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Immunoglobulin Therapy

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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.**

Medical Benefit Therapeutic Alternatives

Certain prescription drugs administered by a health care provider in a clinical or professional setting have therapeutic equivalents or alternatives. Benefits may be limited to certain therapeutic equivalents or alternatives unless a coverage exception is granted. Members and their providers may visit the plan website for more information or may call the number on the member's ID card for further assistance.

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 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.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-G and 24-A s 4234-E (for HMOs) requires all group insurance policies and all health maintenance organization group contracts that provide coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group policies that provide coverage for prescription drugs may not exclude coverage of any such drug used for the treatment of HIV or AIDS on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that drug is recognized for the treatment of that indication in one of the standard reference compendia or in peer-reviewed medical literature. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this provision: "Off-label use" means the prescription and use of drugs for indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a. The United States Pharmacopeia Drug Information or information published by its successor organization; or b. The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

EXCEPTION: For members residing in the state of Maine, 24-A s 2837-F and 24-A s 4234-D (for HMOs) requires that coverage for prescription drugs must provide coverage for off-label use in accordance with the following: A) Group insurance policies that provide coverage for prescription drugs may not exclude

coverage of any such drug used for the treatment of cancer for a medically accepted indication on the grounds that the drug has not been approved by the federal Food and Drug Administration for that indication, as long as that use of that drug is a medically accepted indication for the treatment of cancer. B) Coverage of a drug required by this subsection also includes medically necessary services associated with the administration of the drug. C) This subsection may not be construed to require coverage for a drug when the federal Food and Drug Administration has determined its use to be contraindicated for treatment of the current indication. D) A drug use that is covered pursuant to paragraph A may not be denied coverage based on a "medical necessity" requirement except for a reason that is unrelated to the legal status of the drug use. E) A contract that provides coverage of a drug as required by this subsection may contain provisions for maximum benefits and coinsurance and reasonable limitations, deductibles and exclusions to the same extent that these provisions are applicable to coverage of all prescription drugs and are not inconsistent with the requirements of this subsection. For this requirement: "Medically accepted indication" includes any use of a drug that has been approved by the federal Food and Drug Administration and includes another use of the drug if that use is supported by one or more citations in the standard reference compendia or if the insurer involved, based upon guidance provided by the federal Department of Health and Human Services Medicare program pursuant to 42 United States Code, Section 1395x(t), determines that that use is medically accepted based on supportive clinical evidence in peer-reviewed medical literature. "Off-label use" means the prescription and use of drugs for medically accepted indications other than those stated in the labeling approved by the federal Food and Drug Administration. "Peer-reviewed medical literature" means scientific studies published in at least 2 articles from major peer-reviewed medical journals that present data that supports the proposed off-label use as generally safe and effective. "Standard reference compendia" means: a). The United States Pharmacopeia Drug Information or information published by its successor organization; or b). The American Hospital Formulary Service Drug Information or information published by its successor organization. This applies to Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO.

EXCEPTION: For members residing in the state of Nebraska, §44-788 (Drug Coverage for the Treatment of Cancer and AIDS) mandates that any individual or group policy which provides reimbursement for FDA approved prescription drugs for the treatment of a specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome shall not exclude coverage of any drug or combination of drugs on the basis that the drug or combination of drugs has not been approved by the federal Food and Drug Administration for the treatment of another specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome if: (a) the drug or combination of drugs is recognized for treatment of the other specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome in the United States Pharmacopeia-Drug Information and the drug or combination of drugs is approved for sale by the federal Food and Drug Administration, or (b) the drug or combination of drugs is recognized for treatment of the other specific type of cancer OR human immunodeficiency virus or acquired immunodeficiency syndrome in medical literature and the drug or combination of drugs is approved for sale by the federal Food and Drug Administration. For purposes of this section, medical literature means two articles from major peer-reviewed professional medical journals that have recognized, based on scientific or medical criteria, the safety and effectiveness of the drug or combination of drugs for treatment of the indication for which it has been prescribed unless two articles from major peer-reviewed professional medical journals have concluded, based on scientific or medical criteria, that the drug or combination of drugs is unsafe or ineffective or that the safety and effectiveness of the drug or combination of drugs cannot be determined for the treatment of the indication for which the drug or combination of drugs has been prescribed. Each article shall meet the uniform requirements for manuscripts submitted to biomedical journals established by

the International Committee of Medical Journal Editors or shall have been published in a journal specified by the United States Department of Health and Human Services pursuant to 42 U.S.C. 1395x(t)(2)(B), as amended, as acceptable peer-reviewed medical literature. Peer-reviewed medical literature shall not include publications or supplements that are sponsored to a significant extent by a pharmaceutical manufacturing company or health carrier.

Further, the coverage of a drug or combination of drug under this section shall include medically necessary services associated with the administration of the drug if such services are covered by the policy. This applies to: Fully Insured Small Group, Mid-Market, Large Group, Student PPO, HMO, POS, EPO. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

EXCEPTION: For members residing in the state of Arkansas, § 23-79-1905 (SB181) requires a health benefit plan that is offered, issued, or renewed in this state provide coverage, whether on or off label, for the use of intravenous immunoglobulin, also known as "IVIG", to treat individuals diagnosed with pediatric acute-onset neuropsychiatric syndrome or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Coverage shall be provided if the pediatric patient's primary care physician, in consultation with an Arkansas licensed pediatric psychiatrist and an Arkansas licensed physician who practices in at least one (1) pediatric subspecialty, including a neurologist, rheumatologist, or infectious disease physician who has treated the pediatric patient determines and agrees that the treatment is necessary and follows a patient-specific treatment plan. This applies to the following: Fully Insured Group, Student, HMO, EPO, PPO, POS. Unless indicated by the group, this mandate or coverage will not apply to ASO groups.

Coverage

NOTE 1: Refer to RX502.061 Oncology Medications for oncologic indications of immunoglobulin therapy not specifically addressed on this policy.

NOTE 2: See the Appendix for exception criteria for medications in this class. The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

INTRAVENOUS IMMUNOGLOBULIN THERAPY

Intravenous Immune Globulin (IVIG) **may be considered medically necessary** for the following indications:

Immunodeficiency States

Individuals with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, X-linked hyperimmunoglobulinemia M syndrome, and ataxia telangiectasia.

- Individuals with primary immunodeficiency syndromes should meet **ALL** the following criteria for treatment with immunoglobulin:
 - Laboratory evidence of immunoglobulin deficiency (see Policy Guidelines section);
 - Documented inability to mount an adequate immunologic response to inciting antigens (see Policy Guidelines section); and

- Persistent and severe infections, despite treatment with prophylactic antibiotics.
- Individuals with chronic lymphocytic leukemia (CLL) who have immunoglobulin G (IgG) levels less than 400 mg/dL and persistent bacterial infections.

Infections

- Individuals (children) with human immunodeficiency virus (HIV) who have IgG levels less than 400 mg/dL to prevent opportunistic infections.
- Individuals with severe anemia associated with human parvovirus B19.
- Individuals with toxic shock syndrome.

Autoimmune and Inflammatory Conditions

- Individuals with acute, severe idiopathic thrombocytopenic purpura (see Policy Guidelines section) or chronic idiopathic thrombocytopenic purpura with a disease duration of at least 6 months, presence of symptoms, and with persistent thrombocytopenia (platelet <20,000 per microliter [adult] or 30,000 per microliter [child])-despite treatment with corticosteroids and splenectomy.
- Adults with Guillain-Barré syndrome as an equivalent alternative to plasma exchange.
- Individuals with Kawasaki syndrome.
- Individuals with Wegener granulomatosis.
- Individuals with chronic inflammatory demyelinating polyneuropathy (CIDP) with progressive symptoms for at least 2 months.
- Individuals with multifocal motor neuropathy.
- Individuals with Eaton-Lambert myasthenic syndrome who have failed to respond to anticholinesterase medications and/or corticosteroids.
- Individuals with neuromyelitis optica as an alternative for those with contraindications or lack of response to first-line treatment, particularly in children.
- Individuals with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
- Individuals with myasthenic exacerbation (i.e., an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated.
- Individuals with severe, progressive autoimmune mucocutaneous blistering diseases that include pemphigus, pemphigoid, pemphigus vulgaris, and pemphigus foliaceus who have failed treatment with conventional agents such as corticosteroids, azathioprine, and cyclophosphamide.
- Individuals with dermatomyositis or polymyositis that is refractory to treatment with corticosteroids; in combination with other immunosuppressive agents.
- Individuals with warm antibody hemolytic anemia who are refractory to prednisone and splenectomy.
- Individuals with catastrophic antiphospholipid syndrome.
- Individuals with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections and Pediatric Acute Onset Neuropsychiatric Syndrome (PANDAS/PANS) when the following criteria are met:

- Confirmation that neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professions, AND
- One course of therapy at a dose limit of 1 gm/kg per day for 2 consecutive days.

EXCEPTION FOR ILLINOIS PLAN ONLY: Per Illinois state mandate, the continued use of IVIG is considered covered for the treatment of PANDAS/PANS.

NOTE 3: Additional courses of IVIG therapy for PANDAS/PANS **are considered experimental, investigational and/or unproven.** (See **EXCEPTION FOR ILLINOIS PLAN** above.)

NOTE 4: 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 5: FOR ILLINOIS PLAN ONLY: Per Illinois state mandate the use of IVIG is considered covered for the treatment of PANDAS/PANS when consistent with the criteria outlined in this Medical Policy.

Alloimmune Processes

- Individuals with neonatal alloimmune thrombocytopenia.
- Individuals with hemolytic disease of the fetus and newborn (erythroblastosis fetalis).

Miscellaneous

- Individuals with stiff-person syndrome not controlled by other therapies.

Intravenous immunoglobulin (IVIG) therapy **is considered experimental, investigational and/or unproven** for the following indications:

Immunodeficiency States

- Individuals who have received solid organ transplant for prophylaxis or treatment of acute antibody-mediated rejection.
- Individuals undergoing or who have undergone hematopoietic cell transplantation who have IgG levels less than 400 mg/dL.
- Prior to solid organ transplant, treatment for individuals at high risk of antibody-mediated rejection including highly sensitized individuals and those receiving an ABO-incompatible organ.

Infections

- Individuals with neonatal sepsis (prophylaxis or treatment).
- Individuals (adults) with sepsis.

Autoimmune and Inflammatory Conditions

- Individuals with toxic epidermal necrolysis and Stevens-Johnson syndrome.

- Individuals with inclusion body myositis.
- Individuals with systemic lupus erythematosus.
- Individuals with immune optic neuritis.
- Individuals with Crohn disease.
- Individuals with hemophagocytic lymphohistiocytosis.

Alloimmune Processes

- Individuals with recurrent spontaneous abortion.

Miscellaneous

- Individuals with autism spectrum disorder.
- Individuals with complex regional pain syndrome.
- Individuals with Alzheimer disease.
- Individuals with paraproteinemic neuropathy.
- Individuals with chronic fatigue syndrome.
- Individuals with acute myocarditis.
- Individuals with refractory recurrent pericarditis.
- Individuals with noninfectious uveitis.
- Individuals with postpolio syndrome.
- Individuals with necrotizing fasciitis.
- Individuals with relapsing-remitting multiple sclerosis.
- Individuals with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, paraneoplastic syndromes, epilepsy, chronic sinusitis, asthma, aplastic anemia, Diamond-Blackfan anemia, red cell aplasia, acquired factor VIII inhibitors, acute lymphoblastic leukemia, multiple myeloma, immune-mediated neutropenia, nonimmune thrombocytopenia, cystic fibrosis, recurrent otitis media, diabetes mellitus, Behçet syndrome, adrenoleukodystrophy, organ transplant rejection, Fisher syndrome, IgG subclass deficiency, opsoclonus-myoclonus, birdshot retinopathy, epidermolysis bullosa acquisita, polyradiculoneuropathy (other than CIDP), refractory rheumatoid arthritis, other vasculitides besides Kawasaki disease, including polyarteritis nodosa, Goodpasture syndrome, and vasculitis associated with other connective tissue diseases.

SUBCUTANEOUS IMMUNOGLOBULIN THERAPY

Subcutaneous immunoglobulin therapy (SCIG) **may be considered medically necessary** for the following indications:

- Individuals with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, and CIDP.

Other applications of SCIG therapy **are considered experimental, investigational and/or unproven.**

Policy Guidelines

Black Box Warnings and Precautions

For intravenous immunoglobulin (IVIG):

- Thrombosis may occur with immunoglobulin products. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.
- For individuals at risk of thrombosis, administer immunoglobulin products at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in individuals at risk for hyperviscosity.
- Renal dysfunction, acute renal failure, osmotic nephropathy, and death may occur with the administration of human IVIG products in predisposed individuals. Individuals predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes, age greater than 65 years, volume depletion, sepsis, paraproteinemia, or individuals receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in individuals receiving IVIG products that contain sucrose.
- For individuals at risk of renal dysfunction or renal failure, administer IVIG at the minimum dose and infusion rate practicable. Ensure adequate hydration before administration.

Additional warnings and precautions include:

- Immunoglobulin A (IgA)-deficient individuals with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output, in individuals at risk of developing acute renal failure.
- Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in individuals receiving IVIG therapy.
- Thrombosis may occur. Monitor individuals with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic meningitis syndrome may occur in individuals receiving IVIG therapy, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IVIG treatment. Monitor individuals for signs and symptoms of hemolysis and hemolytic anemia.
- Monitor individuals for pulmonary adverse reactions (transfusion-related acute lung injury).
- Individuals receiving IVIG for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for developing fever, chills, nausea, and vomiting.
- IVIG is made from human plasma and may contain infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent).
- Passive transfer of antibodies may confound serologic testing.

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

Primary Immunodeficiency Syndromes

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

- Laboratory evidence of immunoglobulin deficiency may include the following definitions:
 - Agammaglobulinemia (total immunoglobulin G (IgG) <200 mg/dL),
 - Persistent hypogammaglobulinemia (total IgG <400 mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions),
 - Absence of B lymphocytes.
- Inability to mount an adequate antibody response to inciting antigens may include the following definitions:
 - Lack of appropriate rise in antibody titer following provocation with a polysaccharide antigen,
 - Lack of appropriate rise in antibody titer following provocation with a protein antigen.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Individuals with CIDP should have an established diagnosis based on criteria like those established by the American Academy of Neurology in 1991, (1) or those described in guidelines from the European Federation of Neurological Societies and the Peripheral Nerve Society (PNS) guidelines, published in 2006, and updated in 2021 (as the European Academy of Neurology/ PNS guidelines). (2) The updated guidelines include IVIG as a recommended first-line treatment option in CIDP.

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 immunoglobulin depot injections have been largely abandoned.

IVIG is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. 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.

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, hepatitis B).

Regulatory Status

Several IVIG products have been approved by the U.S. Food and Drug Administration (FDA). These products include but are not limited to: Alyglo® (GC Biopharma), Asceniv® (ADMA Biologics), Bivigam® (ADMA Biologics), Flebogamma DIF® (Instituto Grifols), Gammagard Liquid® (Takeda), Gammagard S/D® (Takeda), Gammaked® (Kedrion Biopharma), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), PANZYGA® (Pfizer), Privigen® (CSL Behring) and Yimmugo® (Biotest AG). (3-5)

Several SCIG products have been approved by the FDA. They include but are not limited to: Cutaquig® (Octapharma), CUVITRU® (Takeda), Gammagard Liquid (Takeda), Gammaked (Kedrion Biopharma), Gamunex-C (Grifols Therapeutics), Hizentra® (CSL Behring AG), Hyqvia® (Takeda), and Xembify® (Grifols Therapeutics). (5)

At least 1 IVIG product is FDA-approved to treat the following conditions (5):

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

Rationale

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.

IMMUNODEFICIENCY STATES

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. (6) The search identified 3 RCTs, several cohort studies, and numerous case series.

For individuals with immunodeficiencies, both IVIG and SCIG are effective. (7-9) 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. (7) 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 immunoglobulin G (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. (10) 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). Reviewers concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection and therefore routine use of IVIG prophylaxis in patients undergoing HCT was not recommended.

Section Summary: HCT (Prophylaxis)

The evidence for IVIG for routine prophylaxis of infection in HCT consists of a systematic review and meta-analysis. 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.

Acute Antibody-Mediated Rejection (ABMR) After Solid Organ Transplant

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, Bourassa-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. The authors noted that the quality of included studies was variable with a high to very high risk of bias and that additional adequately powered RCTs are needed in order to determine if IVIG is an effective intervention.

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)

Nonrandomized Studies

More recent studies have failed to show a reduction in PRA levels, specifically in patients with a PRA greater than 80%. (14-16) 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. (17-19)

Subsection Summary: Prophylaxis for ABMR After Solid Organ Transplant

The evidence for the use of IVIG for prophylaxis prior to solid organ transplant consists of a systematic review, NIH-sponsored RCT, and nonrandomized observational studies. A systematic review involving variable quality studies with high to very high risk of bias concluded that there is insufficient data to support or advise against the use of IVIG prophylaxis in solid organ transplant. More adequately powered RCTs are needed. Additionally, studies have shown conflicting results that prophylaxis with IVIG in patients with high PRA levels prior to solid organ transplant leads to a significant reduction in PRA levels. Compared with the standard of care, IVIG for prophylaxis of infection in patients with high PRA levels was not associated with a consistent survival benefit or reduction in infection.

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) A RCT by Casadei et al. (2011) demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection (21); however, IVIG was ineligible for

inclusion in the Roberts review because 83% of the patients had Banff 1 (pure cellular) rejection on biopsy. (20) According to Roberts et al. (2012), the evidence to support the use of IVIG to treat ABMR is very low (GRADE criteria).

Subsection Summary: Treatment of Acute Antibody-Mediated Rejection After Solid Organ Transplant

The evidence for the use of IVIG in ABMR consists of retrospective case series and a systematic review. According to a 2012 systematic review, the evidence for IVIG treatment of ABMR is very low (GRADE criteria). Compared with the standard of care, IVIG treatment for ABMR has shown potential benefits in retrospective or small prospective studies; however, larger RCTs with longer follow-up are needed to demonstrate improved health outcomes.

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. (22-27) 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. (22) 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: Chronic Lymphocytic Leukemia

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.

INFECTIONS

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. (28) The median length of follow-up was 17 months. Results were stratified by cluster of differentiation 4 (CD4)-positive counts ($\geq 0.2 \times 10^9/\text{L}$ or $< 0.2 \times 10^9/\text{L}$). After 24 months, for children with CD4-positive counts of $0.2 \times 10^9/\text{L}$ 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 ($\text{RR} = 0.68$; $p < .05$); and reduced the number of hospitalizations for acute care ($\text{RR}, 0.65$; $p < .05$). The effect was less marked in children with CD4-positive counts less than $0.2 \times 10^9/\text{L}$.

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 preterm and low birth weight infants who are 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. (29) 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. (30) 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. (31) 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. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability.

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). (32) 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.

A meta-analysis by Pan et al. (2023) pooled 31 RCTS (N=6,276) of IVIG use in patients (adults and neonates) with sepsis. (33) Evidence from the pooled results found that IVIG was highly effective in lowering mortality in patients (RR, 0.86, 95% CI: 0.77 to 0.95; $p=.02$, $I^2= 37\%$). In subgroup analyses, IVIG was shown to have an effect in reducing adult sepsis mortality specifically (RR, 0.70; 95% CI, 0.57 to 0.86; $p=.15$, $I^2= 27\%$). Authors did note the limitation of inclusion of marginally representative data and potential confounders that may have affected the results of the meta-analysis.

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 and a meta-analysis of 31 RCTs. Compared with placebo, IVIG treatment for adult sepsis showed reductions in mortality in the meta-analyses. 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. (34-36) One larger case series by Crabol et al. (2013) retrospectively reported on 10 patients with documented human parvovirus B19 and pure red cell aplasia. (37) 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 (38) and multiple observational studies. (39-42) The RCT by Darenberg et al. (2003) allocated 21 adults with toxic shock syndrome to IVIG or to placebo. (38) 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. (39) 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. (40, 41) 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. (42)

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.

AUTOIMMUNE AND INFLAMMATORY CONDITIONS

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. (43) 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. (44) The primary outcome, the mean number of days with a platelet count greater than $50 \times 10^9/L$ 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) (45) and 1 randomized (IVIG alone versus oral prednisone alone versus IVIG plus oral prednisone) (46) found no differences in platelet counts greater than $50 \times 10^9/L$ at 48 hours or in response rates between groups, respectively.

Section Summary: Idiopathic Thrombocytopenic Purpura

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. (47) 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 ≥ 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. (48) 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. (49) No RCTs were identified.

Section Summary: Guillain-Barré Syndrome

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. (50) 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. (51) 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. (52)

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 Therapy

Systematic Reviews

Eftimov et al. (2013) published a Cochrane review of RCTs on IVIG for treating CIDP. (53) 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, (54-56) and the other 5 were placebo-controlled (n=235). (57-61) 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.

Bus et al. (2024) published an updated Cochrane review of RCTs on IVIG for treating CIDP. (62) Nine RCTs were included (N=372 patients). Only one new trial was included; however, it did not contribute any data to the meta-analysis. (63)

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. (61) 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 [HR], 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.

Subcutaneous Immunoglobulin Therapy

Systematic Reviews

Ramzi et al. (2024) published a systematic review and meta-analysis of SCIG therapy for CIDP. (64) The systematic review included 50 studies whereas the meta-analysis evaluated 20 studies. The meta-analysis results showed that SCIG had fewer, milder side effects, decreased relapse rates, greatly increased muscle strength, and was highly preferred by patients compared to IVIG therapy.

Randomized Controlled Trials

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. (65) 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 SCIG patients ($p<.001$). The trial was limited by missing patient data and inadequate follow-up of those who withdrew. The PATH open-label extension trial (2019) evaluated the long-term safety and efficacy of SCIG in patients with CIDP. (66) Eighty-two patients were enrolled in the trial and 66 patients completed the 48-week study duration. Patients treated with 0.4 g/kg had an overall relapse rate of 10%, whereas those treated with 0.2 g/kg had a rate of 48%. After dose reduction, 19 of 28 who finished the PATH study without experiencing a relapse continued to be relapse-free on the 0.2 g/kg dose. Adverse events were reported in sixty-two patients (76%), the majority of which were mild or moderate and had no associated significant adverse events.

One crossover RCT comparing IVIG and SCIG for CIDP was identified; this trial by Markvardsen et al. (2017) included 20 patients. (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.

A randomized, placebo-controlled study was evaluated for the FDA approval of HYQVIA to treat CIDP. (68) The study included participants ≥ 18 years of age with definite or probable CIDP (N=122). The analysis of the primary endpoint revealed a statistically significant difference in relapse rates between the HYQVIA group (n=57, 14.0%) and the placebo group (n=65, 32.3%) ($p=.0314$). The treatment difference of -18.3% (-3.1%; two-sided 95% CI: -32.1%) demonstrated that HYQVIA was superior to placebo in preventing relapse of CIDP.

Section Summary: SCIG Therapy for CIDP

For individuals who have CIDP who receive SCIG therapy, the evidence includes 1 systematic review, 3 RCTs, and 1 open-label extension study. A randomized, placebo-controlled study supporting the FDA approval of HYQVIA demonstrated statistical superiority in preventing relapse of CIDP.

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). (69) 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: Multifocal Motor Neuropathy

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. (70)

Observational Studies

A number of noncomparative studies have substantiated clinical benefits. (71-74)

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 Elson 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. (75) 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. (76)

Section Summary: Neuromyelitis Optica

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. (77) 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. (78) 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. (79) The trial did not find a statistically significant difference in the efficacy between treatments. Gadjos et al. (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of myasthenia gravis. (80) Mean improvement in the myasthenic muscular scores did not differ significantly between doses after 2 weeks. Gadjos et al. (1997) compared IVIG with plasma exchange in 87 patients with myasthenia gravis exacerbations. (81) 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 systematic reviews. 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. (82) The AAN suggested that IVIG was no longer considered a drug of choice for RRMS.

Section Summary: Relapsing-Remitting Multiple Sclerosis

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). (83) 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. (84) 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). (85) 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. (86) 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. (87)

Section Summary: Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

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; most trials that have, have been uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality.

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 vs 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 individuals 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 prothrombotic effects and possible IVIG-associated azotemia in SLE. (97)

Section Summary: Systemic Lupus Erythematosus

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 (MRI) 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 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 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. (102-104)

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.

ALLOIMMUNE PROCESSES

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 neonates 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 vs. 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 $81 \times 10^9/L$ in the 0.5-g/kg group and $110 \times 10^9/L$ 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 Ernstsén 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.

MISCELLANEOUS INDICATIONS

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/PANS 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/PANS 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 small RCTs. The trials had mixed findings, and both had small sample sizes and short intervention duration.

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.

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: Complex Regional Pain Syndrome

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: Alzheimer Disease

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 are 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 immunoglobulin M (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 individuals 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

Heidendaal 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.

Summary of Evidence

Immunodeficiency States

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 a systematic reviews and 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. The evidence is insufficient 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 a systematic review, a National Institutes of Health (NIH)-sponsored RCT, and nonrandomized observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. The systematic review involving variable quality studies with high to very high risk of bias concluded that there is insufficient data to support or advise against the use of IVIG prophylaxis in solid organ transplant. More adequately powered RCTs are needed. Additionally, studies have shown conflicting results that prophylaxis with IVIG in patients with high panel reactive antibody (PRA) levels prior to solid organ transplant leads to a significant reduction in PRA levels. Compared with the standard of care, IVIG for prophylaxis of infection in patients with high PRA levels was not consistently associated with a survival benefit or reduction in infection. The evidence is insufficient 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 retrospective or small prospective studies; however, larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine 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.

Infections

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 insufficient to determine that the technology results in an improvement in 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. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with sepsis who receive IVIG therapy, the evidence includes meta-analyses. 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. 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.

Autoimmune and Inflammatory Conditions

For individuals who have immune 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 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 sufficient 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 subcutaneous immunoglobulin therapy (SCIG), the evidence includes 1 systematic review, 3 RCTs, and 1 open-label extension study. Relevant

outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. A randomized, placebo-controlled study supporting the FDA approval of HYQVIA demonstrated statistical superiority in preventing relapse of CIDP. The evidence is sufficient 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. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine 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 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 and a case report. 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.

Alloimmune Processes

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.

Miscellaneous Indications

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 trials had mixed findings and both had small sample sizes and short intervention duration. The evidence is insufficient 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. 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 an 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.

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. (147) Table 1 summarizes the conclusions of the Work Group regarding the potential benefit of immune globulin therapy for various disease states.

The AAAAI offered the following regarding PANDAS, “One case control study showed benefit from plasmapheresis and IVIG therapy (1 dose only) [Perlmutter et al. 1999]. The study showed that IVIG was associated with significantly greater reductions in symptoms compared with those with placebo, and treatment gains were maintained long-term; however, additional studies are needed.” Additionally, “...immune-based therapies should be used only in cases in which it is clear that the neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professionals.”

**Table 1. American Academy of Allergy, Asthma, and Immunology Work Group Report
Immune Globulin Recommendations (147)**

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 • 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 urticities • 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 urticities • 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 (IgG₁, IgG₂, IgG₃) 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) • Pseudomembranous colitis • Campylobacter enteritis • Chronic parvovirus B19 • Relapsing-remitting multiple sclerosis • Intractable childhood epilepsy • Postpolio syndrome
Unlikely to be beneficial	• Isolated IgE deficiency • Isolated IgG₄ 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
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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; Ig: immunoglobulin; 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. (6) 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

In 2015, the AAAAI published practice parameters for the diagnosis and management of primary immunodeficiency. (148) 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. (149) 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. (43) 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 2010, the CBS and NAC developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation. (150) The following conclusions were issued on non-kidney solid organ transplantation:

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

Chronic Lymphocytic Leukemia

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines (v.3.2025) on chronic lymphocytic leukemia (CLL) recommend IVIG as supportive care for patients with CLL for the treatment of autoimmune cytopenias and recurrent sinopulmonary infections requiring hospitalization or intravenous antibiotics (IgG levels <500 mg/dL). (151) The guidelines recommend monitoring IVIG levels and administering monthly SCIG or IVIG (0.3 to 0.5 g/kg) to maintain levels of 500 mg/dL.

Infections

Infections in HIV-Infected Children

In 2024, updated joint guidelines on the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published. (152) 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 (IgG <400 mg/dL)."
- "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. (153) 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). (43) 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-Barré 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. (154) 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) (155) and the American College of Rheumatology (2021) (156) 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). (157) 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. (158) 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 may be an acceptable option for chronic treatment."
- "The task force strongly recommended using SCIG for maintenance treatment in CIDP."
- "The task force recommended no preference for either IVIG or SCIG for maintenance treatment in CIDP."
- "During follow-up, the dose should be tailored according to individual treatment response."
- "The task force weakly recommended against using SCIG for induction treatment in CIDP."

Multifocal Motor Neuropathy

The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (level B). (157) 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). (157) Of note, the AAN website states this is a "retired" guideline.

Neuromyelitis Optica

According to the Neuromyelitis Optica Study Group (2024) updated guidelines, high-dose IVIG is potentially beneficial in the long-term treatment of neuromyelitis optica and may be used as an alternative for patients with a contraindication to other treatments or, particularly, in children; it may also be used as an add-on therapy. (159)

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. (160) 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. (161) 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). (157) 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. (82) 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. (162) 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. (163) These guidelines are accredited by the National Institute for Health and Care Excellence (NICE). 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, anti-tumor necrosis factor (TNF) biologics or ciclosporin." (164)

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). (157) Of note, the AAN website states this is a "retired" guideline.

Immune Optic Neuritis

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

Alloimmune Processes

Antiphospholipid syndrome

In 2020, the Task Force on Catastrophic Antiphospholipid Syndrome (CAPS) recommended that "For first-line treatment of patients with CAPS, the panel suggests combination therapy with glucocorticoid, heparin, and plasmapheresis or IVIG over single agents or other combinations of therapies"; however, this is a conditional recommendation graded with a very low certainty of evidence. (165)

Neonatal Alloimmune Thrombocytopenia

The NAC and CBS (2007) published guidelines on the use of IVIG for hematologic conditions. (43)

- 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. (166) 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. (167) 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. (167)

The American Academy of Child and Adolescent Psychiatry (2014) published practice parameters on the assessment and treatment of autism spectrum disorder. (168) The Academy parameters did not address the use of IVIG for the treatment of autism spectrum disorder.

Chronic Fatigue Syndrome

The NICE (2007; updated 2021) issued guidance on the diagnosis and management of chronic fatigue syndrome. (169) 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. (170) The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2002) published a national coverage determination on IVIG for the treatment of autoimmune mucocutaneous blistering diseases. (171) Intravenous immunoglobulin is covered for patients with biopsy-proven disease who have

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

No national coverage determinations on other uses of IVIG or SCIG were identified.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT03194815 ^a	A Randomised Phase II Double-blinded Placebo-controlled Trial of Intravenous Immunoglobulins and Rituximab in Patients with Antibody-associated Psychosis (SINAPPS2)	70	Mar 2027
NCT05584631 ^a	The Influence of Body Composition on Immunoglobulin Disposition After Intravenous and Subcutaneous Administration	20	Dec 2025
NCT06533098 ^a	Multicenter, Open-Label, Randomized Study of Nipocalimab or Intravenous Immunoglobulin (IVIG) in Pregnancies At Risk of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)	50	Dec 2029
NCT05363358 ^a	Evaluating the Safety of GAMMAGARD LIQUID for the Treatment of Patients with Chronic Inflammatory Demyelinating Polyradiculoneuropathy	6086	Dec 2022
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 (Unknown Status)
NCT05986734 ^a	Evaluation of Subcutaneous Immunoglobulin Product Cutaquig in Terms of Safety and Efficacy in the Treatment of Patients With Primary Immunodeficiencies	100	Dec 2023 (Unknown Status)
NCT05104762	IVIG Versus Plasmapheresis and Guillian Barrie Syndrome	81	Mar 2023

NCT: national clinical trial.

^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	90283, 90284, [Deleted 12/31/2024: 0537T, 0538T, 0539T, 0540T]
HCPCS Codes	C9399, J1459, J1551, J1552, J1553, J1554, J1555, J1556, J1557, J1558, J1559, J1561, J1562, J1566, J1568, J1569, J1572, J1575, J1576, J1577, J1599, J3490, J3590, J9999

*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
01/01/2026	Document updated. The following changes were made to Coverage: 1) Added note about oncologic indications; 2) Revised medically necessary statements for all indications; and 3) Updated experimental, investigational and/or unproven statement. Added references 3, 4, 33, 62-64, 66, 68, 147, and 159; others updated/removed. Title changed from “Immunoglobulin (Ig) Therapy (Including Intravenous [IVIG] and Subcutaneous Ig [SCIG])”.
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 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).
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 <u>OR</u> 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

Appendix

The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

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 may apply.

Preferred Drugs	Non-Preferred Drugs
Gammagard Gammaked/Gamunex-C Octagam Privigen	Gammaplex Panzyga Gammagard S/D Bivigam Asceniv Alyglo Yimmugo Qivigy
Hizentra Cutaquig HyQvia Xembify	Cuvitru