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Policy Effective Date	**02/01/2025**
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Immunoglobulin (Ig) Therapy (Including Intravenous [IVIG] and Subcutaneous Ig [SCIG])

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual

policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Continuation Therapy:
Continuation of therapy with non-preferred agents **is considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication for an indication listed below, AND
- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy:
Coverage for non-preferred agents will be provided contingent to the criteria in this section. For individuals initiating therapy, the following criteria would apply prior to non-preferred agent use:

- Individual has tried and failed, is intolerant to, or has a clinical contraindication to the preferred agent; AND
- Physician attests that in their clinical opinion, the same intolerance, contraindications, lack of clinical efficacy, or adverse event would not be expected to occur with non-preferred agents;

OR

- The preferred drugs are experiencing documented drug shortages or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration.

State specific drug criteria my apply.

Preferred Drugs	Non-Preferred Drugs
Gammagard Gammaked/Gamunex-C	Gammaplex Panzyga

Octagam Privigen	Gammagard S/D Bivigam Asceniv Alyglo Yimmugo
Hizentra Cutaquig HyQvia Xembify	Cuvitru

Intravenous Immune Globulin (IVIG) may be considered medically necessary for the following U.S. Food and Drug Administration (FDA) labeled indications when the listed criteria are met.	
INDICATIONS:	**CRITERIA**:
Bone marrow transplant (BMT)	1) To prevent risk of infection in the first 100 days post-transplant; **OR** 2) After 100 days post-transplant with serum IgG < 400 mg/dL.
Human immunodeficiency virus (HIV) infected children	**Children** who meet **ANY** of the following criteria: 1) Hypogammaglobulinemia, serum IgG concentration less than 700 mg/dL; **OR** 2) Recurrent serious bacterial infections, defined as two or more major infections such as bacteremia, meningitis, or pneumonia in a one-year period; **OR** 3) Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine; **OR** 4) Living in areas with high measles prevalence and have no antibody response after two doses of measles, mumps, and rubella virus vaccine live; **OR** 5) Exposed to measles (single dose of IVIG); **OR** 6) Chronic bronchiectasis, poorly responsive to standard therapy.
HIV-associated Thrombocytopenia	1) Significant bleeding in thrombocytopenic individuals or platelet count less than 20,000/µl; **AND** 2) Failure of Rh-immune globulin (RhIg) in Rh-positive individuals.
Chronic Lymphocytic Leukemia (CLL)	Individuals with hypogammaglobulinemia (IgG level less than 700 mg/dL), **AND**

	1) One severe bacterial infection within preceding six months, or two or more bacterial infections in one year; **OR** 2) Evidence of specific antibody deficiency.
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Used either alone or following therapeutic plasma exchange to prolong its effect. **NOTE 1:** For established diagnostic criteria for CIDP see the Description section.
Dermatomyositis	Corticosteroid-resistant individuals or individuals in whom corticosteroids are contraindicated.
Kawasaki disease (Mucocutaneous Lymph Node Syndrome [MCLS])	Documented diagnosis.
Multifocal motor neuropathy	Documented diagnosis.
Primary humoral immunodeficiencies including, but not limited to: • Congenital agammaglobulinemia (X-linked agammaglobulinemia), • Hypogammaglobulinemia, • Common variable immunodeficiency (CVID), • X-linked immunodeficiency, • Severe combined immunodeficiency (e.g., X-SCID, jak3, ZAP70, ADA, PNP, RAG defects, Ataxia Telangiectasia, DiGeorge syndrome), • Wiskott-Aldrich syndrome, • Hyper IgM Syndrome.	When **ANY** of the following criteria are met: 1) Agammaglobulinemia: a) Total IgG < 200 mg/dL, or b) Infants with BTK gene and/or absence of B lymphocytes); **OR** 2) Persistent hypogammaglobulinemia: a) Total IgG < 700 mg/dL, AND b) Recurrent bacterial infections, AND c) Lack of response to protein or polysaccharide antigens (inability to make IgG antibody against **EITHER** diphtheria and tetanus toxoids, OR pneumococcal polysaccharide vaccine, OR both) **(See criteria in "Testing Table" below);** **NOTE 2:** Hypogammaglobulinemia associated with cancer must meet criteria above.
Selective IgG subclass deficiency	1) Selective IgG subclass deficiency: a) Deficiency of one or more IgG subclasses to levels less than two standard deviations below the age-specific mean, assessed on at least two occasions while the patient is free of infections; **AND**

	b) Unexplained recurrent or persistent severe bacterial infections despite adequate treatment; **AND** c) Demonstrated inability to mount an adequate response to protein and polysaccharide antigens (inability to make IgG antibody against **EITHER** diphtheria and tetanus toxoids, **OR** pneumococcal polysaccharide vaccine, **OR** both) **(See criteria in "Testing Table" below).** **NOTE 3:** The physician should consider discontinuing IVIG if the number and/or severity of infections have not been reduced, because not all persons with selective IgG subclass deficiencies benefit from IVIG.
Specific Antibody Deficiency (SAD)	1) Normal total IgG levels, with: a) Evidence of recurrent, persistent, severe, difficult-to-treat infections (e.g., recurrent otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, multiple antibiotic hypersensitivities, chronic or recurrent sinusitis) despite aggressive management and treatment with antibiotics, **AND** b) Severe polysaccharide nonresponsiveness **(See criteria in "Testing Table" below).**
Idiopathic Thrombocytopenia purpura (ITP)	• Acute, Severe Idiopathic Thrombocytopenia purpura (ITP) with platelet counts below 30,000/mm; **OR** • Chronic ITP; in individuals with at least 6 months' duration of disease, and with persistent thrombocytopenia, despite treatment with corticosteroids and splenectomy. **NOTE 4**: Acute, severe ITP may be defined by the following parameters: • Acute ITP with major bleeding, e.g., life-threatening bleeding and/or clinically important mucocutaneous bleeding, • Acute ITP with severe thrombocytopenia and at high risk for bleeding complications, • Acute ITP with severe thrombocytopenia and a slow or inadequate response to corticosteroids, or

	• Acute ITP with severe thrombocytopenia and a predictable risk of bleeding in the future (e.g., a procedure or surgery with a high bleeding risk).

Testing Table-For Initiation of IVIG Therapy
NOTE 5: Testing applies ONLY to:
--Primary humoral immunodeficiencies (as noted above)
--Selective IgG Subclass Deficiency
--Specific antibody deficiency (SAD)

Serum antibody titers to tetanus and/or diphtheria

- Obtain serum antibody titer prior to immunization with diphtheria and/or tetanus vaccine, and then again three to four weeks after immunization.
- An inadequate response is defined as less than a fourfold rise in antibody titer and lack of protective antibody level (as defined by laboratory performing the assay).

OR

Serum antibody titers to pneumococcus

- Obtain serum antibody titer prior to immunization, and then again three to six weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (Pneumovax 23).
- An inadequate antibody response is defined as failure to generate a protective antibody titer (defined as specific IgG concentration greater than 1.3 mcg/ml) AND failure to increase the baseline titer at least 2-fold.
- A failed overall challenge test (with Pneumovax 23) is failure in 12 or more serotypes (50% or more) in a child under 6 years of age or failure in 7 or more serotypes (30% or more) in patients age 6 years or older.

Intravenous Immune Globulin may be considered medically necessary *when standard intervention, treatment, and/or therapy has failed, become intolerable, and/or is contraindicated* for **ANY** of the following off-label indications when the listed criteria are met.

INDICATIONS:	**CRITERIA**:
Acute inflammatory demyelinating polyneuropathy, including Guillain-Barré syndrome	Individuals who have one or more of the following: • Rapid deterioration with acute symptoms for less than two weeks; **OR** • Rapidly deteriorating ability to ambulate; **OR** • Unable to ambulate independently for ten meters; **OR** • Deteriorating pulmonary function tests.

	NOTE 6: IVIG is given as an equivalent alternative to plasma exchange in children and adults. (**CAUTION** - this is not the same as chronic fatigue syndrome. Refer to the listing of conditions that are considered experimental, investigational, and/or unproven.)
Acute lymphoblastic leukemia (ALL)	Only for individuals with hypogammaglobulinemia (IgG level less than 700 mg/dL), **AND** • One severe bacterial infection within preceding six months, or two or more bacterial infections in one year; **OR** • Evidence of specific antibody deficiency.
Catastrophic Antiphospholipid Syndrome (CAPS)	• Individuals who have developed widespread thrombotic disease with organ damage, **AND** • Used in combination with anticoagulation and glucocorticoid therapy, **AND** • One course of therapy at dose limit of 2 g/kg in divided doses over 2 to 5 days.
Autoimmune hemolytic anemia	Refractory to corticosteroids or splenectomy.
Autoimmune mucocutaneous blistering diseases (e.g., pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [a.k.a., cicatricial pemphigoid], epidermolysis bullosa acquisita)	Diagnosis has been confirmed by biopsy and pathology report, **AND** • Individual either has failed, has contraindications to, or has experienced significant complications from conventional therapy; **OR** • Individual's disease is aggressively progressing, extensive, or debilitating such that clinical response would not be rapid enough with conventional treatment alone and IVIG will be given along with conventional treatment until conventional treatment takes effect.
Autoimmune neutropenia	Non-responsive to other treatment modalities or those treatments are contraindicated.
Chimeric antigen receptor (CAR) T-cell therapy	Documentation confirming previous chimeric antigen receptor (CAR) T-cell therapy administration; **AND** 1) Individuals with severe hypogammaglobulinemia (serum IgG < 400 mg/dL): **OR** 2) Individuals with hypogammaglobulinemia (IgG level less than 700 mg/dL), AND one severe bacterial infection within preceding six months, or two or more bacterial infections in one year.

Hyperimmunoglobulin E (HIE) syndrome (Job's syndrome, Hyper IgE syndrome)	For documented diagnosis when standard intervention, treatment, and/or therapy has failed, become intolerable, and/or is contraindicated.
Infections, neonates	High-risk, preterm, low-birth-weight neonates, as prophylaxis and/or treatment adjunct.
Refractory polymyositis	Corticosteroid-resistant individuals or individuals in whom corticosteroids are contraindicated.
Lambert-Eaton myasthenic syndrome (LEMS)	Not controlled by anticholinesterases and diaminopyridine.
Limbic encephalitis in a child	For documented diagnosis.
Multiple Myeloma	• "Plateau Phase" (more than three months since diagnosis); **AND** • IgG level <700 mg/dL; **AND** 1. Two or more significant infections in last year or a single life-threatening infection; **OR** 2. Evidence of specific antibody deficiency.
Multiple Sclerosis (MS)	• <u>Severe manifestations of relapsing-remitting type only</u>, **AND** • Other therapy (e.g., interferon beta, glatiramer) has failed, become intolerable, and/or is contraindicated. (**CAUTION** - this is not the same as chronic- [primary- or secondary-] progressive multiple sclerosis. Refer to the listing of conditions that are considered experimental, investigational, and/or unproven.)
Myasthenia gravis (MG)	• Acute severe decompensation when other treatments have been unsuccessful or are contraindicated; **OR** • Myasthenia crisis (i.e., an acute episode of respiratory muscle weakness) in patients with contraindications to plasma exchange; **OR** • Chronic debilitating disease in spite of treatment with cholinesterase inhibitors, and/or complications from or failure of steroids and/or azathioprine, **OR** • Periodical use to maintain remission in patients with MG that is not well controlled despite the use of chronic immunomodulating drugs. **NOTE 7:** For myasthenia crisis, IVIG is administered over 2-5 days.
Neonatal alloimmune thrombocytopenia, severe	When other interventions have failed or are contraindicated.

	(**CAUTION** - this is not the same as non-immune thrombocytopenia. Refer to the listing of conditions that are considered experimental, investigational, and/or unproven.)
Neuromyelitis optica	For documented diagnosis when standard intervention, treatment, and/or therapy has failed, become intolerable, and/or is contraindicated.
Fetal-Neonatal Alloimmume Thrombocytopenia (F/NAIT)	• Pregnant women with a previously affected pregnancy; **OR** • Pregnant women with a familial history of F/NAIT, or those found on screening to have platelet alloantibodies. **NOTE 8**: Timing of IVIG should be based on the severity of fetal thrombocytopenia, determined by cordocentesis, generally around 20-30 weeks.
Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis)	For documented diagnosis when standard intervention, treatment, and/or therapy has failed, become intolerable, and/or is contraindicated.
Neonatal hemochromatosis	For treatment of high-risk pregnant women who have a history of previous pregnancy ending due to hemochromatosis, or an infant affected by hemochromatosis.
Post transfusion purpura severe	For documented diagnosis when standard intervention, treatment, and/or therapy has failed, become intolerable, and/or is contraindicated.
Pure red cell aplasia	• With documented parvovirus B19 infection; **OR** • As salvage therapy for severe anemia refractory to first-line immunosuppressive therapy.
Solid organ transplant	• Prior to transplant for treatment of individuals at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ; **OR** • Following transplant for treatment of antibody-mediated rejection. **NOTE 9:** Initial authorization for a maximum dose of 2 grams/kg monthly for 3 months. Reauthorization for up to 3 months is dependent on documented beneficial clinical response.
Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)	For severe, acute case.
Stiff person syndrome (Moersch-Woltman syndrome)	• Anti-GAD antibody is present; **AND** • Other therapy has failed (i.e., benzodiazepines and/or baclofen, phenytoin, clonidine, tizanidine.

Systemic lupus erythematosus (SLE)	Individuals with severe active illness for whom other interventions have been unsuccessful or intolerable.
Toxic shock syndrome or toxic necrotizing fasciitis due to streptococcal or staphylococcal organisms	• Infection is refractory to several hours of aggressive therapy; **OR** • Undrainable focus is present; **OR** • Individual has persistent oliguria with pulmonary edema.
Vasculitis syndromes	Individuals with severe active illness for whom other interventions have been unsuccessful or intolerable.
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANDAS/PANS).	• Diagnosed with moderate to severe PANDAS/PANS (must rule out more specific disorders before starting IVIG therapy [autoimmune encephalitis, central nervous system vasculitis, neuropsychiatric systemic lupus erythematosus, acute disseminated encephalomyelitis, infectious encephalitis, etc.] **AND** • Laboratory confirmation that the patient is <u>not</u> IgA deficient, **AND** • Documentation that the patient is free of strep infections and other treatable infections, **AND** • One course of therapy at dose limit of 2 grams/kg of child's weight (1 gm/kg per day for 2 days). **EXCEPTION FOR ILLINOIS PLAN ONLY:** Per Illinois state mandate, the continued use of IVIG is considered covered for the treatment of PANDAS/PANS. Additional courses of IVIG therapy for moderate to severe PANDAS/PANS **are considered experimental, investigational and/or unproven**. (See **EXCEPTION FOR ILLINOIS PLAN** above.) **NOTE 10**: It is recommended by the Pandas Physicians Network (PPN) that antibiotics should be prescribed at treatment level dosages for 2 to 4 weeks before initiating IVIG. **NOTE 11: FOR ILLINOIS PLAN ONLY:** Per Illinois state mandate the use of intravenous immunoglobulin (IVIG) is considered covered for the treatment of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANDAS/PANS) when consistent with the criteria outlined in this Medical Policy.

Subcutaneously administered immunoglobulin (SCIG) may be considered medically necessary as an alternative to intravenous Ig therapy when the criteria listed above are met.

The use of **intravenous and/or subcutaneous immunoglobulin is considered experimental, investigational and/or unproven for any indication not listed above**, including but not limited to the following:

- Acquired Factor VIII inhibition;
- Acquired von Willebrand's syndrome;
- Acute disseminated encephalitis (ADEM);
- Acute myocarditis;
- Acute renal failure;
- Adrenoleukodystrophy;
- Alzheimer's disease;
- Amyotrophic lateral sclerosis (ALS or Lou Gehrig disease);
- Aplastic anemia;
- Asthma and inflammatory chest disease;
- Autism [see also medical policy PSY301.014, Autism Spectrum Disorders (ASD)];
- Autoimmune Autonomic Ganglionopathy (AAG);
- Behçet's syndrome;
- Burns;
- Chronic (primary or secondary) progressive multiple sclerosis;
- Chronic fatigue syndrome;
- Chronic sinusitis;
- Complex regional pain syndrome;
- Congenital heart block;
- Crohn's disease;
- Cystic fibrosis;
- Demyelinating optic neuritis;
- Diabetes mellitus;
- Diamond-Blackfan anemia;
- Endotoxemia;
- Epilepsy;
- Euthyroid ophthalmopathy;
- Fisher Syndrome;
- Hemolytic transfusion reaction (except post-transfusion purpura);
- Hemolytic uremic syndrome;
- Hemophagocytic syndrome;
- Inclusion-body myositis;
- Membranous nephropathy;
- Motor neuron syndromes;
- Multiple myeloma (except multiple myeloma with stable plateau phase disease who are at high risk of recurrent infections—see Off-Label indications above);

- Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD);
- Myelopathy, HTLV-1 associated;
- Nephrotic syndrome;
- Non-immune thrombocytopenia;
- Opsoclonus-myoclonus syndrome;
- Paraproteinemic neuropathy;
- Post-infectious sequelae;
- Post-polio syndrome;
- Post-transplant viral infections (e.g., viral myocarditis, BK viremia);
- Progressive lumbosacral plexopathy;
- Rasmussen encephalitis (chronic focal encephalitis);
- Recent-onset dilated cardiomyopathy;
- Recurrent otitis media;
- Recurrent spontaneous abortion or recurrent pregnancy loss (not attributed to Catastrophic Antiphospholipid Syndrome (CAPS);
- Refractory recurrent pericarditis;
- Refractory rheumatoid arthritis, adult and juvenile;
- Sepsis in adult patients;
- Thrombotic thrombocytopenic purpura;
- Uveitis;
- Vasculitides (other than Kawasaki disease), including: vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener granulomatosis, polyarteritis nodosa), Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases.

Policy Guidelines

None.

Description

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 (IMIg) 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. This product has been used to correct immunodeficiencies in patients with inherited or acquired immunodeficiencies and

has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIG products are available for clinical use in the United States. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (e.g., Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

SCIG therapy is used for treating patients with primary immunodeficiencies. A genetic basis for more than 80 different types of primary immunodeficiencies has been discovered, the most common immunodeficiency being primary antibody deficiency that is associated with low levels or total lack of normal circulating immunoglobulins. With SCIG, it is possible for patients to self-administer the therapy.

Immunodeficient disorders are a group of diverse conditions caused by one or more immune system defects resulting in increased susceptibility to infections followed by severe, acute, recurrent, and chronic illnesses. Immunodeficiencies can be primary or secondary, acquired or congenital. High doses of IVIG have been beneficial to some antibody deficient patients not responding well to conventional doses.

Autoimmune disorders are conditions in which the immune system produces auto-antibodies to an antigen within the body, resulting in injury to the body's tissues. The mode of action in autoimmune disorders may be the blocking of abnormal antibody formation.

This medical 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, or hepatitis B).

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

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
CIDP (also known as chronic inflammatory demyelinating polyradiculoneuropathy) is an acquired, immune mediated neuropathy affecting peripheral nerves and nerve roots, typically characterized by a relapsing remitting or progressive course of symmetric weakness of proximal and distal muscles. CIDP is identified by electrodiagnostic and/or pathologic features of demyelination and responsiveness to immunomodulatory treatments. (1)

Patients with CIDP should have an established diagnosis based on criteria like those established by the American Academy of Neurology in 1991, (2) or those described in guidelines from the European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) guidelines, revised in 2021. The 2021 EAN/PNS guidelines are the 2nd revision of the European Federation of Neurological Societies (EFNS)/PNS guidelines. (3) There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

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

Diagnostic Criteria for CIDP

Table 1. European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS) guidelines: Diagnostic Criteria for CIDP (3)

Clinical Criteria for CIDP	
Typical CIDP	**CIDP Variants**
All of the following: • Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least two limbs. • Developing over at least 8 weeks. • Absent or reduced tendon reflexes in all limbs.	One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs): • Distal CIDP: distal sensory loss and muscle weakness predominantly in lower limbs. • Multifocal CIDP: sensory loss and muscle weakness in a multifocal pattern, usually asymmetric, upper limb predominant, in more than one limb. • Focal CIDP: sensory loss and muscle weakness in only one limb. • Motor CIDP: motor symptoms and signs without sensory involvement. • Sensory CIDP: sensory symptoms and signs without motor involvement.
Motor nerve conduction criteria	
1) Strongly supportive of demyelination: At least one of the following: (a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or (b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or (c) Prolongation of F-wave latency ≥20% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN), or (d) Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN) + ≥1 other demyelinating parametera in ≥1 other nerve, or (e) Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥20% of LLN in two nerves; or in one nerve + ≥ 1 other demyelinating parametera except absence of F-waves in ≥1 other nerve, or (f) Abnormal temporal dispersion: >30% duration increase between the proximal and distal	

negative peak CMAP (at least 100% in the tibial nerve) in ≥2 nerves, or
(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥1 nerve[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

- (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms
- (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms
- (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms
- (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms

(2) Weakly supportive of demyelination
As in (1) but in only one nerve.

Note 1. These criteria have been established by using a frequency filter bandpass of 2 Hz to 10 kHz for all parameters, except for distal CMAP duration prolongation where separate criteria were defined for four different LFFs of 2, 5, 10, and 20 Hz. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus.
Note 2. Extensiveness of motor nerve conduction studies (number of nerves to be studied and proximal studies):
• To apply motor nerve conduction criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested.
• If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated at the axilla and at Erb's point.
• Motor conduction block or slowing is not considered in the ulnar nerve across the elbow or the peroneal nerve across the knee.
• Between Erb's point and the wrist, at least 50% CMAP amplitude reduction is required for conduction block in the ulnar and median nerves. Proximal studies of the median nerve may require collision techniques to avoid ulnar nerve components in the median nerve CMAP when recorded from the abductor pollicis brevis muscle (but not when recorded from the flexor carpi radialis muscle).
• For ulnar motor conduction block in the forearm, a Martin-Gruber anastomosis should be ruled out with stimulation of the median nerve at the elbow recording over the abductor digiti minimi muscle.
• For median motor conduction block in the forearm, co-stimulation of the ulnar nerve at the wrist must be ruled out. Stimulation of the median nerve at the wrist while simultaneously recording over the abductor pollicis brevis muscle and the abductor digiti minimi muscle can detect ulnar nerve co-stimulation; stimulation should be adapted so that no CMAP is recorded from the ulnar nerve-innervated abductor digiti minimi muscle.
• If distal CMAP amplitudes are severely reduced (<1 mV), recording from more proximal muscles innervated by the peroneal, median, ulnar or radial nerve may be attempted to demonstrate motor nerve conduction abnormalities meeting electrodiagnostic criteria.

Sensory nerve conduction criteria

(1) CIDP

- Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves.

(2) Possible CIDP

- As in (1).
- Sensory CIDP with normal motor nerve conduction studies needs to fulfil a. or b.
  a) sensory nerve conduction velocity <80% of LLN (for SNAP amplitude >80% of

LLN) or <70% of LLN (for SNAP amplitude <80% of LLN) in at least two nerves (median, ulnar, radial, sural nerve), or

b) sural sparing pattern (abnormal median or radial sensory nerve action potential [SNAP amplitude] with normal sural nerve SNAP amplitude) (excluding carpal tunnel syndrome).

Note 1. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus. 1. Since these criteria do not permit to identify normal reference values compatible with sensory nerve demyelination, sensory CIDP cannot be more than a possible diagnosis as based on clinical and electrophysiological criteria.

Note 2. Decline in sural nerve action potential amplitude occurs with age and use of age-dependent reference values after age 60 is advised.

CIDP indicates chronic inflammatory demyelinating polyneuropathy; LLN, lower limit of normal value; SNAP, sensory nerve action potential; ULN, upper limit of normal value; CMAP, compound muscle action potential; LFF, low frequency filter.

[a] Any nerve meeting any of the criteria (a-g).

[b] Mitsuma et al.

Chronic immune sensory polyradiculopathy (CISP): Patients suspected to have clinically sensory CIDP, but with normal motor and sensory nerve conduction studies may have CISP. Somatosensory evoked potentials may be absent or show very proximal slowing in CISP because sensory axons proximal to the dorsal root ganglia are affected. Because the sensory neurons in the dorsal root ganglia remain intact, standard sensory nerve conduction studies are normal. Although most likely immune-mediated and responding to immune treatment, there is not enough evidence to determine if CISP is demyelinating or related to sensory CIDP and has therefore not been included in the CIDP variant classification. (3)

Regulatory Status

Several IVIG products have been approved by the U.S. Food and Drug Administration (FDA). These products include Carimune® (CSL Behring AG), Flebogamma DIF® (Instituto Grifols), GammaSTAN S/D® (Grifols Therapeutics), Gammagard Liquid® (Takeda), Gammagard S/D® (Takeda), Gammaked® (Kedrion Biopharma), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), Privigen® (CSL Behring), Bivigam™ (ADMA Biologics), Panzyga (Pfizer), and Asceniv™ (ADMA Biologics). (4)

At least 1 IVIG product is FDA-approved to treat the following conditions (4):

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

Several subcutaneous immunoglobulin (SCIG) products have been approved by the FDA. They include Vivaglobin® (ZLB Behring, Kankakee, IL, discontinued by the company in 2013), Hizentra® (CSL Behring AG), Gammagard Liquid (Takeda), Gamunex-C® (Grifols Therapeutics), Gammaked®

(Kedrion Biopharma, Cambridge, MA) and CUVITRU® (Takeda), HyQvia (Takeda), Cutaquig® (Octapharma), Xembify (Grifols Therapeutics). (4)

Rationale

This policy was created in 1990. The policy was updated regularly with searches of the PubMed database. The most recent literature update was performed through December 27, 2023.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Primary Humoral Immune Deficiencies

Clinical Context and Therapy Purpose

The purpose of intravenous immunoglobulin (IVIG) therapy and subcutaneous immunoglobulin (SCIG) therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with primary humoral immunodeficiency.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with primary humoral immunodeficiency. Primary humoral immune 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.

Interventions
The therapies being considered are IVIG and SCIG.

Comparators
The following practice is currently being used to treat primary humoral immunodeficiency: standard of care, which often consists of antibiotics, antiviral drugs, and immunoglobulin therapies.

Outcomes
The general outcomes of interest are overall survival (OS), symptoms, change in disease status, morbid events, functional outcomes, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Clinical Studies
In 2010, the National Advisory Committee on Blood and Blood Products and Canadian Blood Services published guidelines on the use of immunoglobulin therapy for patients with primary immune deficiency; recommendations were based on a systematic review of evidence by a panel of experts. (5) The search identified 3 RCTs, several cohort studies, and numerous case series.

For individuals with immunodeficiencies, both IVIG and SCIG are effective. (6, 7, 8) Use of SCIG for the treatment of primary immunodeficiencies was approved by the U.S. Food and Drug Administration based on an open label, nonrandomized, prospective, multicenter study. (6) Generally, many 10% IVIG solutions can be administered subcutaneously or intravenously, but more concentrated products (e.g., 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse events and provides more stable serum IgG levels. In contrast, SCIG has not been studied as extensively in autoimmune and inflammatory disorders.

Section Summary: Primary Humoral Immune Deficiencies

The evidence for the use of IVIG and SCIG therapy in primary humoral immune deficiencies consists of multiple RCTs and noncomparative studies. The literature was summarized in an evidence-based guideline (involving 102 reports) initiated by the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products. Compared with the standard of care, IVIG and SCIG therapy improved disease-related outcomes.

Hematopoietic Cell Transplantation (HCT) (Prophylaxis)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals are undergoing HCT.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are individuals who are undergoing HCT. HCT is the intravenous infusion of hematopoietic stem and progenitor cells designed to establish marrow and immune function in patients with various acquired and inherited malignant and nonmalignant disorders.

Interventions

The therapy being considered is IVIG therapy.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are disease-specific survival (DSS), symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review and meta-analysis by Raanani et al. (2009) included 30 trials with 4223 patients undergoing HCT. (9) There was no difference in all-cause mortality between IVIG and cytomegalovirus-IVIG compared with controls (relative risk [RR], 0.99; 95% confidence interval

[CI], 0.88 to 1.12; RR=0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections with IVIG compared with control (RR=1.00; 95% CI, 0.90 to 1.10).

Randomized Controlled Trials

The initial use of immunoglobulin for prophylaxis in HCT was based on the RCT by Sullivan et al. (1990) in 369 patients undergoing HCT. (10) The trial showed that neither survival nor risk of relapse was altered by IVIG. However, IVIG treatment was associated with a reduction in the incidence of acute graft versus host disease compared with controls (51% vs 34%) and deaths due to transplant-related causes after transplantation of human leukocyte antigen-identical marrow (46% vs 30%). There were many methodologic flaws in the trial, including a lack of control for type I error for multiple comparisons, the inclusion of a heterogeneous group of patients, and a lack of a placebo control. Subsequent to this pivotal trial, multiple trials have been conducted and systematic reviews have assessed the efficacy of immunoglobulin prophylaxis in HCT to prevent infection and prolong survival.

Section Summary: HCT (Prophylaxis)

The evidence for IVIG for routine prophylaxis of infection in HCT consists of systematic review and meta-analysis and RCTs. A RCT concluded that passive immunotherapy with intravenous immunoglobulin decreases the risk of acute GVHD, associated interstitial pneumonia, and infections after bone marrow transplantation. The most recent systematic review and meta-analysis published in 2009 included 30 trials and concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection.

Solid Organ Transplant - Antibody-Mediated Rejection (ABMR)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are at risk of acute ABMR after a solid organ transplant or who have acute ABMR after solid organ transplant.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals who are at risk of acute ABMR after a solid organ transplant or who have acute ABMR after a solid organ transplant. Acute rejection after transplant can be broadly divided into 2 categories: the more common acute cellular rejection related to activation of T cells, and the less common acute 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 2 years is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Prophylaxis
The risk of ABMR is related to the presence of preformed alloantibodies in the recipient due to prior blood transfusions, transplants, or pregnancies. The presence of alloantibodies is assessed using a panel reactive antibody (PRA) screen. Those with a PRA screen greater than 20% are referred to as "sensitized," and these patients often have prolonged waiting times to identify a compatible donor. Recipients of ABO mismatched donor organs are also at risk of ABMR.

Systematic Review
In 2019, Bourasssa-Blanchette and colleagues published a systematic review involving 18 trials (with 8 RCTs) investigating the impact of IVIG prophylaxis on infection, rejection, graft loss, and death following kidney transplantation. (11) Results revealed that IVIG administration did not reduce cytomegalovirus infection (odds ratio [OR], 0.68; 95% CI, 0.39 to 1.21; 6 studies, n=295), rejection (OR, 0.96; 95% CI, 0.50 to 1.82; 4 studies, n=187), or graft loss (OR, 1.03; 95% CI, 0.46 to 2.30; 6 studies, n=265) in the RCTs. Among the included nonrandomized studies, IVIG administration was associated with a reduction in rejection and graft loss but not cytomegalovirus infection or death.

Randomized Controlled Trials
In the National Institutes of Health (NIH)-sponsored IG02 study, 101 adults with a PRA screen of 50% or higher were randomized to IVIG 2 g/kg monthly for 4 months or placebo. (12) If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reductions in PRA levels compared with placebo (35% vs. 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80% IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than a placebo in reducing anti-human leukocyte antigen antibody levels and improving transplantation rates in highly sensitized patients with end-stage renal disease. In a follow-up

study, the combination of high-dose IVIG and B-cell depletion therapy reduced PRA from 77% to 44% at the time of transplantation. (13)
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Nonrandomized Studies
More recent studies have failed to show a reduction in PRA levels, specifically in patients with a PRA greater than 80%. (14, 15, 16) Nonrandomized clinical observations have suggested that a combination of plasmapheresis plus low-dose IVIG and interleukin-2 blockade or rabbit anti-thymocyte globulin for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients. (17, 18, 19)

Treatment
Systematic Review
Most studies of IVIG treatment for ABMR are retrospective case series from single-institutions. A systematic review by Roberts et al. (2012) of treatments for acute ABMR in renal allografts identified 10,388 citations but only 5 small RCTs, none of which addressed the use of IVIG in the treatment of ABMR. (20) Encouraging results, including those from RCTs, showed some benefit from plasma exchange followed by IVIG in patients with AMR kidney rejection and those with steroid-resistant rejection. (21, 22, 23, 24) A study published by Lefaucheur et al. (2009) compared IVIG, plasmapheresis and rituximab in 24 patients with AMR; 12 were treated with high-dose IVIG alone, and 12 with a combination of IVIG/plasmapheresis/rituximab. Three-year allograft survival was 50% in the IVIG alone and 91.7% in combination treatment group. (25)

Section Summary: Solid Organ Transplant - ABMR
The evidence for the use of IVIG in patients with high PRA levels prior to solid organ transplant consists of multiple RCTs and noncomparative observational studies. Although RCTs have shown conflicting results, prophylaxis with IVIG in patients with high PRA levels prior to solid organ transplant may result in PRA level reduction.

The evidence for the use of IVIG in ABMR consists of retrospective case series, RCTs, and a systematic review of small RCTs. According to results of RCTs, some benefit was shown from plasma exchange followed by IVIG in patients with AMR kidney rejection and those with steroid-resistant rejection.

Chronic Lymphocytic Leukemia (CLL)
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest are individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia. CLL is a disorder characterized by

progressive accumulation of functionally incompetent lymphocytes; most patients develop hypogammaglobulinemia at some point in the course of their disease. Patients experiencing recurrent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of IVIG.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat CLL: standard of care.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Multiple trials and a meta-analysis comparing IVIG with placebo have shown decreased bacterial infections but not decreased mortality. (26, 27, 28, 29, 30, 31) Use of IVIG has not been directly compared with prophylactic antimicrobials. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. Treatment with IVIG has not been shown to increase QOL or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both. (26) Although minor or moderate bacterial infections were significantly less common in patients receiving IVIG, there was no impact on the incidence of major infections, mortality, or nonbacterial infections.

Section Summary: CLL
The evidence for the use of IVIG therapy for prophylaxis of infection in CLL consists of multiple RCTs and a meta-analysis. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in CLL patients has shown reductions in minor and moderate infections without a reduction in other clinically important outcomes, including mortality.

Human Immunodeficiency Virus (HIV)-Infected Children

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in children who have HIV infection and recurrent bacterial infections associated with hypogammaglobulinemia.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is children with HIV infection and recurrent bacterial infections associated with hypogammaglobulinemia. 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 HIV-related opportunistic infections and deaths.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat HIV-infected children: standard of care.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 18 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

A 1991 double-blind RCT allocated 372 HIV-infected children to IVIG or placebo every 28 days. (32) The median length of follow-up was 17 months. Results were stratified by CD4 (cluster of differentiation 4)-positive counts ($\geq 0.2\times10^9$/L or $<0.2\times10^9$/L). After 24 months, for children with CD4-positive counts of 0.2×10^9/L or greater, IVIG treatment compared with placebo significantly increased infection-free rates (67% vs 48% respectively; $p<.05$); reduced overall the number of serious and minor bacterial infections (RR=0.68; $p<.05$); and reduced the number of

hospitalizations for acute care (RR=0.65; p<.05). The effect was less marked in children with CD4-positive counts less than 0.2×10^9/L.

Subsection Summary: HIV-Infected Children

The evidence for the use of IVIG for prophylaxis of opportunistic infections in children with HIV consists of a single RCT. 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.

Neonatal Sepsis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are preterm and low birth weight infants and at risk for sepsis or who have sepsis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is infants who are preterm, low birth weight, and at risk for sepsis or who have 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat preterm, low birth weight infants at risk for sepsis or who have sepsis: standard of care.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Prophylaxis

A Cochrane review by Ohlsson and Lacy (2013) assessed IVIG for the prevention of infection in preterm and/or low birth weight infants. (33) Reviewers identified 19 RCTs that compared IVIG against placebo or no intervention for approximately 5000 preterm (<37 weeks of gestational age) and/or low birth weight (<2500 g) infants. Five of the 19 studies were considered to be high-quality; the other had potential biases (e.g., lack of caregiver blinding in 10 studies). In a meta-analysis of 10 studies, IVIG was associated with a statistically significant reduction in sepsis (≥1 episodes; RR=0.85; 95% CI, 0.75 to 0.98). Moreover, a meta-analysis of 16 studies showed a significant reduction in serious infection (≥1 episodes) with IVIG (RR=0.82; 95% CI, 0.74 to 0.92). However, IVIG was not associated with a significant reduction in mortality. A meta-analysis of 15 studies that reported all-cause mortality found a RR of 0.89 (95% CI, 0.75 to 1.05), and a meta-analysis of 10 studies that reported mortality due to infection found a RR of 0.83 (95% CI, 0.56 to 1.22). Reviewers noted that a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without a reduction in other clinically important outcomes, including mortality, were of marginal clinical importance. No major adverse events related to IVIG administration were reported.

Subsection Summary: Prophylaxis of Neonatal Sepsis

The evidence for the use of IVIG therapy for prophylaxis of infection in preterm and/or low birth weight infants consists of a Cochrane review involving multiple RCTs. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection (considered of marginal clinical importance) with no improvement in any of the other clinically important outcomes, including mortality.

Treatment

Systematic Reviews

A Cochrane review by Ohlsson and Lacy (2020) identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or confirmed infection. (34) Studies included a total of 3,973 infants; the largest trial had a sample size of 3,493 and contributed 90% of the data. Meta-analysis of all 9 trials found no statistically significant difference in mortality rate with IVIG versus the control therapy (RR, 0.95; 95% CI, 0.80 to 1.13). Meta-analysis of 3 trials found that IVIG significantly reduced the length of the hospital stay compared with a control intervention (mean difference [MD], -4.08; 95% CI, -6.47 to -1.69). Results were not pooled for other outcomes.

Randomized Controlled Trials

The trial with a large sample size was published by the International Neonatal Immunotherapy Study group (2011); it was conducted in 9 countries. (35) Infants receiving antibiotics for suspected or confirmed serious infection were randomized to 2 infusions of IVIG at a dose of 500 mg/kg of body weight (n=1759) or a matching volume of placebo (n=1734). Infusions were given 48 hours apart. The primary study outcome was the rate of death or major disability (according to predefined criteria) at age 2 years. By age 2 years, 686 (39%) of 1759 children in the IVIG group had died or suffered major disability compared with 677 (39%) of 1734 children

in the placebo group (RR=1.00; 95% CI, 0.92 to 1.08). There were also no statistically significant differences in the primary outcome when prespecified subgroups (e.g., birthweight, gestational age at birth, sex) were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIG group (including 2 deaths) versus 10 in the placebo group (including 4 deaths).

Section Summary: Treatment of Neonatal Sepsis

The evidence for the use of IVIG treatment for suspected or confirmed infection in neonates consists of a systematic review and multiple RCTs. The largest RCTs in 3493 neonates showed that there was no difference in the rates of death or major disability between IVIG treated neonates and placebo-treated neonates. A meta-analysis (nine studies) also did not find a significant difference in mortality rates or major disability with IVIG versus control. Neonatal sepsis has been most extensively evaluated; a meta-analysis of trials found a 6-fold decrease in mortality when IVIG was added to conventional therapies. This benefit was far greater than that derived from the prophylactic use of IVIG in preventing neonatal sepsis. Another meta-analysis report reviewed data from 10 randomized studies that assessed the use of IVIG in suspected fungal or bacterial infection in neonates <1 month of age and demonstrated a significant reduction in mortality (relative risk 5 0.55; 95% CI, 0.38-0.89). (36)

Sepsis in Adults

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in adults with sepsis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is adults with sepsis.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat adults with sepsis: standard of care.

Outcomes

The general outcomes of interest are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A meta-analysis by Busani et al. (2016), which pooled 18 RCTs, showed that the use of IVIG reduced the mortality risk of septic patients by half (odds ratio [OR], 0.50; 95% CI, 0.34 to 0.71). (37) However, there was a preponderance of small, low-quality studies in the evidence base, which was further complicated by heterogeneous dosing regimens and types of IVIG preparations used across studies that were conducted over a long-time horizon. Reviewers concluded that the evidence did not support the widespread use of IVIG as adjunctive therapy for sepsis in adults.

Section Summary: Sepsis in Adults
The evidence for the use of IVIG treatment for sepsis in adults consists of a meta-analysis of 18 RCTs. 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. These factors 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.

Severe Anemia Associated with Human Parvovirus B19
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with severe anemia associated with human parvovirus B19.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with severe anemia associated with human parvovirus B19. Human parvovirus B19 is a common single-stranded deoxyribonucleic acid (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.

Interventions
The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat severe anemia associated with human parvovirus B19 virus: standard of care.

Outcomes
The general outcomes of interest are a change in disease status, treatment-related mortality and morbidity. Follow-up at 12 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Case Series
No controlled trials have evaluated IVIG for severe anemia associated with parvovirus B19. Only small case series and case reports are available. (38, 39, 40) One larger case series, by Crabol et al. (2013), retrospectively reported on 10 patients with documented human parvovirus B19 and pure red cell aplasia. (41) Following a mean of 2.7 courses of IVIG treatment, hemoglobin level was corrected in 9 of 10 patients. Four patients had adverse events associated with IVIG (2 cases of acute reversible renal failure, 2 cases of pulmonary edema). In the same article, the authors reported on findings of a literature search in which they identified 123 cases of pure red cell aplasia treated with IVIG (other than the 10 patients in their series). Among 86 (70%) of 123 patients available at 12-month follow-up, hemoglobin was corrected in 36 (42%) patients, and the remaining 50 (58%) patients had persistent anemia.

Section Summary: Severe Anemia Associated with Human Parvovirus B19
The evidence for the use of IVIG treatment for severe anemia associated with human parvovirus B19 consists of case series. Although observed improvements in outcomes have suggested potential benefits with IVIG therapy, data are retrospective. Randomized controlled trials are needed to demonstrate improved health outcomes.

Toxic Shock Syndrome
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with toxic shock syndrome.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions
The therapy being considered is IVIG therapy. IVIG is used for the treatment of toxic shock syndrome to boost antibody levels via passive immunity.

Comparators
The following therapy is currently being used to treat toxic shock syndrome: corticosteroids.

Outcomes
The general outcomes of interest are OS, change in disease status, morbid events, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
The evidence for the use of IVIG treatment for toxic shock syndrome is limited and includes a small RCT (42) and multiple observational studies. (43, 44, 45, 46) The RCT by Darenberg et al. (2003) allocated 21 adults with toxic shock syndrome to IVIG or to placebo. (42) Mortality rates were 10% and 36%, respectively, but the difference in mortality rates was not statistically significant. Additionally, the trial was originally planned to enroll 120 patients, so it was likely underpowered to detect any significant differences.

Prospective and Retrospective Studies
In a prospective observational study, Linner et al. (2014) compared 23 patients receiving IVIG therapy with 44 patients receiving a placebo. (43) The odds for survival were 5.6 for IVIG versus placebo (p=.03). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls. (44, 45) While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups poses difficulties when interpreting the results. A retrospective study by Shah et al. (2009),

which included 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG. (46)

Section Summary: Toxic Shock Syndrome

The evidence for the use of IVIG treatment for toxic shock syndrome consists of a small RCT and multiple observational studies. Compared with placebo, IVIG treatment for toxic shock syndrome in patients has shown reductions in mortality in a small RCT and in multiple observational studies.

Idiopathic Thrombocytopenic Purpura (ITP)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with ITP.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are individuals with ITP. ITP, also known as primary immune thrombocytopenia, is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. It is a more common cause of thrombocytopenia in otherwise asymptomatic adults.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat ITP: corticosteroids.

Outcomes

The general outcomes of interest are DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized and Nonrandomized Trials

In 2007, the National Advisory Committee on Blood and Blood Products and the Canadian Blood Services issued guidelines on the use of IVIG for hematologic conditions, including ITP, based on 6 RCTs and 1 nonrandomized trial of IVIG for adult ITP. (47) Three of the trials compared IVIG with corticosteroids, and 4 trials evaluated different doses of IVIG. None compared IVIG with no therapy. The largest trial, by Godeau et al. (2002), compared IVIG with corticosteroids in 122 patients with severe acute ITP. (48) The primary outcome, the mean number of days with a platelet count greater than $50x10^9$/L at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG versus corticosteroids) (49) and 1 randomized (IVIG alone versus oral prednisone alone versus IVIG plus oral prednisone) (50) found no differences in platelet counts greater than $50x10^9$/L at 48 hours or in response rates between groups, respectively.

Section Summary: ITP

For individuals who have ITP who receive IVIG therapy, the evidence includes multiple RCTs and noncomparative studies. Compared with corticosteroids, IVIG therapy improved platelet counts.

Guillain-Barré Syndrome (GBS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with GBS.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with GBS. 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat GBS: plasma exchange, immunoadsorption, and supportive care.

Outcomes

The general outcomes of interest are OS, DSS, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Follow-up at 4 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

An updated Cochrane review by Hughes et al. (2014) evaluated results from randomized trials of immunotherapy for GBS. (51) Reviewers identified 12 randomized trials; none were placebo-controlled. Seven trials compared IVIG with plasma exchange, 3 trials compared IVIG with supportive treatment only, 2 trials compared plasma exchange, and 2 others compared IVIG with immunoabsorption (1 compared IVIG plus immunoabsorption with immunoabsorption only). Four trials included adults only, 5 included children only, 1 included both, and 2 included adults and possibly children. The primary outcome of the review was change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIG with plasma exchange did not find significant differences between groups in change in the number of disability grades at 4 weeks (mean difference [MD],-0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIG versus plasma exchange (e.g., number of patients who improved by $\geq$ 1 grades). There were insufficient data to pool results for comparisons of IVIG with other interventions or for subgroup analysis by age. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR, 0.14; 95% CI, 0.05 to 0.36).

Most trials in this review had small sample sizes. The largest was a 1997 multicenter, randomized trial of 383 adults that compared IVIG, plasma exchange, and combination IVIG plus plasma exchange. (52) Trial objectives were to establish that IVIG is equivalent or superior to plasma exchange and to establish that plasma exchange followed by IVIG is superior to a single treatment. Noninferiority was defined as no more than a 0.5-grade difference in change in disability grade at 4 weeks. At 4 weeks, the difference in improvement between the IVIG and plasma exchange group was 0.09 grade (95% CI, -0.23 to 0.42); this met the predefined criterion for equivalence of these treatments. Differences were 0.29 grade (95% CI, -0.04 to 0.63) between the IVIG plus plasma exchange group and the IVIG only group, and 0.20 grade (95% CI, -0.14 to 0.54) between the IVIG plus plasma exchange group and the plasma exchange only group. Thus, neither combined treatment group proved superior to either treatment alone.

Miller Fisher syndrome is a variant of GBS characterized by impairment of eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). A Cochrane review by Overell et al. (2007) evaluated acute immunomodulatory therapies in Miller Fisher syndrome or its variants. (53) No RCTs were identified.

Section Summary: GBS

For individuals who have GBS who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes.

Kawasaki Disease

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Kawasaki disease.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Kawasaki disease. Kawasaki disease is a very common vasculitides of childhood; it is characterized by fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. It is typically self-limiting but may cause cardiovascular complications, particularly coronary artery aneurysms, which can lead to coronary occlusion and cardiac ischemia ultimately leading to significant morbidity and even death.

Interventions

The therapy being considered is IVIG therapy. Although the mechanism of action of IVIG in Kawasaki disease is not understood, its use early in the course of the disease has reduced the prevalence of coronary artery abnormalities.

Comparators

The following practice is currently being used to treat Kawasaki disease: standard of care.

Outcomes

The general outcomes of interest are DSS, change in disease status, and treatment-related mortality and morbidity. Follow-up at 30 days is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Multiple RCTs and meta-analysis, have demonstrated the efficacy of IVIG in preventing cardiac consequences of Kawasaki disease in children. A Cochrane review of RCTs by Broderick et al.

(2023) identified 31 trials for meta-analysis. (54) Comparator therapies included aspirin, prednisolone, or infliximab. Results showed a significant decrease in new coronary artery abnormalities in favor of IVIG compared with aspirin at 30 days (OR, 0.60; 95% CI, 0.41 to 0.87). Adverse effects were similar between groups. There was low certainty evidence comparing aspirin and IVIG for acute coronary syndrome and need for additional treatment. Comparisons between IVIG and prednisolone had low certainty. Reviewers concluded that high dose IVIG probably reduces coronary artery abnormalities compared to aspirin or medium or low dose IVIG regimens.

Section Summary: Kawasaki Disease

For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes a systematic review and meta-analysis of multiple RCTs. Compared with aspirin, IVIG therapy has shown significant decreases in new coronary artery abnormalities.

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with granulomatosis with polyangiitis (Wegener granulomatosis).

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with granulomatosis with polyangiitis (Wegener granulomatosis).

Interventions

The therapy being considered is IVIG therapy for maintenance therapy.

Comparators

The following practice is currently being used to treat granulomatosis with polyangiitis: standard of care.

Outcomes

The general outcomes of interest are DSS, change in disease status, and treatment-related mortality and morbidity. Follow-up at 3 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

The success of IVIG therapy for Kawasaki disease led to a study of IVIG therapy for other vasculitides such as Wegener granulomatosis. A Cochrane review by Fortin et al. (2013) identified 1 RCT on IVIG for Wegener granulomatosis. (55) This trial, published by Jayne et al. (2000), compared single course IVIG (n=17) with placebo (n=17) and found significantly more responders in the IVIG treatment group at 3 months but no significant differences after 3 months or in the frequency of relapse or use of other medications. (56)

Section Summary: Granulomatosis with Polyangiitis (Wegener Granulomatosis)

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes a systematic review with a single relevant RCT. 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.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Clinical Context and Therapy Purpose

The purpose of IVIG and SCIG therapies is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with CIDP.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are individuals with CIDP. 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. The disease is difficult to diagnose due to its heterogeneous presentation (both clinical and electrophysiological).

Interventions

The therapies being considered are IVIG and SCIG.

Comparators

The following therapies are currently being used to treat CIDP: plasma exchange, immunoadsorption, and supportive care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Follow-up as long as 48 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Intravenous Immunoglobulin (IVIG) Therapy for CIDP

Systematic Reviews

Eftimov et al. (2013) published a Cochrane review of RCTs on IVIG for treating CIDP. (57) Reviewers identified 8 RCTs that enrolled 332 patients with definite or probable CIDP and that compared IVIG with placebo, corticosteroids, or plasma exchange. Three trials compared IVIG with another active treatment, (58, 59, 60) and the other 5 were placebo-controlled (n=235). (61, 62, 63, 64, 65) The primary trial outcome was the proportion of participants with a significant improvement in disability within 6 weeks of starting treatment. Studies used a variety of disability measures. When possible, reviewers transformed the data on disability into a modified 6-point Rankin Scale for disability. Data from the 5 placebo-controlled randomized trials were pooled. The pooled RR for improvement in the IVIG group compared with the placebo group was 2.40 (95% CI, 1.72 to 3.36; p<.001). When data were pooled from 3 studies on IVIG versus placebo in which the disability measures could be converted to the Rankin Scale, the RR was similar (2.40) but not statistically significant (95% CI, 0.98 to 5.83; p=.054). Pooled analyses of data from these 3 placebo-controlled trials found a statistically higher rate of any adverse event with IVIG, but no serious adverse events. Data from studies comparing IVIG with active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

Randomized Controlled Trials

The ICE study reported by Hughes et al. (2008), the largest included in the meta-analysis, was a double-blind, multicenter trial that randomized 117 patients to IVIG or placebo. (65) The primary outcome measure was the proportion of patients showing clinically meaningful reductions in disability at week 24. Results showed that the proportion of patients meeting the primary endpoint was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase were re-randomized to IVIG or placebo. Relapse rates were significantly lower for patients treated with IVIG (13% vs 45%; hazard ratio, 0.19; 95% CI, 0.05 to 0.70). Benefits of IVIG treatment extended to as long as 48 weeks with maintenance treatments of 1 g/kg every 3 weeks.

Subsection Summary: IVIG Therapy for CIDP

For individuals who have CIDP who receive IVIG therapy, the evidence includes a systematic review and RCTs. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability.

Subcutaneously Administered Immunoglobulin (SCIG) Therapy for CIDP

In the randomized, double-blind, placebo-controlled, phase 3 PATH trial, van Schaik et al. (2018) studied relapse rates in 172 patients with CIDP given SCIG and placebo. (66) Patients were randomized in a 1:1:1 ratio to a placebo group (n=57 [33%]), a low-dose group (n=57 [33%]), and a high-dose group (n=57 [33%]). The trial found that both SCIG doses were effective and well-tolerated, suggesting that SCIG can be used as maintenance treatment for CIDP. Seventy-seven patients withdrew from the trial due to relapse or other reasons: 36 (63%; 95% CI, 50% to 74%) placebo patients, 22 (39%; 95% CI, 27% to 52%) low-dose SCIG patients, and 19 (33%; 95% CI, 22% to 46%) high-dose patients (p<.001). The trial was limited by missing patient data and inadequate follow-up of those who withdrew.

One crossover RCT comparing IVIG and SCIG for CIDP was identified; this trial by Markvardsen et al. (2017) included 20 patients. (67) Patients underwent 10 weeks of treatment with SCIG and IVIG, in random order, for a total intervention duration of 20 weeks. The primary efficacy outcome was change in isokinetic muscle strength. Fourteen (20%) of 20 patients completed the trial. Isokinetic muscle strength increased by 7.4% with SCIG and 14% with IVIG; the difference between groups was not statistically significant. Conclusions about the relative efficacy of SCIG and IVIG cannot be drawn from this trial due to the small sample size, high dropout rate, short-term follow-up, and the crossover design without a washout period.

Section Summary: SCIG Therapy for CIDP

For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (e.g., 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIDP might be effective, with relatively low adverse events, but this trial also had a number of limitations (e.g., small sample, 30% dropout rate).

Multifocal Motor Neuropathy (MMN)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with MMN.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with MMN. MMN is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities, a presentation similar to that of motor neuron disease.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat MMN: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. A follow-up at 4 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Keddie et al. (2022) updated a 2005 Cochrane review identifying a total of 6 crossover RCTs (N=90 patients). (68) Studies included patients with definite or probable MMN treated with IVIG or SCIG. Outcomes included muscle strength, disability, or electrophysiological conduction block. In 3 trials (N=18) of induction treatment, IVIG improved disability in 39% of patients compared with 11% of placebo-treated patients (risk ratio, 3.00; 95% CI, 0.89 to 10.12). In the 3 trials (N=27) evaluating strength, 78% of IVIG-treated patients improved compared with 4% of placebo-treated patients (risk ratio, 11.00; 95% CI, 2.86 to 42.25). Conduction block results nonsignificantly favored IVIG to placebo in 4 trials of 28 patients (risk ratio, 7.00; 95% CI, 0.95 to 51.70). Adverse effects were increased in patients with IVIG; however, only 1 serious event (a pulmonary embolism) was documented. Most patients who responded to IVIG deteriorated with treatment withdrawal.

Section Summary: MMN
For individuals who have MMN who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength.

Lambert-Eaton Myasthenic Syndrome
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Lambert-Eaton myasthenic syndrome.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with Lambert-Eaton myasthenic syndrome. Lambert-Eaton myasthenic syndrome is an autoimmune disease with antibodies directed against the neuromuscular junction. Patients have muscle weakness of the lower extremities, autonomic dysfunction, and extra-ocular muscle impairment. This is a paraneoplastic syndrome associated most commonly with small-cell lung cancer.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat Lambert-Eaton myasthenic syndrome: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
A crossover RCT by Bain et al. (1996) evaluated 9 patients treated with IVIG therapy (1 g/kg/d for 2 days) or placebo showed statistically significant improvements in serial measurements of limb, respiratory, and bulbar muscle strength associated with treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude. (69)

Observational Studies
A number of noncomparative studies have substantiated clinical benefits. (70, 71, 72, 73)

Section Summary: Lambert-Eaton Myasthenic Syndrome
For individuals who have Lambert-Eaton myasthenic syndrome who receive IVIG therapy, the evidence includes a RCT and multiple observational studies. Compared with placebo, IVIG

therapy has shown clinically meaningful improvements in outcomes assessing muscle strength and activity.

Neuromyelitis Optica (NMO)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with NMO.

The following PICO was used to select literature to inform this policy.

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat NMO: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 2 years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies

A retrospective review by Elsone et al. (2014) of 10 patients treated with IVIG for acute relapses after lack of response to steroids with or without plasma exchange showed improvement in about 50% of patients. (74) A case series by Magraner et al. (2013) assessed 9 Spanish NMO patients and yielded positive results using bimonthly IVIG treatment (0.7 g/kg body weight per day for 3 days) for up to 2 years. (75)

Section Summary: NMO

For individuals who have NMO who receive IVIG therapy, the evidence includes multiple observational studies. Studies have shown that IVIG treatment may benefit patients who are refractory to first-line treatment with steroids or plasma exchange, particularly children.

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with severe refractory myasthenia gravis or myasthenic exacerbation.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals with severe refractory myasthenia gravis or myasthenic exacerbation. Myasthenia gravis 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat myasthenia gravis: plasma exchange.

Outcomes

The general outcomes of interest are OS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Treatment of 2 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A Cochrane review by Gadjos et al. (2012) assessed IVIG therapy for acute exacerbations or for chronic long-term myasthenia gravis. (76) Reviewers identified 7 RCTs including an unpublished trial, all of which investigated short-term benefit. The trials varied in inclusion criteria,

comparator interventions, and outcome measures and, thus, trial findings were not pooled. Five trials evaluated IVIG for treating myasthenia gravis worsening or exacerbation, and 2 evaluated IVIG for treatment of moderate or severe myasthenia gravis. Several trials were small, with insufficient statistical power. Reviewers concluded that there was some evidence for efficacy in exacerbations of myasthenia gravis, and that evidence for treating chronic myasthenia gravis was insufficient to form conclusions about efficacy.

Randomized Controlled Trials

Zinman et al. (2007) conducted the only RCT that compared IVIG with placebo in 51 patients who had myasthenia gravis with progressive weakness. (77) The primary outcome measure was the difference between arms in the Quantitative Myasthenia Gravis Score for Disease Severity from baseline to days 14 and 28. In IVIG-treated patients, a clinically meaningful improvement in Quantitative Myasthenia Gravis Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a Quantitative Myasthenia Gravis Score for Disease Severity greater than 10.5.

Other RCTs either compared IVIG with plasma exchange or compared 2 doses of IVIG. Barth et al. (2011) compared IVIG with plasma exchange in 84 patients with moderate-to-severe myasthenia gravis. (78) The trial did not find a statistically significant difference in the efficacy between treatments. Gajdos et al. (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of myasthenia gravis. (79) Mean improvement in the myasthenic muscular scores did not differ significantly between doses after 2 weeks. Gajdos et al. (1997) compared IVIG with plasma exchange in 87 patients with myasthenia gravis exacerbations. (80) The trial also did not find a statistically significant difference in the efficacy between the 2 treatments; however, the trial did report that IVIG was better tolerated. Nine patients experienced adverse events (8 in the plasma exchange group, 1 in the IVIG group).

Section Summary: Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. 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.

Relapsing-Remitting Multiple Sclerosis (RRMS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with RRMS.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with RRMS. 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.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat RRMS: standard of care.

Outcomes
The general outcomes of interest are OS, DSS, symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Treatment of 2 weeks is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Based on a technology assessment by Goodin et al. (2002), the American Academy of Neurology (AAN) recommended the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation) for the treatment of RRMS. (81) The AAN suggested that IVIG was no longer considered a drug of choice for RRMS.

Section Summary: RRMS
For individuals who have RRMS who receive IVIG therapy, the evidence includes a technology assessment. According to the technology assessment, IVIG therapy is no longer considered a treatment of choice for RRMS.

Autoimmune Mucocutaneous Blistering Diseases (AMBDs)
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with autoimmune mucocutaneous blistering diseases.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat autoimmune mucocutaneous blistering diseases: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A systematic review by Gurcan et al. (2010) identified 23 studies evaluating IVIG for autoimmune mucocutaneous blistering diseases (1 RCT, 22 case series). (82) The studies included 260 patients treated with IVIG: 191 patients had pemphigus, and 69 patients had pemphigoid. Of the 260 patients, 245 (94%) improved after IVIG treatment.

Randomized Controlled Trials
Amagai et al. (2017) evaluated IVIG for bullous pemphigoid in a multicenter, double-blind, and placebo-controlled randomized trial that included 56 patients. (83) The IVIG group received 400 mg/kg/d for 5 days and the placebo group received saline for 5 days. The primary endpoint was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant (p=.089). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15 (p=.041). In patients with severe disease, there were significantly lower DAS scores in the

IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.

Another RCT by the same research group was published by Amagai et al. (2009); this study was multicenter, placebo-controlled and double-blind in design and included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥20 mg/d). (84) Patients were randomized to a single cycle of IVIG 400 mg/kg/d for 5 days, IVIG 200 mg/kg/d for 5 days or a placebo infusion for 5 days. The primary endpoint was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (i.e., time to escape protocol). Time to escape protocol was significantly longer for patients in the IVIG 400mg group than for patients in the placebo group but not between the IVIG 200mg group and the placebo group. Furthermore, a significant decrease in a pemphigus activity score was detected at all study observation points for patients in the IVIG 400mg group and at all study observation points after day 15 in the IVIG 200mg group. The pemphigus activity score did not decrease significantly at any time point in the placebo group.

Section Summary: Autoimmune Mucocutaneous Blistering Diseases

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes 2 RCTs and a systematic review. A systematic review found improvements in over 90% of patients. Randomized controlled trials have reported benefits in disease activity in the population as a whole (1 trial) or in a subgroup of patients with severe disease (1 trial).

Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with TEN or SJS.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals with TEN or SJS.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat TEN or SJS: standard of care.

Outcomes

The general outcomes of interest are DSS symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Several systematic reviews have evaluated the literature on TEN and SJS. More recently, Huang et al. (2016) identified 11 studies evaluating IVIG for TEN or SJS, none of which were RCTs. (85) Three of the studies had control groups and 2 of these included historical controls. IVIG was not found to reduce mortality in TEN or SJS. The pooled standardized mortality ratio in the 10 studies was 1.00 (95% CI, 0.76 to 1.32, p=.67). A meta-analysis by Barron et al. (2015) also did not demonstrate a survival advantage of IVIG for TEN and/or SJS. (86)

Retrospective Review

A retrospective review evaluated the effectiveness of IVIG in reducing mortality in 16 individuals with TEN. The dose of IVIG was 1 gram/kg every day for 4 days for 15 individuals and 1 individual received a dose of 0.4 gram/kg. The investigators evaluated each individual using the SCORTEN system, which is a validated predictor of TEN mortality. Based on the SCORTEN evaluation, 5.81 individuals (36.3%) were expected to die while the actual mortality rate was 1 individual (6.25%). All of the 16 individuals showed clinical improvement and disease resolution. (87)

Section Summary: TEN and SJS

For individuals who have TEN or SJS who receive IVIG therapy, the evidence includes systematic reviews of observational studies. No RCTs identified evaluated IVIG for TEN or SJS. There are several systematic reviews of observational studies, controlled and uncontrolled including a retrospective review evaluated the effectiveness of IVIG in reducing mortality in 16 individuals with TEN. All of the 16 individuals showed clinical improvement and disease resolution.

Idiopathic Inflammatory Myopathies

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with dermatomyositis, polymyositis, or inclusion body myositis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals with dermatomyositis, polymyositis, or 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.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat dermatomyositis, polymyositis, or inclusion body myositis: standard of care.

Outcomes
The general outcomes of interest area a change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity.

Follow-up at 39 months is of interest for dermatomyositis and polymyositis to monitor outcomes. Follow-up at 6, 12, and 24 months is of interest for inclusion body myositis to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

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

Wang et al. (2012) published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis. (89) Reviewers identified 14 studies including 2 RCTs, 9

prospective case series, and 3 retrospective case series. Eleven of the 14 studies included patients with refractory disease. For example, a trial by Dalakas et al. (1993) compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis. (90) At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified Medical Research Council scale (84.6 IVIG vs 78.6 placebo) and the Neuromuscular Symptom Scale (51.4 IVIG versus 45.7 placebo). Repeated transfusions every 6 to 8 weeks can be required to maintain a benefit.

Section Summary: Dermatomyositis and Polymyositis

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes systematic reviews of observational studies and RCTs. The evidence supports the efficacy of IVIG for improving muscle strength in these individuals.

Inclusion Body Myositis

Randomized Controlled Trials

Dalakas et al. (1997) reported on a double-blind, placebo-controlled crossover study that compared IVIG with placebo in 19 patients with inclusion body myositis. (91) There was no statistically significant improvement in overall muscle strength in the IVIG group compared with the placebo group. Two more recent RCTs published in 2000 and 2001 (58 IVIG patients) also found no significant functional improvement when IVIG treatment was compared with placebo. (92, 93)

Section Summary: Inclusion Body Myositis

For individuals who have inclusion body myositis who receive IVIG therapy, the evidence includes multiple RCTs. Compared with placebo, IVIG therapy failed to show improvements in muscle strength.

Systemic Lupus Erythematosus (SLE)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with SLE.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with SLE. 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 and can affect any organ system, but mainly attacks the skin, joints, kidneys, blood cells, and nervous system.

Interventions

The therapy being considered is IVIG therapy. IVIG therapy is proposed for SLE because of its immunomodulatory properties and because it prevents infection in individuals taking immunosuppressive drugs.

Comparators
The following practice is currently being used to treat SLE: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A systematic review by Sakthiswary et al. (2014) identified 13 studies on IVIG for the treatment of SLE. (94) Three studies had control groups, and only 1 was an RCT. (95) Most studies were small; only 3 had more than 50 patients, and the single RCT included only 14 patients. In a meta-analysis of 6 studies (N=216 patients), there was a statistically significant difference in SLE disease activity in IVIG-treated groups (standardized mean difference [SMD]=0.58; 95% CI, 0.22 to 0.95). This analysis was limited because there were few data in non-IVIG-treated patients. A meta-analysis of data from 8 studies on the effect of IVIG on complement levels found a pooled response rate of 30.9% (95% CI, 22.1% to 41.3%). Findings on other outcomes were not pooled.

Cajamarca-Barón et al. (2022) published a systematic review on IVIG in patients with lupus nephritis. (96) A total of 28 articles were included with case reports or series comprising the vast majority of the evidence. Only 1 RCT (N=14) was identified. In the RCT, 11 patients remained in remission after 1.5 years of follow-up. In compiled data from the case reports and case series, a complete response occurred in 30.4% of patients with 33.9% of patients having a partial response. Although IVIG appears effective for lupus nephritis based on this analysis, there is a lack of RCTs to support the use of IVIG in this setting.

There has been limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE. (97)

Section Summary: SLE
For individuals who have SLE who receive IVIG therapy, the evidence includes systematic reviews, primarily of observational data. 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.

Immune Optic Neuritis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with immune optic neuritis.

The following PICO was used to select literature to inform this policy.

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat immune optic neuritis: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Follow-up at 6 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Two RCTs have evaluated the potential benefit of IVIG for immune optic neuritis. Roed et al. (2005) randomized 68 patients in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34). (98) The authors found no differences in the visual outcome measure or disease activity as measured by magnetic resonance imaging after 6 months.

Noseworthy et al. (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo. (99) The trial was terminated early after 55 patients were enrolled because investigators did not find a difference in the logarithm of the minimum angle of resolution (logMAR) visual scores at 6 months (p=.766).

Section Summary: Immune Optic Neuritis

For individuals who have immune optic neuritis who receive IVIG therapy, the evidence includes 2 RCTs. Compared with placebo, IVIG therapy has failed to show improvements in vision-related outcomes.

Crohn's Disease

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Crohn's disease.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with Crohn's disease. Crohn's 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat Crohn's disease: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review by Rogosnitzky et al. (2012) of IVIG therapy for Crohn's disease did not identify any randomized or nonrandomized controlled trials. (100) Reviewers found 5 case reports of IVIG used for single patients with Crohn's disease, and the remaining literature identified included conference papers, abstracts only, or a nonsystematic review.

Section Summary: Crohn's Disease

For individuals who have Crohn's disease who receive IVIG therapy, the evidence includes multiple case reports of single individuals summarized in a systematic review.

Hemophagocytic Lymphohistiocytosis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with hemophagocytic lymphohistiocytosis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat hemophagocytic lymphohistiocytosis: supportive care alone, chemotherapy, and allogeneic cell transplantation.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review by Rajagopala et al. (2012) on diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics identified 156 cases; a portion of these patients were treated with IVIG. (101) Steroids were the most common treatment. IVIG was used in 30% of children and in 4% of adults. Hemophagocytic syndrome-related mortality occurred in 32% of children and in 28% of adults.

Case Series

Published literature on the use of IVIG in hemophagocytic syndrome is limited to small case series. (102, 103, 104)

Section Summary: Hemophagocytic Lymphohistiocytosis

For individuals who have hemophagocytic lymphohistiocytosis who receive IVIG therapy, the evidence includes multiple case reports summarized in a systematic review and case series.

Warm Antibody Autoimmune Hemolytic Anemia

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with warm antibody hemolytic anemia, refractory to prednisone and splenectomy.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with warm antibody hemolytic anemia, refractory to prednisone and splenectomy. 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat warm antibody hemolytic anemia: prednisone, splenectomy, and cytotoxic medications.

Outcomes

The general outcomes of interest are a change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 3 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Studies

Published literature on the use of IVIG in warm antibody autoimmune hemolytic anemia is limited to observational data for 37 patients pooled from 3 institutions (105) and a case report. (106) Overall, 29 (39.7%) of 73 patients responded to IVIG therapy. Because of limited therapeutic value, it is used in patients refractory to conventional therapy with prednisone and splenectomy or as a conjunctive therapy in patients with very severe disease. Further, the effect is usually transient, unless repeated courses are given every three weeks.

Section Summary: Warm Antibody Autoimmune Hemolytic Anemia

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. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select patients with refractory autoimmune hemolytic anemia. Randomized controlled trials are needed to demonstrate improved health outcomes.

Antiphospholipid Syndrome

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with antiphospholipid syndrome.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat antiphospholipid syndrome: anticoagulant and antiplatelet therapy.

Outcomes

The general outcomes of interest are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Case Reports

Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry. (107) Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received therapy with anticoagulants, corticosteroids, plasma exchange, and/or IVIGs compared with combinations that did not use plasma exchange, IVIG, or both.

Section Summary: Antiphospholipid Syndrome

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Observed improvements in outcomes have suggested potential mortality benefit with IVIG therapy in catastrophic antiphospholipid syndrome. Randomized controlled trials are needed to demonstrate improved health outcomes.

Neonatal Alloimmune Thrombocytopenia

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with neonatal alloimmune thrombocytopenia.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is neonates with 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, routine screening for this condition is not recommended 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practices are currently being used to treat neonatal alloimmune thrombocytopenia: platelet transfusion and supportive care alone.

Outcomes
The general outcomes of interest are DSS, change in disease status, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Rayment et al. (2011), in a Cochrane review, summarized the results of 4 RCTs on the maternal administration of corticosteroids and IVIG in pregnancies with neonatal alloimmune thrombocytopenia in 206 women. (108) Reviewers concluded that the optimal management of fetomaternal alloimmune thrombocytopenia remains unclear. Lack of complete data sets for 2 trials and differences in interventions precluded the pooling of data from these trials.

Randomized Controlled Trials
Paridaans et al. (2015) evaluated the effectiveness of a lower dose of IVIG (0.5 g/kg/wk versus 1 g/kg/wk) in an RCT of 23 women. (109) The primary outcome was fetal or neonatal ICH. The median newborn platelet count was 81×10^9/L in the 0.5-g/kg group and 110×10^9/L in the 1-g/kg group (p=.644).

Berkowitz et al. (2007) showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies. (110) In another trial, Berkowitz et al. (2006) did not demonstrate a difference in standard-risk pregnancies but did demonstrate that IVIG and prednisone were more effective in raising the fetal platelet count in high-risk pregnancies. (111)

Bussel et al. (1996) did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids. (112) Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because the natural history of the disease suggests that subsequent births should be similar, if not more severely, affected with thrombocytopenia. The trial reported a mean increase in platelet count of 69,000/mL. There were no instances of ICH, although hemorrhage had occurred previously in 10 untreated siblings.

There are no RCTs evaluating the efficacy of IVIG or steroids alone versus placebo in alloimmune thrombocytopenia. Trials of this nature would be unethical because of the known risk of ICH with this condition.

Observational Trial

One large, retrospective comparative study by Ernstsen et al. (2022) compared neonatal outcomes in 71 untreated alloimmunized pregnancies with 403 IVIG-treated pregnancies in women who previously had a child with neonatal alloimmune thrombocytopenia. (113) In low-risk pregnancies (alloimmunized pregnancy history without ICH) IVIG did not affect neonatal outcomes; however, in high-risk pregnancies (alloimmunized pregnancy history with ICH) IVIG-treated patients had lower rates of neonates with ICH compared with untreated patients (5.6% vs. 29%).

Section Summary: Neonatal Alloimmune Thrombocytopenia

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple RCTs, a large observational study, and a systematic review. 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.

Recurrent Spontaneous Abortion

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in women with recurrent spontaneous abortion.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is women with recurrent spontaneous abortion. Recurrent spontaneous abortion is defined as 3 or more pregnancies resulting in 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat recurrent spontaneous abortion: supportive care.

Outcomes

The general outcomes of interest are DSS, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A Cochrane review by Porter et al. (2006) assessed various immunotherapies for treating recurrent miscarriage and concluded that IVIG therapy provides no significant beneficial effect over placebo in preventing further miscarriages. (114) Meta-analyses published in 2015 and 2016 that included 11 RCTs also found no significant difference in the number of live births with IVIG versus placebo or treatment as usual. (115, 116)

Randomized Controlled Trials

An RCT by Christiansen et al. (2002) evaluated 58 women with at least 4 unexplained miscarriages and compared IVIG with placebo. (117) Using an intention to treat analysis, the live birth rate was similar for both groups; also, there were no differences in neonatal data (e.g., birth weight, gestational age at delivery).

Likewise, a multicenter RCT by Branch et al. (2000) compared heparin plus low-dose aspirin with or without IVIG in women with a lupus anticoagulant, anticardiolipin antibody, or both, and found no significant differences. (118)

A blinded RCT by Jablonowska et al. (1999) assessed 41 women treated with IVIG or saline placebo also found no differences in live birth rates. (119)

Section Summary: Recurrent Spontaneous Abortion

For individuals who have a recurrent spontaneous abortion who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. In multiple RCTs, compared with placebo, IVIG therapy alone did not show any beneficial effects in preventing spontaneous abortions.

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal (PANDAS) Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in children with PANDAS/PANS.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is children with PANDAS/PANS. PANDAS is a term used to describe a subset of children whose symptoms of obsessive-compulsive disorder (or tic disorders) are exacerbated by group A streptococcal infection. This syndrome is not well-understood, and the diagnosis of PANDAS requires expert consultation.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat PANDAS/PANS: antibiotic therapy alone.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related mortality and morbidity. Follow-up at 1 month is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Williams et al. (2016) randomized 35 children who met diagnostic criteria for PANDAS and had moderate-to-severe obsessive-compulsive disorder symptoms to treatment with 2 treatment sessions of IVIG or placebo. (120) After a 6-week double-blind treatment phase, nonresponders could continue treatment on an open-label basis. The primary outcome at 6 weeks, the Children's Yale-Brown Obsessive Compulsive Scale total score, did not differ significantly between groups. There was a mean decrease in the Children's Yale-Brown Obsessive-Compulsive Scale of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvements in other outcomes (e.g., mean Clinical Global Impressions improvement scores) also did not differ significantly between groups. A total of 24 participants met the criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the Children's Yale-Brown Obsessive-Compulsive Scale improved significantly compared with 6 weeks; however, the 12-week analysis did not include a placebo comparison.

An RCT by Perlmutter et al. (1999) included 30 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections. (121) Patients were randomized to IVIG, plasma exchange, or placebo (10 per group). At the 1-month follow-

up, IVIG and plasma exchange showed statistically significant improvements in obsessive-compulsive symptoms, anxiety, and overall functioning.

Section Summary: PANDAS/PANS

For individuals who have PANDAS who receive IVIG therapy, the evidence includes 2 placebo-controlled randomized trials have evaluated IVIG for PANDAS/PANS. A 2016 trial with 35 children did not find significant benefits with IVIG compared with placebo at the end of the 6-week double-blind phase. The other trial did find significant benefits of IVIG over placebo at one-month. The evidence is sufficient to draw conclusions about the impact of IVIG on health outcomes in children with PANDAS/PANS.

Autism Spectrum Disorder

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with an autism spectrum disorder.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with an 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat autism spectrum disorder: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Follow-up at 6 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

Case Series

The evidence base supporting the use of IVIG in autism includes case series. One included 10 patients with abnormal immune parameters who received IVIG therapy monthly. (122) After 6 months, 5 of 10 patients showed marked improvement in several autistic characteristics. Another 2-case series failed to replicate these findings. In the second, 1 of 10 patients showed improvements in autistic symptoms after receiving IVIG. (123) No improvements were observed in the third series. (124)

No randomized comparative trials evaluating IVIG therapy in autism were identified.

Section Summary: Autism Spectrum Disorder

For individuals who have autism spectrum disorder who receive IVIG therapy, the evidence includes case series. Although improvements were observed in 1 case series, the other 2 reported negative findings.

Complex Regional Pain Syndrome (CRPS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with CRPS.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with CRPS. 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat CRPS: standard of care.

Outcomes

The general outcomes of interest are symptoms, morbid events, QOL, and treatment-related mortality and morbidity. Follow-up at 14 days is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Goebel et al. (2017) conducted a 1:1 parallel, randomized, placebo-controlled, multicenter trial to confirm the efficacy of low-dose IVIG compared with placebo in reducing pain in adults who had CRPS of 1 to 5 years in duration. (125) IVIG 0.5 g/kg of body weight or saline placebo on days 1 and 22 were administered after 111 patients were randomized. An 11-point (0- to 10-point) rating scale was used to measure the primary outcome of 24-hour average pain intensity. Mean pain scores were 6.9 points for placebo and 7.2 points for IVIG at 6 weeks demonstrating that low-dose immunoglobulin treatment was not effective in relieving pain in moderate-to-severe CRPS patients.

Goebel et al. (2010) reported on the use of IVIG treatment for CRPS in a crossover double-blinded RCT conducted at an academic pain management center in the U.K. (126) The trial randomized 13 patients refractory to standard treatment to IVIG or normal saline. Median daily pain intensity score for each 14-day period was 6.21 after IVIG infusion versus 7.35 after saline infusion, a difference of 1.14 points. Trialists reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; p<.001).

Section Summary: CRPS

For individuals who have CRPS who receive IVIG therapy, the evidence includes 2 RCTs. In 1 trial, compared with placebo, IVIG therapy was associated with improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 13 patients. In the other RCT, low-dose IVIG was ineffective in relieving pain in CRPS.

Alzheimer Disease (AD)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with AD.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with AD.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat AD: standard of care.

Outcomes
The general outcomes of interest are OS, DSS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 12 or 24 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Three placebo-controlled double-blind, randomized trials in patients with AD were identified. Two included patients with mild-to-moderate AD. Relkin et al. (2017) reported on 390 patients treated with 1 of 2 doses of IVIG (0.2 or 0.4 g/kg every 2 weeks for 18 months) or placebo. (127) The primary outcomes were a change from baseline to 18 months on the cognitive subscale of the Alzheimer Disease Assessment scale and on the Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory. Neither outcome was significantly improved in either IVIG group compared with the placebo group.

Kile et al. (2017) assessed 50 patients with mild cognitive impairment (MCI) related to AD. (128) Patients were stratified into early and late MCI stages based on scores on the Clinical Dementia Rating, Sum of Boxes test (≤1 for the early MCI group and >1 for the late MCI group). Patients received a total IVIG dose of 2g/kg over 5 sessions, or placebo. The primary outcome was brain atrophy, defined as annualized percent change in the ventricular volume measured by magnetic resonance imaging (MRI). In unadjusted analyses, the annualized percent change in the ventricular volume did not differ significantly between groups at 12 or 24 months. In a subgroup analysis, the annualized percent change in the ventricular volume was significantly lower in the IVIG compared with the placebo group in patients with early MCI but not late MCI at 12 months, and there was no significant difference at 12 months in either the early or late MCI groups. Secondary outcomes, cognition scores, and conversion to AD dementia did not differ between the IVIG and placebo groups at 12 or 24 months. As with the primary outcome, for several secondary outcomes, IVIG showed a significant benefit in the early MCI group at 12 months but not 24 months.

In a trial by Dodel et al. (2013) with 56 patients, the primary outcome (area under the curve of plasma amyloid β 1-40) did not differ between the IVIG and the placebo groups. (129) Secondary outcomes, including cognitive and functional scales, also did not differ between groups.

Section Summary: AD

For individuals who have AD who receive IVIG therapy, the evidence includes 3 RCTs. With the exception of a few subgroup analyses using MCI 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 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI.

Paraproteinemic Neuropathy

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with paraproteinemic neuropathy.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat paraproteinemic neuropathy: standard of care.

Outcomes

The general outcomes of interest area change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 2 weeks is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

An RCT by Comi et al. (2002) focused on short-term outcomes at 2 weeks in 22 patients. (130) No significant differences were found between the treatment and placebo groups.

Results of a double-blind, placebo-controlled, randomized crossover trial by Dalakas et al. (1996) compared IVIG with placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients. (131)

Section Summary: Paraproteinemic Neuropathy

For individuals who have paraproteinemic neuropathy who receive IVIG therapy, the evidence includes 2 small RCTs. Compared with placebo, IVIG showed mild and transitory improvements in 1 trial but failed to show any improvement in another.

Chronic Fatigue Syndrome

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with chronic fatigue syndrome.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with chronic fatigue syndrome. Chronic fatigue syndrome (also called systemic exertion intolerance disease) is a complex and controversial disease with multiple definitions.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat chronic fatigue syndrome: standard of care.

Outcomes

The general outcomes of interest are symptoms, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials

Numerous noncomparative studies have shown subjective benefits of IVIG therapy on chronic fatigue syndrome, but a double-blind randomized, placebo-controlled trial by Vollmer-Conna et al. (1997) in 99 patients with chronic fatigue syndrome reported no therapeutic benefit of IVIG. (132)

Section Summary: Chronic Fatigue Syndrome

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes a RCT and anecdotal reports. Compared with placebo, IVIG therapy has shown no therapeutic benefits.

Acute Myocarditis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute myocarditis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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 ongoing damage from a virus, a postinfectious inflammatory reaction, or a combination of the 2.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapy is currently being used to treat acute myocarditis: heart failure therapy alone.

Outcomes

The general outcomes of interest are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

The literature has been summarized in a Cochrane review by Robinson et al. (2015) (133), updated in 2020 (134), that included a 2001 placebo-controlled randomized trial of 62 adults with recent-onset dilated cardiomyopathy (135), a randomized, multicenter trial in Japan of 41 adults with a clinical diagnosis compatible with acute myocarditis (136) and a randomized, placebo-controlled study from Egypt in 86 children with acute onset dilated cardiomyopathy. (137) The overall certainty of the included evidence was very low, with an unclear risk of bias in the 2 adult studies and a low risk of bias in the pediatric study. In adults, the evidence regarding the effect of IVIG on event-free survival and OS is uncertain (event free survival: risk ratio: 1.76; 95% CI, 0.48 to 6.40 and overall survival: pooled risk ratio: 0.91; 95% CI, 0.23 to 3.62). For the pediatric study, the evidence for overall survival was also uncertain (risk ratio of death: 0.48; 95% CI, 0.20 to 1.15).

Huang et al. (2019) published a meta-analysis assessing IVIG for patients with acute myocarditis. (138) Thirteen studies (1534 participants), published between 1994 and 2017, were included. In-hospital mortality rates (pooled results: OR 0.44; 95% CI 0.17 to 0.71, p<.001) were significantly reduced for the IVIG group compared with patients who did not receive IVIG, and left ventricular ejection fraction (OR 1.73; 95% CI 1.34 to 2.13; p<.001) was significantly increased for IVIG. The study was limited by the IVIG doses not being uniformly predefined and by the limited follow-up durations (mainly between 6 and 12 months) across the included studies.

Retrospective Studies

Heidendael et al. (2018) reported on 94 children with new onset dilated cardiomyopathy in a retrospective cohort study with a median follow-up of 33 months. (139) After viral tests were performed, 18 (19%) children met diagnostic criteria for “probably or definite viral myocarditis,” and IVIG was administered to 21 (22%) patients. Treatment was associated with a higher recovery rate within 5 years, compared with nontreated children (70% versus 43%; p=.045); however, the hazard ratio for recovery with IVIG was not significant (hazard ratio, 2.1; 95% CI, 1.0 to 4.6; p=.056) after correction for possible cofounders. The authors concluded that IVIG treatment was associated with better improvement of systolic left ventricular function and better recovery but did not influence transplant-free survival.

Section Summary: Acute Myocarditis

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.

Refractory Recurrent Pericarditis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with refractory recurrent pericarditis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapy is currently being used to treat refractory recurrent pericarditis: heart failure therapy alone.

Outcomes

The general outcomes of interest are OS, change in disease status, QOL, and treatment-related mortality and morbidity. A follow-up to 36 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Imazio et al. (2016) conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports). (140) Approximately 47% of patients had idiopathic recurrent pericarditis, 10% had an infective cause, and the remainder had a systemic inflammatory disease. IVIG was generally administered at a dose of 400 to 500 mg/kg/d for 5 consecutive days, with repeated cycles according to the clinical response. Overall, recurrences occurred in

26.6% of cases after the first IVIG cycle, and 22 (73.3%) of the 30 patients were recurrence-free after a mean follow-up of approximately 33 months.

Section Summary: Refractory Recurrent Pericarditis

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes a systematic review of multiple case reports and case series. Although improvements were observed in some patients, controlled trials are lacking.

Stiff-Person Syndrome

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with stiff-person syndrome.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with 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.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat stiff-person syndrome: benzodiazepines and baclofen.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Follow-up at 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trial

The benefit of IVIG in stiff-person syndrome was confirmed in a small, randomized crossover study by Dalakas et al. (2001), which compared IVIG with placebo in 16 patients who had stiff-person syndrome and anti-GAD65 autoantibodies who were maintained on current doses of benzodiazepines throughout the study. (141) After a 1-month washout period, patients were crossed over to 3 months of the alternative treatment. Stiffness scores decreased significantly on IVIG, but not on placebo, regardless of order. Eleven (69%) patients were able to walk more easily or without assistance; the frequency of falls decreased, and patients were able to perform work-related or household tasks. The duration of benefit lasted 6 weeks to 1 year without additional treatment. In a cohort of patients (N=36) treated long-term, monthly IVIG maintained efficacy in 67% of patients for a median of 3.3 years. (142)

Section Summary: Stiff-Person Syndrome

For individuals who have stiff-person syndrome who receive IVIG therapy, the evidence includes a small, randomized crossover study. Compared with placebo, IVIG therapy has shown decreases in stiffness scores and improvements in functional outcomes.

Noninfectious Uveitis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with noninfectious uveitis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are individuals with noninfectious uveitis. Noninfectious uveitis is inflammation of the eye that results from eye trauma, anomalous immune processes, or unknown etiology.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies are currently being used to treat noninfectious uveitis: topical glucocorticoids, difluprednate, intraocular glucocorticoids, systemic glucocorticoids, and systemic immunomodulating agents.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Case Series

Two small case series of 18 and 10 patients, respectively, have reported measurable improvements in visual acuity after IVIG therapy. (143, 144) Collectively, these 2 studies represent insufficient evidence to draw conclusions about efficacy.

Section Summary: Noninfectious Uveitis

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. 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.

Post-polio Syndrome

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with post-polio syndrome.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with post-polio syndrome. Although polio no longer poses a major public health threat in the U. S., many patients live with the sequelae of paralytic polio. Many polio survivors experience a modest decline in function and muscle strength over many years that may reflect the natural history of polio.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following practice is currently being used to treat post-polio syndrome: supportive care alone.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Follow-up at 3 months is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Huang et al. (2015) published a systematic review and meta-analysis of RCTs and nonrandomized prospective studies on IVIG treatment of the post-polio syndrome. (145) Reviewers identified 3 RCTs (n=241 patients) and 5 prospective studies (n=267 patients). The primary outcomes of interest were the severity of pain, fatigue, and change in muscle strength 2 to 3 months after IVIG administration. Meta-analyses of RCT data found no statistically significant differences between IVIG- and placebo-treated groups for any of these outcomes. For example, the pooled mean difference in pain scores (0-to-10 visual analog scale) from the 3 RCTs was -1.02 (95% CI, -2.51 to 0.47). Meta-analysis of the 2 RCTs that reported a change in fatigue scores found a weighted mean difference 0.28 (95% CI, -1.56 to 1.12). The small number of RCTs and the negative findings of this systematic review represent insufficient evidence of the efficacy of IVIG for the post-polio syndrome.

Section Summary: Post-polio Syndrome

For individuals who have post-polio syndrome who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs and nonrandomized prospective studies. Compared with placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength.

Necrotizing Fasciitis

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with necrotizing fasciitis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with necrotizing fasciitis.

Interventions

The therapy being considered is IVIG therapy.

Comparators

The following therapies and practices are currently being used to treat necrotizing fasciitis: antibiotics and surgical removal of tissue.

Outcomes
The general outcomes of interest are OS, symptoms, functional outcomes, and treatment-related mortality and morbidity. A follow-up at 3 months is of interest to monitor outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Madsen et al. (2017) published a placebo-controlled, randomized trial evaluating IVIG for patients with necrotizing soft tissue infection (e.g., necrotizing fasciitis). (146) The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admission to the intensive care unit. The primary outcome was patient-reported physical function at 6 months, assessed using the Physical Component Summary score of the 36-Item Short-Form Health Survey. The mean Physical Component Summary score adjusted for the site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant (p=.81). Other outcomes (i.e., mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

Section Summary: Necrotizing Fasciitis
For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes a RCT. 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.

Hemolytic Disease of the Fetus and Newborn
Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for hemolytic disease of the fetus and newborn.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest are fetus and newborn with hemolytic disease. Hemolytic disease of the fetus and newborn (HDFN), also called erythoblastosis fetalis, is caused by maternal antibodies that pass though the placenta and attack fetal red blood cells. The disease presents with anemia and hydrops (edema) in fetuses, and with anemia and jaundice in newborns. Common treatment options are phototherapy and exchange transfusion (ET). IVIG is proposed as a less invasive alternative to ET.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following therapies and practices are currently being used to treat hemolytic disease of the fetus and newborn: phototherapy and exchange transfusion.

Outcomes
The general outcomes of interest are OS, symptoms, functional outcomes, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
In 2014, Louis et al. published a systematic review and meta-analysis of studies on IVIG for treatment of HDFN. (147) The authors identified 12 RCTs, which they assessed using the Cochrane risk of bias tool; 3 trials were judged to have low risk of bias, and 9 had high risk of bias. All trials reported adequate sequence generation for randomization, but only 3 reported details about allocation concealment, and only 3 reported details of blinding. The primary outcome of interest was need for ET. In the 3 studies with low risk of bias, a meta-analysis found no significant difference in the need for ET with IVIG or a control intervention (RR=0.82; 95% CI, 0.53 to 1.26). However, a meta-analysis of 6 studies considered to be at high risk of bias found significantly greater reductions in the need for ET with IVIG (RR=0.23; 95% CI, 0.13 to 0.40). The authors also presented analyses separately for studies of neonates with Rh isoimmunization (n=9 trials, 426 neonates) and those with ABO isoimmunization (n=5 trials, 350 neonates). IVIG significantly reduced the need for ET in these stratified analyses, but most of the studies in the Rh isoimmunization analysis and all studies in the ABO isoimmunization analysis were judged to have high risk of bias.

Previously, in 2002, a Cochrane review identified 3 RCTs with a total of 189 infants on IVIG for isoimmune hemolytic jaundice in newborns. (148) All 3 studies, published in the 1990s compared a single dose of IVIG in combination with phototherapy to phototherapy alone. Meta-analysis found that the need for ET was significantly lower in the group receiving IVIG than the control group (pooled RR=0.28; 95% CI, 0.17 to 0.47). Moreover, the mean number of ETs per neonate was significantly lower in the IVIG group (weighted mean difference [WMD], -0.52; 95% CI, -0.70 to -0.35). No adverse reactions were reported in the IVIG group, but 3 infants in the control group had adverse reactions (1 case each of hypoglycemia, hypocalcemia, and sepsis).

Section Summary: Hemolytic Disease of the Fetus and Newborn

Data from meta-analyses of RCTs found significant reduction in ET use in newborns with HDFN treated with IVIG. A number of studies were judged to be at high risk of bias, but this was largely due to a lack of blinding, and blinding may not be critical given the objective outcome measures.

Additional Indications

Treatment with IVIG has also been investigated for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and post-transplant viral infections (e.g., viral myocarditis, BK viremia). There are currently no U.S. Food and Drug Administration (FDA)-approved products for these indications.

Summary of Evidence

For individuals who have primary humoral immunodeficiency who receive intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) therapy, the evidence includes multiple randomized controlled trials (RCTs) and noncomparative studies. Relevant outcomes are overall survival (OS), 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 an improvement in the net health outcome.

For individuals who are undergoing hematopoietic cell transplantation (HCT) who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs, systematic reviews, and a meta-analysis. Relevant outcomes are disease-specific survival (DSS), symptoms, change in disease status, morbid events, quality of life (QOL), hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG for routine prophylaxis of infection in patients undergoing HCT was not associated with survival benefit or reduction in infection. However, a RCT concluded that passive immunotherapy with intravenous immunoglobulin decreases the risk of acute GVHD, associated interstitial pneumonia, and infections after bone marrow transplantation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are at risk of acute antibody-mediated rejection (ABMR) after solid organ transplants who receive IVIG therapy, the evidence consists of multiple RCTs, noncomparative observational studies, systematic reviews, and meta-analysis. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Although RCTs have shown conflicting results, prophylaxis with IVIG in patients with high panel reactive antibody (PRA) levels prior to solid organ transplant may result in PRA level reduction. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG treatment for ABMR has shown potential benefits in small RCTs, retrospective and prospective studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic lymphocytic leukemia (CLL) with recurrent bacterial infections associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in CLL patients has shown reductions in minor and moderate infections without 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.

For individuals who are human immunodeficiency virus (HIV)-infected children with recurrent bacterial infection associated with hypogammaglobulinemia who receive IVIG therapy, the evidence includes a single RCT. Relevant outcomes are OS, 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.

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 OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection (considered of marginal clinical importance) with no improvement in any of the other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology is likely to improve the net health outcome.

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 OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Neonatal sepsis has been most extensively evaluated, and a meta-analysis of trials found a 6-fold decrease in mortality when IVIG was added to conventional therapies. The evidence is sufficient to determine that the technology is likely to improve the net health outcome.

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes a meta-analysis involving multiple RCTs. Relevant outcomes are OS, 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.

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.

For individuals who have toxic shock syndrome who receive IVIG therapy, the evidence includes a small RCT and multiple observational studies. Relevant outcomes are OS, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for toxic shock syndrome in patients 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.

For individuals who have idiopathic thrombocytopenic purpura (ITP) who receive IVIG therapy, the evidence includes multiple RCTs and noncomparative studies. Relevant outcomes are DSS, 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.

For individuals who have Guillain-Barré Syndrome (GBS) who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs. Relevant outcomes are OS, DSS, 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.

For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes a systematic review and a meta-analysis of multiple RCTs. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. Compared with aspirin, 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.

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes a systematic review with a single 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 insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic inflammatory demyelinating polyneuropathy (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, QOL, 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 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (e.g., 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIDP 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 that the technology results in an improvement in the net health outcome.

For individuals who have Multifocal Motor Neuropathy (MMN) who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, 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.

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, QOL, 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.

For individuals who have Neuromyelitis Optica (NMO) who receive IVIG therapy, the evidence includes multiple observational studies. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. Studies have shown that IVIG treatment may benefit patients who are refractory to first-line treatment with steroids or plasma exchange, particularly children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, symptoms, change in disease status, QOL, 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.

For individuals who have Relapsing-Remitting Multiple Sclerosis (RRMS) who receive IVIG therapy, the evidence includes a technology assessment. Relevant outcomes are OS, DSS, symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. According to the technology assessment, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes 2 RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. A systematic review found improvements in over 90% of patients. RCTs have reported benefits in disease activity in the population as a whole (1 trial) or in a subgroup of patients with severe disease (1 trial). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) who receive IVIG therapy, the evidence includes systematic reviews of observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. No RCTs have evaluated IVIG for TEN or SJS; most trials that have, have been uncontrolled, however a retrospective review evaluated the

effectiveness of IVIG in reducing mortality in 16 individuals with TEN. All of the 16 individuals showed clinical improvement and disease resolution. The evidence is sufficient to determine that the technology results in an improvement in the health outcome.

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes systematic reviews of observational studies and RCTs. Relevant outcomes are a change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. In 1 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 an improvement in the net health outcome.

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

For individuals who have systemic lupus erythematosus (SLE) who receive IVIG therapy, the evidence includes systematic reviews of multiples studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals who have immune optic neuritis who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals who have Crohn's disease who receive IVIG therapy, the evidence includes multiple case reports of single patients summarized in a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, DSS, change in disease status, QOL, and treatment-related mortality

and morbidity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data. Relevant outcomes are a change in disease status, QOL, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select patients with refractory autoimmune hemolytic anemia. 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.

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Relevant outcomes are OS, change in disease status, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple RCTs, a large observational study, and a systematic review. Relevant outcomes are DSS, 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.

For individuals who have a recurrent spontaneous abortion who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Relevant outcomes are DSS, 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 that the technology results in an improvement in the net health outcome.

For individuals who have Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal (PANDAS) Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANS) who receive IVIG therapy, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related mortality and morbidity. The two controlled trials both showed a “moderate effect size” with a single dose (2 gm/kg administered as 1 gm/kg on two consecutive days). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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, QOL, and treatment-related mortality and morbidity. Although improvements were observed in 1 case series, the other 2 reported negative findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Complex Regional Pain Syndrome (CRPS) who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related mortality and morbidity. In 1 trial, compared with placebo, IVIG therapy was associated with improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 13 patients. In the other RCT, low-dose IVIG was ineffective in relieving pain in CRPS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Alzheimer Disease (AD) who receive IVIG therapy, the evidence includes 3 RCTs. Relevant outcomes are OS, DSS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. With the exception of a few subgroup analyses using mild cognitive impairment (MCI) 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 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes a RCT and anecdotal reports. Relevant outcomes are symptoms, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown no therapeutic benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes a meta-analysis, RCTs, and a retrospective study. Relevant outcomes are OS, change in disease status, QOL, and treatment-related mortality and morbidity. 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 that the technology results in an improvement in the net health outcome.

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes a systematic review of multiple case reports and case series. Relevant outcomes are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Although improvements were observed in some patients, controlled trials are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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, QOL, 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 an improvement in the net health outcome.

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. Relevant outcomes are symptoms, functional outcomes, QOL, 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 that the technology results in an improvement in the net health outcome.

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, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes a RCT. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

For individuals who have hemolytic disease of the fetus and newborn (HDFN) the evidence includes systematic reviews and meta-analysis of studies on IVIG for treatment of HDFN. Relevant outcomes are OS, symptoms, functional outcomes, and treatment-related mortality

and morbidity. Data from meta-analyses of RCTs found significant reduction in exchange transfusion (ET) use in newborns with HDFN treated with IVIG. A number of studies were judged to be at high risk of bias, but this was largely due to a lack of blinding, and blinding may not be critical given the objective outcome measures. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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. (36) Table 2 summarizes the conclusions of the Work Group regarding the potential benefit of immune globulin therapy for various disease states.

Table 2. American Academy of Allergy, Asthma, and Immunology Work Group Report Immune Globulin Recommendations (36)

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 • CIDP • Multifocal motor neuropathy • Guillan-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

	• Immunoglobulin M (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 • 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 • 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

In 2010, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services (CBS) published guidelines on the use of immunoglobulin therapy for patients with primary immune deficiency. (5) The guidelines reported that there was sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, lowers mortality, and improves quality of life. Treatment should be started at a dose of 400 to 600 mg/kg per 4 weeks for IVIG or 100 to 150 mg/kg per week for subcutaneous immunoglobulin (SCIG) infusion.

American Academy of Allergy, Asthma, and Immunology (AAAAI)

In 2015, the American Academy of Allergy, Asthma, and Immunology published practice parameters for the diagnosis and management of primary immunodeficiency. (149) The Academy advised that treatment of these conditions include antibiotic prophylaxis and immunoglobulin G (IgG) replacement.

Secondary Immunodeficiency

In 2022, AAAAI published a guideline on the diagnosis and management of secondary hypogammaglobulinemia. (150) 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)

In 2007, the NAC and CBS published guidelines on the use of IVIG for hematologic conditions. (47) The guidelines stated that evidence does not support the use of IVIG after hematopoietic cell transplantation.

Acute Antibody-Mediated Rejection for Solid Organ Transplant

In 2011, the Clinical guidelines for immunoglobulin use (second edition) published by the London Department of Health included the following recommendations regarding solid organ transplants: (151)

- Patients in whom renal, heart or lung transplant is prevented because of antibodies can receive IVIG.
- Patients experiencing steroid resistant rejection or where other therapies are contraindicated after renal, heart and/or lung transplant can receive IVIG.

In 2010, the CBS and NAC developed guidelines addressing the use of IVIG for solid organ transplantation; a panel of experts reviewed findings from a systematic review of evidence. (152) In their literature search, reviewers identified 3 RCTs, all on kidney transplant, and numerous observational studies or case series on several types of organ transplantation. Key recommendations of the panel are as follows:

- When kidney transplantation involves use of a living donor, IVIG is recommended to decrease donor-specific sensitization.
- There is insufficient evidence to recommend for or against the use of IVIG for ABO-incompatible kidney transplantation.
- To reduce the risk of acute antibody-mediated rejection, IVIG is recommended for kidney transplant patients who have donor-specific antibodies preoperatively. IVIG is not recommended for kidney transplant patients who do not have donor-specific antibodies.
- IVIG is recommended after plasmapheresis for patients who have received a living donor or deceased kidney donor transplant and who have acute antibody-mediated rejection. Consider IVIG when patients have corticosteroid-resistant rejection, or when other therapies are deemed unacceptable or ineffective.
- There is insufficient evidence to recommend for or against the use of IVIG for desensitization for patients undergoing heart, lung, or liver transplantation. (152)

Kidney Disease Improving Global Outcomes (KDIGO) published clinical practice guideline recommendations regarding antibody-mediated rejection (AMR) that includes implications stating that most individuals should receive the recommended course of action while suggestions imply that different choices will be appropriate for different individuals. (2009) KDIGO recommends corticosteroids for the initial treatment of acute cellular rejection. The guideline suggests treating acute AMR with one or more of the following alternatives, with or without corticosteroids, plasma exchange; intravenous immunoglobulin; anti-CD20 antibody (rituximab); lymphocyte-depleting antibody. It is stated that therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or IVIG and rituximab to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection. However, the optimal protocol remains to be determined. There are no randomized controlled trials with adequate statistical power to compare the efficacy of these different strategies. (153)

Chronic Lymphocytic Leukemia
National Comprehensive Cancer Network
The National Comprehensive Cancer Network guidelines (v.3.2023) on chronic lymphocytic leukemia recommend IVIG as supportive care for patients with chronic lymphocytic leukemia: for the treatment of autoimmune cytopenias and recurrent sinopulmonary infections requiring hospitalization or intravenous antibiotics (IgG levels <500 mg/dL). (154) The guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.30.5 g/kg) to maintain levels of 500 mg/dL.

Infections
Infections in HIV-Infected Children
In 2022, updated joint guidelines on the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published. (155) The guidelines, endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and other agencies and societies, included the following statements:

- "Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia."
- "In rare situations in which combination antiretroviral therapy and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, IVIG prophylaxis can be considered for secondary prophylaxis."

Neonatal Sepsis
In 2018, the American Academy of Pediatrics published guidelines on the management of neonates with suspected or proven early-onset bacterial sepsis. (156) The guidelines did not address the use of IVIG to treat neonatal sepsis.

Autoimmune and Inflammatory Conditions
Idiopathic Thrombocytopenic Purpura
In 2007, the NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including idiopathic thrombocytopenic purpura (ITP). (47) Recommendations for patients with ITP are as follows:

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

Guillain-Barré Syndrome
The American Academy of Neurology (AAN; 2003, reaffirmed January 2022) guidelines on immunotherapy for Guillain-Barre syndrome concluded that IVIG is as efficacious as plasmapheresis and should be offered as a treatment option to adults who require aid to walk within 2 to 4 weeks of neuropathic symptom onset. (157) The guidelines indicated that there was insufficient evidence to support or refute the use of IVIG in children but both IVIG and plasmapheresis are listed as treatment options.

Kawasaki Syndrome and Other Vasculitides
The American Heart Association (2017) (158) and the American College of Rheumatology (2021) (159) 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). (160) The guidelines indicated that data are insufficient to compare the efficacy of prednisone and IVIG in the treatment of CIDP. Of note, the AAN website states this is a "retired" guideline.

The European Academy of Neurology and the Peripheral Nerve Society published updated guidelines on the management of CIDP in 2021. (161) Recommendations regarding immunoglobulin therapy included:

- "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 patients with good vascular access, plasma exchange my 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). (160) There were insufficient data to determine the optimal treatment interval, dosing, and duration. Of note, the AAN website states this is a "retired" guideline.

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). (160)

Neuromyelitis Optica
According to the Neuromyelitis Optica Study Group (2014) updated guidelines, high-dose IVIG is potentially beneficial in the long-term treatment of neuromyelitis optica and may be used as an alternative for patients with a contraindication to 1 of the other treatments or, particularly, in children. (162)

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 that focused on the appropriate management of myasthenia gravis. (163) The authors of this guidance recommended the use of IVIG or plasma exchange for short-term treatment in patients with myasthenia gravis with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients 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 IVIG 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 IVIG is less certain. The use of IVIG as maintenance therapy can be considered for patients with refractory myasthenia gravis or for those in whom immunosuppressive agents are relatively contraindicated.

The Myasthenia Gravis Foundation of America in conjunction with an international task force updated guidelines (2020) for myasthenia gravis. (164) The authors added a recommendation for the combination of high-dose steroids with either plasma exchange or IVIG in patients who have myasthenia gravis related to the use of immune checkpoint inhibitors.

The AAN (2012) guidelines on the treatment of neuromuscular disorders concluded that IVIG therapy is probably effective in treating patients with severe myasthenia gravis and should be considered in the treatment plan (level B). (160) There was insufficient evidence to compare IVIG and plasmapheresis in the treatment of these patients. Of note, the AAN website states this is a "retired" guideline.

Relapsing-Remitting Multiple Sclerosis
In 2002, The AAN published a technology assessment on therapies for multiple sclerosis. (81) The assessment was reviewed and reaffirmed in 2018. The assessment offered the following recommendations on IVIG:

- Studies of IVIG to date have generally involved small numbers of patients, have lacked complete data on clinical and magnetic resonance imaging (MRI) outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIG reduces the attack rate in relapsing-remitting multiple sclerosis (type C recommendation: 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).

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. (165) 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 Necrolysis and Stevens-Johnson Syndrome
The British Association of Dermatologists (2016) published guidelines on the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in adults. (166) 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 necrolysis 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, antitumor necrosis factor (TNF) biologics or ciclosporin.” (167)

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). (160)

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 2014, 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." (168) This is a Grade B recommendation.

Neonatal Alloimmune Thrombocytopenia

The NAC and CBS (2007) published guidelines on the use of IVIG for hematologic conditions. (47)

- 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. (169) The guideline concluded that IVIG does not prevent further miscarriage in women with recurrent miscarriages (level B).

Miscellaneous

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

In 2007, the NAC and CBS convened a panel of national experts to develop evidence-based practice guidelines on the use of IVIG for neurologic conditions. (170) 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 are uncertain.

Autism Spectrum Disorder

The NAC and CBS (2007) guidelines on neurologic conditions did not recommend IVIG for autism. (170)

The American Academy of Child and Adolescent Psychiatry (2014) published practice parameters on the assessment and treatment of autism spectrum disorder. (171) 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. (172) 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 American College of Cardiology Foundation and the American Heart Association issued joint guidelines in 2013, updated in 2017 and 2022, on the management of heart failure. (173) The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. 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 2024
NCT05584631	The Influence of Body Composition on Immunoglobulin Disposition After Intravenous and Subcutaneous Administration	20	Oct 2024
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
Completed			
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
NCT02176863[a]	A Multicenter, Prospective, Randomized, Placebo-controlled, Double-blind, Parallel-Group Clinical Trial to Assess the Efficacy and Safety of Immune Globulin Intravenous	191	Nov 2022 (terminated)

	(Human) Flebogamma® 5% DIF in Patients With Post-Polio Syndrome		

NCT: national clinical trial.
No: number.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	0537T, 0538T, 0539T, 0540T, 90283, 90284
HCPCS Codes	C9399, J1459, J1551, J1552, J1554, J1555, J1556, J1557, J1558, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1575, J1576, J1599, J3490, J3590, J9999 [Deleted 4/2021: C9072]

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to "Initial Therapy" criteria. No new references added.
01/01/2025	Document updated. The following changes were made to Coverage: Added information on preferred and non-preferred products. No new references added.
05/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Added conditional coverage for IVIG post Chimeric antigen receptor T-cell (CAR-T) therapy. 2) Added Post-transplant viral infections (e.g., viral myocarditis, BK viremia) and Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) to the experimental, investigational and/or unproven for any indication not listed above, including but not limited to coverage statement. 3) Moved Dermatomyositis to the medically necessary FDA labeled indications from the medically necessary off label use. References 54, 68, 88, 96, 113, 142, 146, 150, 156, 157, 159, 164, 173, and 174 were added; some updated and others removed.
10/15/2023	Document updated. The following change was made to Coverage: Added "EXCEPTION FOR ILLINOIS PLAN ONLY: Per Illinois state mandate, the continued use of IVIG is considered covered for the treatment of PANDAS/PANS."
12/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Added "After 100 days with serum IgG < 400 mg/dL" to criteria for the Bone Marrow Transplant medically necessary indication, 2) Replaced "Antiphospholipid Syndrome" with "Catastrophic Antiphospholipid Syndrome (CAPS)" and the following criteria was added: "Patients who have developed widespread thrombotic disease with organ damage, AND", "Used in combination with anticoagulation and glucocorticoid therapy, AND", and "One course of therapy at dose limit of 2 g/kg in divided doses over 2 to 5 days." 3) Replaced "Antiphospholipid Syndrome" with "Catastrophic Antiphospholipid Syndrome (CAPS)" in the indication "recurrent

	spontaneous abortion or recurrent pregnancy loss (not attributed to antiphospholipid syndrome)" on the experimental, investigational and/or unproven coverage statement. References 2, 13, 36, 38, 138, 140, 141, 160, 161, 163, 164, and 167 were added; some updated and others removed.
04/01/2021	Reviewed. No changes.
10/01/2020	Document updated with literature review. The following changes were made to Coverage: 1) The indication of AIDS and criteria were removed from the U.S. Food and Drug Administration (FDA) labeled indications medically necessary statement; 2) Neuromyelitis optica was added to the FDA off-label indications medically necessary statement; 3) Added NOTE 10: initial authorization for a maximum dose of 2 grams/kg monthly for 3 months. Reauthorization for up to 3 months is dependent on documented beneficial clinical response as additional criteria to the solid organ transplant indication; 4) Added the following statement: Additional courses of IVIG therapy for moderate to severe PANDAS/PANS are considered experimental, investigational and/or unproven; 5) Acute myocarditis, autoimmune autonomic ganglionopathy (AAG), and refractory recurrent pericarditis were added to the list of indications considered experimental, investigational and/or unproven; 6) Added or recurrent pregnancy loss (not attributed to Antiphospholipid Syndrome) to Recurrent spontaneous abortion; 7) Removed Exception: GAMUNEX®-C, GAMMAGARD®, and GAMMAKED™ may only be administered as subcutaneously Ig therapy in patients with Primary Humoral Immunodeficiency from the Subcutaneously administered immunoglobulin (SCIG) medically necessary statement. References 1-4, 13-20, 22-34, 38-39, 44-53, 56, 60-61, 63-67, 69-71, 75-82, 84-86, 90-92, 94, 104-105, 112-118, 121-122, 126, 128-131, 133-134, 139, 141-144, 151-152, 154-163, and 165-169 were added and some references removed.
03/15/2018	Reviewed. No changes.
11/15/2017	Partial update. Removed bulleted criteria on antibiotic use and added the following NOTE: "It is recommended by the Pandas Physicians Network (PPN) that antibiotics should be prescribed at treatment level dosages for 2 to 4 weeks before initiating IVIG".
09/01/2017	Partial update. The following medically necessary conditional criteria was added to the coverage section specific to IVIG for the treatment of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute Onset Neuropsychiatric Syndrome (PANS): 1) Diagnosed with moderate to severe PANDAS/PANS (must rule out more specific disorders before starting IVIG therapy [AE, CNS vasculitis, NPSLE, ADEM, infectious encephalitis, etc.] AND 2) Antibiotics should be prescribed at "treatment level" dosages for 2 to 4 weeks before initiating IVIG, AND 3) Laboratory confirmation that the patient is not IgA deficient, AND 4) Documentation that the patient is free of strep infections and any other bacterial or viral infections at the time of the IVIG infusion, AND 5)

	Dosing is limited to 2 grams/kg of child's weight (1 gm/kg per day for 2 days). In addition, the following NOTE was added specific to the Illinois plan: FOR ILLNOIS PLAN ONLY: Per Illinois state mandate the use of intravenous immunoglobulin (IVIG) is considered covered for the treatment of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANDAS/PANS).
05/15/2017	Document updated with literature review. The following clarification was added to the criteria for treatment of acute idiopathic thrombocytopenia purpura (ITP): "…with platelet counts below 30,000/mm". In addition, antiphospholipid syndrome was added as a covered off-label indication.
01/01/2017	Document updated with literature review. The following was added to the indications considered medically necessary: 1) Idiopathic Thrombocytopenia purpura (ITP); the following criteria added: Acute, Severe Idiopathic Thrombocytopenia purpura (ITP) or Chronic ITP; in patients with at least 6 months' duration of disease, and with persistent thrombocytopenia, despite treatment with corticosteroids and splenectomy. In addition, the following NOTE added: "NOTE: Acute, severe ITP may be defined by the following parameters: Acute ITP with major bleeding, e.g., life-threatening bleeding and/or clinically important mucocutaneous bleeding; acute ITP with severe thrombocytopenia and at high risk for bleeding complications; acute ITP with severe thrombocytopenia and a slow or inadequate response to corticosteroids; or acute ITP with severe thrombocytopenia and a predictable risk of bleeding in the future (e.g., a procedure or surgery with a high bleeding risk). 2) Myasthenia gravis; the following criteria added: Periodical use to maintain remission in patients with MG that is not well controlled despite the use of chronic immunomodulating drugs. 3) Hemolytic disease of the fetus and newborn (aka erythroblastosis fetalis) changed from experimental, investigational and/or unproven to a medically necessary indication with no criteria. In addition, moved acute lymphoblastic leukemia (ALL) listed in the experimental, investigational and/or unproven listing to the listing of medically necessary indications with the following noted medically necessary criteria: "Only for patients with hypogammaglobulinemia (IgG level less than 700 mg/dL), AND One severe bacterial infection within preceding six months, or two or more bacterial infections in one year; or evidence of specific antibody deficiency." The following indication was added as experimental, investigational and/or unproven: "Post-polio syndrome".
02/01/2016	Reviewed. No changes.
09/01/2014	Document updated with the following changes to coverage: Platelet count < 30,000/mm^3 was added to criteria for treatment of thrombocytopenia.
04/15/2014	Document updated with the following changes to coverage: 1) IgG level was raised to 700 mg/dL for any indication that cited an IgG level; 2)"Normal

	total IgG" was redefined as specific antibody deficiency (SAD); 3) Statement for Primary Humoral Immunodeficiency was rearranged for clarity regarding the situations requiring testing for immune response; 4) Testing Table was edited for clarity.
09/01/2013	Document updated with literature review. The following was added to the list of covered indications when criteria are met: 1) Limbic encephalitis, 2) Neonatal hemochromatosis, 3) Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). The following covered indications were modified: 1) Bone marrow transplant—age limit was removed, 2) CIDP—NOTE was added regarding diagnostic criteria, 3) Primary humoral immunodeficiencies—NOTE was added regarding cancer, 4) PRCA—criteria is now parvovirus B19 OR salvage therapy for severe refractory anemia (previously was AND). The following indications were added to the list of examples of experimental, investigational and unproven indications: 1) Acute disseminated encephalitis; 2) Alzheimer's disease; 3) Chronic sinusitis; 4) Complex regional pain syndrome; 5) Crohn's disease; 6) Opsoclonus-myoclonus syndrome; 7) Rasmussen encephalitis; 8) Vasculitides (other than Kawasaki disease), including: vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., Wegener's granulomatosis, polyarteritis nodosa), Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases.
03/15/2011	Document updated with literature review. The following changes were made: 1) "Malignancies of various types" was removed from the list of medically necessary indications; 2) Examples of first line therapy—"(e.g., interferon beta, glatiramer)"—were added to the criteria for multiple sclerosis.
01/15/2011	Coverage revised as follows: re-evaluation requirement was changed to within 18 months after initiating therapy, and/or the first spring season following the first 12 months of therapy, after discontinuing IVIG at least 4 months.
07/01/2008	Coverage Revised
04/01/2008	CPT/HCPCS code(s) updated
11/15/2007	Revised/Updated Entire Document
03/01/2004	Coverage Revised
06/01/2001	Codes Revised/Added/Deleted
09/01/1999	Revised/Updated Entire Document
12/01/1996	Revised/Updated Entire Document
05/01/1996	Medical policy number changed
10/01/1994	Revised/Updated Entire Document
04/01/1994	Revised/Updated Entire Document
04/01/1993	Revised/Updated Entire Document
10/01/1992	Revised/Updated Entire Document
04/01/1991	Revised/Updated Entire Document

03/01/1991	Revised/Updated Entire Document
12/01/1990	New Medical Document