type of vaccine given and prior immunization history. The following parameters are examples of criteria for the diagnosis of the primary immunodeficiency syndromes.

- Laboratory evidence of immunoglobulin deficiency may include the following definitions:
    - Agammaglobulinemia (total immunoglobulin G [IgG] < 200 mg/dL)
    - Persistent hypogammaglobulinemia (total IgG < 500 mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions)
    - Absence of B lymphocytes

- Inability to mount an adequate antibody response to inciting antigens may include the following definitions:
    - Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen.
    - Lack of appropriate rise in antibody titer following provocation with a protein antigen

Chronic Inflammatory Demyelinating Polyneuropathy

Individuals 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[1] or those described in guidelines from the European Federation of Neurological Societies and the Peripheral Nerve Society, published in 2006 and updated in 2010 and 2021 (as the European Academy of Neurology/Peripheral Nerve Society PNS guidelines).[2] The updated guidelines include IVIG as a recommended first-line treatment option in CIDP.

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 individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, 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 individuals above the age of 13.

The ages stated in this policy for which the drugs are considered medically necessary are based on the US Food and Drug Administration (FDA) labeling for this drug.

Benefit Application

Based on benefits or contract language, SCIG may be considered either a pharmacy or medical benefit and IVIG is considered a 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 inpatient and outpatient settings. 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 (SCIG). 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 individuals 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 (e.g., Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

This policy only addresses nonspecific pooled preparations of IVIG; it does not address other immunoglobulin preparations specifically used for passive immunization to prevent or attenuate

infection with specific viral diseases (e.g., respiratory syncytial virus, cytomegalovirus, hepatitis B).

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 randomized controlled trails (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 the 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 individuals with various acquired and inherited malignant and nonmalignant disorders.

For individuals who are undergoing HCT who receive IVIG therapy (prophylaxis), the evidence includes a systematic review, 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 the standard of care, IVIG for routine prophylaxis of infection in individuals undergoing HCT was not associated with survival benefit or reduction in infection. The evidence is insufficient to determine the effects of the technology on health outcomes.

Acute Antibody-Mediated Rejection After Solid Organ Transplant

Acute rejection after transplant can be broadly divided into two 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 transplants who receive IVIG therapy, the evidence consists of a systematic review, NIH-sponsored RCT, and nonrandomized observational studies. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. The systematic review involving variable quality studies with high to very high risk of bias concluded that there is insufficient data to support or advise against the use of IVIG prophylaxis in solid organ transplants. More adequately powered RCTs are needed. Additionally, studies have shown conflicting results that prophylaxis with IVIG in individuals with high panel reactive antibody (PRA) levels prior to solid organ transplant leads to a significant reduction in PRA levels. Compared with the standard of care, IVIG for prophylaxis of infection in individuals with high panel reactive antibody levels was not consistently 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 transplants 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 the standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective studies; however, 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.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes; most individuals develop hypogammaglobulinemia at some point in the course of their disease. Individuals experiencing recurrent bacterial infections

associated with hypogammaglobulinemia (less than 500 mg/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 individuals has shown reductions in minor and moderate infections without a 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.

Infections

HIV-Infected Children

Prevention of opportunistic infections remains a critical component of care for HIV-infected children even though the 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. The relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for the prevention of opportunistic infections in HIV-infected children has shown reductions in minor and serious infections without a reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in an 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 results in an improvement in 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 a Cochrane review involving multiple RCTs. 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 one or more episodes of any serious infection (considered of marginal clinical importance) with no improvement in any of the other clinically important outcomes, including mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Treatment of Sepsis in Adults

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes a meta-analysis involving multiple RCTs. 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 the routine use of IVIG to treat sepsis. They include the preponderance of small low-quality studies, the 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 that the technology results in an improvement in the net health outcome.

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, the 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 a change in disease status,

treatment-related mortality, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefits with IVIG therapy, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 individuals has shown reductions in mortality in a small RCT and in multiple observational studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Autoimmune and Inflammatory Conditions

Immune thrombocytopenia

Immune thrombocytopenia (ITP), previously known as idiopathic thrombocytopenic purpura, 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 an 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 an improvement in the net health outcome.

Kawasaki Disease

Kawasaki disease is a very common vasculitis 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 an 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 the technology results in an 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, a systematic review, and RCTs. 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 an improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes two RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Only one RCT has directly compared SCIG with IVIG in individuals who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (e.g., 45% of individuals 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 (e.g., 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 an improvement in the net health outcome.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is an autoimmune disease with antibodies directed against the neuromuscular junction. Individuals 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 Lambert-Eaton 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 an improvement in the net health outcome.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder 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 neuromyelitis optica spectrum disorder 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 individuals 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 an 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 systematic review. 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 an 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 a technology assessment. 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 insufficient to determine the effects of the technology on health outcomes.

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 includes two RCTs and a systematic review. 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 individuals. RCTs have reported benefits in disease activity in the population as a whole (one trial) or in a

subgroup of individuals with severe disease (one trial). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

For individuals who have Toxic Epidermal Necrosis (TEN) or Stevens-Johnson Syndrome (SJS) who receive IVIG therapy, the evidence includes systematic reviews of observational studies. The 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: Dermatomyositis and Polymyositis, Inclusion Body Myositis

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 a systematic review and RCTs. The 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 significant improvements in muscle strength. 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. The 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 insufficient to determine the effects of the technology on health outcomes.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease 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 a systematic review of multiple studies. 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 mainly retrospective. More 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 two 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 insufficient to determine the effects of the technology on health outcomes.

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 individuals 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 and case series. 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 and a case report. Relevant outcomes are a change in disease status, quality of life, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select individuals with refractory autoimmune hemolytic anemia. 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 an antibody 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 in catastrophic antiphospholipid syndrome. 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) occurs 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 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 an 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 a 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 insufficient to determine the effects of the technology on health outcomes.

Miscellaneous Indications

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 the diagnosis of PANDAS requires expert consultation.

For individuals who have PANDAS who receive IVIG therapy, the evidence includes two 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 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 one 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 lesions.

For individuals who have CRPS who receive IVIG therapy, the evidence includes two RCTs. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. In one trial, compared with placebo, IVIG therapy was associated with improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 13 individuals. In the other RCT, low-dose IVIG was ineffective in relieving pain in CRPS. 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 three 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 mild cognitive impairment status, IVIG therapy was not significantly better than a 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 individuals with early mild cognitive impairment. 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 two small RCTs. Relevant outcomes are a change in disease status, quality of life, and

treatment-related mortality and morbidity. Compared with placebo, IVIG showed mild and transitory improvements in one 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 the myocardium that can occur 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 a 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 a meta-analysis, RCTs and a retrospective study. Results from a Cochrane review concluded that, after pooling the available data, there was uncertain evidence of the effect of IVIG in preventing deaths. More RCT evidence is required before IVIG can be routinely recommended in the setting of myocarditis. 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 a systematic review of multiple case reports and case series. The relevant outcomes are

overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Although improvements were observed in some individuals, 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, stiff person syndrome 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 a small, randomized crossover study. 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 scores 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 inflammation of the 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 two small case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity. The case series 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 individuals 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 a systematic review of multiple RCTs and nonrandomized prospective studies. 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 insufficient to determine the effects of the technology on health outcomes.

Necrotizing Fasciitis

For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes an RCT. The 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 (e.g., 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 seven rare conditions. There was consensus, or near-consensus, that IVIG is investigational for six 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 three reviewers on any specific clinical or individual characteristics that can be used to select individuals with severe anemia due to parvovirus B19 for treatment with IVIG and on any treatments that should be used by these individuals before IVIG.

Practice Guidelines and Position Statements

American Academy of Allergy, Asthma, and Immunology Work Group Report

In 2017, the American Academy of Allergy, Asthma, and Immunology (AAAAI) published an updated Work Group Report on the use of immunoglobulin in human disease that evaluated published data through June 2015.[138], Table 1 summarizes the conclusions of the Work Group regarding the potential benefit of immune globulin therapy for various disease states.

Table 1. AAAAI Work Group Report Immune Globulin Recommendations[138]

Benefit of Immune Globulin Therapy	Disease State
Definitely beneficial	• Primary immune defects with absent B cells • Primary immune defects with hypogammaglobulinemia and impaired specific antibody production • Distinct genetically defined primary immunodeficiencies with variable defects in antibody quality and quantity • Graves ophthalmopathy • ITP • Kawasaki disease • Reduction of secondary infections in pediatric HIV infection • CMV pneumonitis in solid organ transplants

Benefit of Immune Globulin Therapy	Disease State
	• CIDP • Multifocal motor neuropathy • Guillain-Barré syndrome
Probably beneficial	• Chronic lymphocytic leukemia with reduced IgG and history of infections • Prevention of bacterial infection in HIV-infected children • Primary immune defects with normal IgG and impaired specific antibody production • Dermatomyositis • Birdshot retinopathy • Henoch-Schonlein purpura • Neonatal sepsis • Rotaviral enterocolitis • Bacterial infections in lymphoproliferative disease • Toxic shock syndrome • Enteroviral meningoencephalitis • IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy • Lambert-Eaton myasthenia syndrome • Myasthenia gravis • Stiff-person syndrome • Toxic epidermal necrolysis and Stevens-Johnson syndrome
May provide benefit	• Rasmussen syndrome • Acute disseminated encephalomyelitis • Human T-lymphotropic virus I-associated myelopathy • Cerebral infarctions with anti-phospholipid antibodies • Demyelinative brain stem encephalitis • Lumbosacral or brachial plexitis • Paraproteinemic neuropathy • Autoimmune encephalitides • Opsoclonus myoclonus syndrome • Postinfectious cerebellar ataxia • Acute idiopathic dysautonomia • Autoimmune optic neuropathy • Paraneoplastic cerebellar degeneration • Brown-Vialetto-Van Laere syndrome • Alzheimer disease • Narcolepsy with cataplexy • Limbic encephalitis • Prevention of infection and acute GVHD post-BMT • Prevention of acute humoral rejection in renal transplantation • PANDAS • Delayed pressure urtictimes

Benefit of Immune Globulin Therapy	Disease State
	• Severe persistent high-dose steroid-dependent asthma • Treatment of acute humoral rejection in renal transplantation • Autoimmune blistering skin diseases and manifestation of systemic diseases • Chronic urtictimes • Autoimmune liver disease • Acute myocarditis • Atopic dermatitis • Prevention of unexplained spontaneous recurrent abortion • Prevention of neonatal sepsis • Transient hypogammaglobulinemia of infancy • Other immune mechanism driving recurrent infections that affect B-cell function • Selective antibody deficiency "memory phenotype" • Isolated IgG subclass deficiency (IgG_1, IgG_2, IgG_3) with recurrent infections • Juvenile idiopathic arthritis • Anti-phospholipid antibody syndrome in pregnancy • Severe rheumatoid arthritis • Still disease • Felty syndrome • Macrophage activation syndrome • Polyarteritis nodosa • Post-transfusion purpura • Thrombotic thrombocytopenic purpura • ANCA syndromes • Autoimmune neutropenia • Autoimmune hemolytic anemia/Evan syndrome • Autoimmune hemophilia • Systemic lupus erythematosus • Neonatal alloimmune thrombocytopenia • Neonatal isoimmune hemolytic jaundice • Cystic fibrosis with hypogammaglobulinemia • Postoperative sepsis • Respiratory syncytial virus lower respiratory tract infection (proven for palivizumab) • Pseumdomembranous colitis • Camplylobacter enteritis • Chronic parvovirus B19 • Relapsing-remitting multiple sclerosis • Intractable childhood epilepsy • Postpolio syndrome
Unlikely to be beneficial	• Isolated IgE deficiency

Benefit of Immune Globulin Therapy	Disease State
	• Isolated IgG_4 deficiency • Selective IgA deficiency • Isolated IgM deficiency • Inclusion body myositis • Autoimmune diabetes mellitus • Inflammatory bowel disease • Chronic fatigue syndrome • Cystic fibrosis without hypogammaglobulinemia • Acute rheumatic fever • Viral load in HIV infection • Demyelinating neuropathy associated with monoclonal IgM • Adrenoleukodystrophy • Amyotrophic lateral sclerosis • POEMS syndrome • Paraneoplastic cerebellar degeneration, sensory neuropathy or encephalopathy • Brachial plexopathy • Autism • Non-steroid dependent asthma • Dilated cardiomyopathy

ANCA=anti-neutrophil cytoplasmic autoantibody; BMT=bone marrow transplant; CIDP=chronic inflammatory demyelinating polyneuropathy; CMV=cytomegalovirus; GVHD=graft versus host disease; HIV=human immunodeficiency virus; IgG=immunoglobulin G; ITP=idiopathic thrombocytopenic purpura; PANDAS= pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; POEMS=polyneuropathy, organomegaly, endocrinopathy, monoclonal protein.

Disease State Guidelines

Immunodeficiency States

Primary Humoral Immune Deficiencies

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

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services (CBS) (2010) published guidelines on the use of immunoglobulin therapy for individuals with primary immune deficiency.[4] The guidelines reported that there was sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in individuals 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 (SCIG) infusion.

American Academy of Allergy, Asthma, and Immunology

The American Academy of Allergy, Asthma, and Immunology (2015) 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.

Secondary Immunodeficiency

The American Academy of Allergy, Asthma, and Immunology (2022) published a guideline on the diagnosis and management of secondary hypogammaglobulinemia.[162] The guideline states that using immunoglobulin replacement therapy (with either IVIG or SCIG) is a complex decision that may or may not be based on recommendations from a disease-state specific guideline. Several disease-state specific guidelines are summarized with IgG thresholds for starting therapy, if available for the disease state. The guideline also provides an algorithm that considers patient-specific factors such as history of infection and the effect of a trial of prophylactic antibiotics.

Hematopoietic Cell Transplantation (Prophylaxis)

The NAC and CBS (2007) 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

The CBS and NAC (2010) 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 individuals 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 individuals 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 individuals 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.3.2025) on chronic lymphocytic leukemia recommend IVIG as supportive care for individuals 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 to 0.5 g/kg) to maintain levels of 500 mg/dl.

Infections

Infections in HIV-Infected Children

In 2025, updated joint guidelines on the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published. 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."

- In rare situations in which cART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis."

Neonatal Sepsis

The American Academy of Pediatrics (2018) published guidelines on the management of neonates with suspected or proven early-onset bacterial sepsis.[143] The guidelines did not address the use of IVIG to treat neonatal sepsis.

In 2020, the Surviving Sepsis Campaign, an international panel formed by multiple professional organizations, including the Society of Critical Care Medicine (SCCM), published guidelines on the management of septic shock and sepsis-associated organ dysfunction in children.[158,] Related to IVIG, the authors suggested against the routine use of IVIG in children with septic shock or other sepsis-associated organ dysfunction, based on low quality of evidence.

Autoimmune and Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

The NAC and CBS (2007) issued guidelines on the use of IVIG for hematologic conditions, including immune thrombocytopenia (ITP).[40] Recommendations for individuals with ITP are as follows:

- Adult acute ITP with bleeding: IVIG is 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 is not recommended as first-line therapy alone, except for individuals 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. Individuals should be reevaluated every three to six months, and alternative therapies to IVIG should be considered for individuals who do not achieve a durable response for a minimum of two to three weeks.

Guillain-Barré Syndrome

The American Academy of Neurology (AAN; reaffirmed January 2022) 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).[144] The guidelines indicated that there was insufficient evidence to support or refute the use of IVIG in children.

Kawasaki Syndrome and Other Vasculitides

The American College of Rheumatology (2021)[163] and the American Heart Association (2017)[147] have supported the use of IVIG in the treatment of Kawasaki syndrome.

Chronic Inflammatory Demyelinating Polyneuropathy

The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is effective and should be offered as a long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) (level A).[144] The guidelines indicated that data are insufficient to compare the efficacy of prednisone and IVIG in the treatment of CIDP.

The EFNS and the Peripheral Nerve Society published updated guidelines on the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) in 2021.

- "Both IVIG and oral or intravenous corticosteroids are first-line treatments for CIDP. Based on the level of evidence, the task force did not recommend an overall preference for either treatment modality and weakly recommended either IVIG or corticosteroid treatment. "
- "Both short- and long-term effectiveness, risks, ease of implementation, and cost should be considered:
    - IVIG may be preferable when it comes to short-term treatment effectiveness, or when (relative) contraindications for corticosteroids exist.
    - There is some indication that pulsed corticosteroids may be preferable for long-term treatment effectiveness, because of a possible higher rate and longer duration of remission, or when IVIG is unaffordable or unavailable."

- "Although the evidence from studies is limited, the task force weakly recommended treatment with IVIG compared with plasma exchange, mainly based on the ease of administration of IVIG.
    - In some individuals with good vascular access, plasma exchange may be an acceptable option for chronic treatment."
- "The task force strongly recommended using SCIG for maintenance treatment in CIDP."
- "The task force recommended no preference for either IVIG or SCIG for maintenance treatment in CIDP."
- "During follow-up, the dose should be tailored according to individual treatment response."
- "The task force weakly recommended against using SCIG for induction treatment in CIDP."

Multifocal Motor Neuropathy

The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (level B).[144] There were insufficient data to determine the optimal treatment interval, dosing, and duration.

Lambert-Eaton Myasthenic Syndrome

The AAN (2012) 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).[144]

Neuromyelitis Optica Spectrum Disorder

According to the Neuromyelitis Optica Study Group (2024) updated guidelines, high-dose IVIG is potentially beneficial in the long-term treatment of neuromyelitis optica and may be used as an alternative for individuals with a contraindication to one of the other treatments or, particularly, in children; it may also be used as an add-on therapy.[164]

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

In 2013, the Myasthenia Gravis Foundation of America appointed a task force to develop an international consensus guidance [149] that focused on the appropriate management of myasthenia gravis. The authors of this guidance recommended the use of IGIV or plasma exchange for short-term treatment in individuals with myasthenia gravis with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in individuals with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. Additionally, the guidance notes that the choice between plasma exchange and IGIV depends on individual patient factors and availability and that each therapy is probably equally effective in the treatment of severe generalized myasthenia gravis. For milder myasthenia gravis or ocular myasthenia gravis, the efficacy of IGIV is less certain. The use of IGIV as maintenance therapy can be considered for individuals with refractory myasthenia gravis or for those in whom immunosuppressive agents are relatively contraindicated.

The AAN (2012) guidelines on the treatment of neuromuscular disorders concluded that IVIG therapy is probably effective in treating individuals with severe myasthenia gravis and should be considered in the treatment plan (level B).[144] There was insufficient evidence to compare IVIG and plasmapheresis in the treatment of these individuals.

Relapsing-Remitting Multiple Sclerosis

The AAN (2002) published a technology assessment on therapies for multiple sclerosis.[78] 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 individuals, 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).

The EFNS (2008) issued guidelines on the use of IVIG for the treatment of neurologic disorders.[145] 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

In 2003, a consensus statement on the use of immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases was published.[150], The authors of this statement recommended that immune globulin products be administered in the following situations:

- Failure of conventional therapy
- Contraindications to, or significant adverse effects of, standard treatment
- Progressive disease while receiving appropriate therapy
- Uncontrolled rapidly progressive disease

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

The British Association of Dermatologists (2016) published guidelines on the management of toxic epidermal necrosis and Stevens-Johnson syndrome in adults.[151] These guidelines are accredited by the National Institute for Health and Care Excellence. The guidelines indicated that evidence for the use of IVIG in the treatment of toxic epidermal necrosis and Stevens-Johnson syndrome was not of sufficient quality or consistency.

The British Association of Dermatologists (2019) published guidelines for the management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children and young people, which said, "There is no reliable evidence on the benefits or lack of benefit of any systemic treatments including prednisolone, IVIg, anti-tumor necrosis factor (TNF) biologics or ciclosporin."[152]

Idiopathic Inflammatory Myopathies

The AAN (2012) 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).[144]

Immune Optic Neuritis

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

Alloimmune Processes

Antiphospholipid syndrome

In 2020, the Task Force on Catastrophic Antiphospholipid Syndrome concluded that triple therapy involving anticoagulation with heparin, glucocorticoids, plus either plasma exchange, IVIG, or both "has affected mortality compared to other strategies that did not use plasma exchange, IVIG, or both."[153,] This is a Grade B recommendation.

Neonatal Alloimmune Thrombocytopenia

The NAC and CBS (2007) 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

The Royal College of Obstetricians and Gynecologists (2023) issued guidelines on the treatment of recurrent miscarriages.[154] 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 B).

Miscellaneous

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

The American Academy of Pediatric (AAP) issued a clinical report in 2025 on pediatric acute-onset neuropsychiatric syndrome.[171,] The use of immunoglobulin was noted as investigational and no consensus was made about its use in treatment.

The NAC and CBS (2007) convened a panel of national experts to develop evidence-based practice guidelines on the use of IVIG for neurologic conditions.[155] 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 NAC and CBS (2007) guidelines on neurologic conditions did not recommend IVIG for autism.[155]

The American Academy of Child and Adolescent Psychiatry (2014) published practice parameters on the assessment and treatment of autism spectrum disorder.[156] The Academy parameters did not address the use of IVIG for the treatment of autism spectrum disorder.

Chronic Fatigue Syndrome

The National Institute for Health and Care Excellence (2007; updated 2021) issued guidance on the diagnosis and management of chronic fatigue syndrome.[157]. 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 the supervision of a specialist. The use of IVIG was not addressed.

Viral Myocarditis

The, the American College of Cardiology Foundation and the American Heart Association issued joint guidelines on the management of heart failure in 2013, updated in 2017 and 2022.[158] The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2002) published a national coverage determination on IVIG for the treatment of autoimmune mucocutaneous blistering diseases.[160] IVIG is covered for individuals with biopsy-proven disease who have failed conventional therapy or for whom conventional therapy is contraindicated, and to supplement conventional therapy in individuals 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 ongoing and unpublished trials that might influence this policy are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03194815	A Randomised Phase II Double-blinded Placebo-controlled Trial of Intravenous Immunoglobulins and Rituximab in Patients With Antibody-associated Psychosis (SINAPPS2)	70	Mar 2027
NCT05584631	The Influence of Body Composition on Immunoglobulin Disposition After Intravenous and Subcutaneous Administration	20	Dec 2025
NCT05986734	Evaluation of Subcutaneous Immunoglobulin Product Cutaquig in Terms of Safety and Efficacy in the Treatment of Patients With Primary Immunodeficiencies	100	Dec 2023
NCT05832034	Treatment With add-on IVIg in Myositis Early In the diSease Course May be sUperior to Steroids Alone for Reaching CLinical improvemEnt	48	Sep 2024
NCT06533098	Multicenter, Open-Label, Randomized Study of Nipocalimab or Intravenous Immunoglobulin (IVIG) in Pregnancies At	50	Dec 2029

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Risk of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)		
Unpublished			
NCT05363358[a]	Evaluating the Safety of GAMMAGARD LIQUID for the Treatment of Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy	6086	Dec 2022
NCT05104762	IVIG Versus Plasmapheresis and Guillian Barrie Syndrome	81	Mar 2023

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Regulatory Status

Many IVIG products have been approved by the FDA. These products include but are not limited to Alyglo (GC Biopharma), Asceniv (ADMA Biologics), Bivigam (ADMA Biologics), Flebogamma DIF (Instituto Grifols), Gammagard Liquid (Takeda), Gammagard S/D (Takeda), Gammaked (Kedrion Biopharma), Gammaplex (Bio Products Lab), Gamunex-C (Grifols Therapeutics), Octagam (Octapharma), Panzyga (Pfizer), Privigen (CSL Behring), and Yimmugo (Biotest AG).[3]

Many subcutaneous immunoglobulin products have been approved by the FDA. They include but are not limited to Cutaquig (Octapharma), Cuvitru (Takeda), Gammagard Liquid (Takeda), Gammaked (Kedrion Biopharma), Gamunex-C (Grifols Therapeutics), Hizentra CSL (Behring AG), Hyqvia (Takeda), and Xembify (Grifols Therapeutics).[3]

At least one IVIG product is FDA-approved to treat the following conditions[3]:

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

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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

Date	Comments
	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 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

Date	Comments
	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 erythroblastosis fetalis), Stevens-Johnson syndrome, toxic epidermal necrolysis. Clarified B-Cell-like pathology indications under hematologic subheading. Postpolio syndrome added to Investigational policy 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 are 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.

Date	Comments
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, were 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.
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.

Date	Comments
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.
01/01/20	Annual Review, approved December 10, 2019. Policy updated with literature search through August 2019; references added. Policy statements unchanged. Added Cuvitru and Hyqvia to policy.
07/01/20	Coding update. Added code J1558.
01/01/21	Annual Review, approved December 8, 2020. Policy updated with literature search through August 24, 2020; references added. The following were changed from medically necessary to investigational: IVIG for prophylactic use post HCT, CLL, lymphoma, multiple myeloma or solid organ transplant, and prior to solid organ transplant, treatment for patients at high risk of antibody-mediated rejection including highly sensitized patients and those receiving an ABO-compatible organ. Also, some first-line treatments have been updated and other minor edits made for clarity. Removed HCPCS code J1562. Added HCPCS code C9072. Policy changes effective for dates of service on or after April 7, 2021, following provider notification.
04/07/21	Coding update. Added HCPC code J1554 and added term date 4/1/2021 to HCPC C9072.
11/01/21	Annual Review, approved October 21, 2021. Policy update with literature search through August 31, 2021; references added. Policy statements unchanged. Added site of service review for Asceniv (immune globulin intravenous, human – slra) for dates of service on or after February 4, 2022. Added HCPCS code J3590.
07/01/22	Coding update. Added HCPCS code J1551. Removed HCPCS codes C9072 and J3590.

Date	Comments
08/01/22	Annual Review, approved July 12, 2022. Added site of service review for Cutaquig (immune globulin) for dates of service on or after November 4, 2022.
04/01/23	Annual Review, approved March 14, 2023. Added treatment for encephalitis as investigational. Added medical necessity coverage for acute antibody-mediated transplant rejection. Changed the wording from "patient" to "individual" throughout the policy for standardization.
07/01/23	Coding update. Added new HCPCS code J1576.
02/01/24	Annual Review, approved January 9, 2024. Added site of service review for Panzyga (immune globulin). Removed HCPCS code J1566 for Carimune as it has been removed from the market.
03/01/24	Coding update. Added HCPCS code J1566 back to the policy.
08/01/24	Interim Review, approved July 9, 2024. Clarified IVIG coverage criteria for Guillain-Barré syndrome. Updated IVIG coverage criteria to include treatment of certain individuals with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Updated IgG level requirements from <400 mg/dL to <500 mg/dL across the initial criteria in the policy. Added re-authorization requirement to have an IgG ≥300 mg/dL.
09/01/24	Interim Review, approved August 26, 2024. The following policy change is effective December 5, 2024, following 90-day provider notification. Added site of service review for Alyglo (immune globulin intravenous, human-stwk).
12/01/24	Interim Review, approved November 12, 2024. Added Yimmugo (immune globulin intravenous, human-dira) to the policy. Added treatment for certain individuals in a humoral immunodeficiency state with acute lymphocytic leukemia (ALL). Removed the requirement to have recurrent or persistent infections from the humoral immunodeficiency states coverage criteria. Added HCPCS code J3590 to report Yimmugo.
01/01/25	Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Removed HCPCS code J1599 that was used to report Alyglo and replaced with new HCPCS code J1552.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
07/01/25	Interim Review, approved June 10, 2025. Added measles post-exposure prophylaxis treatment for certain individuals. The following policy changes are effective October 3, 2025, following 90-day provider notification. Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.

Date	Comments
01/01/26	Coding update. Notated HCPCS code J1572 is termed effective January 1, 2026.
04/01/26	Annual Review, approved March 10, 2026. Added Qivigy (immune globulin intravenous, human-kthm) to the policy. Added new HCPCS code J1553. The following policy changes are effective July 2, 2026, following 90-day provider notification. Updated coverage criteria for antiphospholipid syndrome to medically necessary for catastrophic antiphospholipid syndrome when plasma exchange is not an option and IVIG treatment is not being used as chronic or prophylactic therapy. Updated criteria for treatment of Guillain-Barre syndrome to include individuals who has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness) and initial treatment is within 4 weeks of symptom onset. Updated criteria for multifocal motor neuropathy to include individual has stepwise or slowly progressive asymmetric limb weakness for at least 1 month, motor involvement of at least 2 nerves on nerve conduction studies, and sensory nerve conduction studies are normal except for minor vibration loss in lower limbs. Updated coverage criteria for neuromyelitis optica spectrum disorder to include diagnosis is confirmed by one clinical characteristic. Added site of service review for Yimmugo (immune globulin intravenous, human - dira).
07/01/26	Coding update. Added new HCPCS J1577, effective July 1, 2026. Corrected HCPCS code description J1569.
08/01/26	Interim Review, approved July 14, 2026. Updated treatment of CIDP criteria to include a revised requirement for electrophysiologic findings. Removed reference to non-formulary exception reviews. Removed Qivigy from J3590 due to assignment of HCPCS code J1577. The following policy changes are effective November 6, 2026, following 90-day provider notification. Added site of service review for Qivigy (immune globulin). Added site of service to HCPCS code J1577.

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