Medical Policy

Title: Intravenous and Subcutaneous Immune Globulin Therapy

PRE-DETERMINATION of services is required.

Predetermination Request Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf
BCBSKS will review all prior authorization requests.
Link to Drug List (Formulary): http://www.bcbsks.com/drugs/

Professional

Original Effective Date: June 1, 1998
Revision Date(s): November 11, 1999; April 20, 2000; August 9, 2001; May 16, 2002; June 19, 2003; June 23, 2003; April 21, 2004; April 21, 2005; August 18, 2005; December 15, 2005; March 1, 2006; January 12, 2007; September 12, 2007; July 1, 2007; September 25, 2007; January 1, 2008; February 28, 2011; July 15, 2011; August 19, 2011; January 1, 2012; April 13, 2012; July 30, 2013; January 21, 2014; September 12, 2014; November 12, 2014; February 5, 2015; July 10, 2015; August 20, 2015; January 1, 2016; January 4, 2017; February 15, 2017; October 1, 2017; November 8, 2017; January 1, 2018; November 7, 2018
Current Effective Date: August 20, 2015

Institutional

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Current Effective Date: August 20, 2015

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

Populations	Interventions	Comparators	Outcomes
Individuals: • With primary humoral immunodeficiency	Interventions of interest are: • Intravenous immunoglobulin therapy • Subcutaneous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Change in disease status • Morbid events • Functional outcomes • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are undergoing hematopoietic cell transplantation	Interventions of interest are: • Intravenous immunoglobulin therapy (prophylaxis)	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are at risk of acute antibody-mediated rejection after solid organ transplant	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • With acute antibody-mediated rejection after solid organ transplant	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who have chronic lymphocytic leukemia with recurrent bacterial infections associated with hypogammaglobulinemia	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are HIV-infected children with recurrent bacterial infections associated with hypogammaglobulinemia	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are preterm and low birth weight infants and at risk for sepsis	Interventions of interest are: • Intravenous immunoglobulin therapy (prophylaxis)	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals:	Interventions of interest are:	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival

Populations	Interventions	Comparators	Outcomes
• Who are preterm and low birth weight infants with sepsis	• Intravenous immunoglobulin therapy (treatment)		• Symptoms • Morbid events • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are adults with sepsis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Hospitalizations • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe anemia associated with human parvovirus B19 virus	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With toxic shock syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Corticosteroids	Relevant outcomes include: • Overall survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With idiopathic thrombocytopenic purpura	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Corticosteroids	Relevant outcomes include: • Disease-specific survival • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Guillain-Barré syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Plasma exchange • Immunoadsorption • Supportive care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Kawasaki disease	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With granulomatosis with polyangiitis (Wegener granulomatosis)	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic inflammatory demyelinating polyneuropathy	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Plasma exchange • Corticosteroids • Supportive care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic inflammatory demyelinating polyneuropathy	Interventions of interest are:	Comparators of interest are: • Plasma exchange • Corticosteroids • Supportive care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events

Populations	Interventions	Comparators	Outcomes
	• Subcutaneous immunoglobulin therapy		• Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With multifocal motor neuropathy	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Eaton-Lambert myasthenic syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With neuromyelitis optica	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe refractory myasthenia gravis or myasthenic exacerbation	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Plasma exchange	Relevant outcomes include: • Overall survival • Symptoms • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With relapsing-remitting multiple sclerosis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With autoimmune mucocutaneous blistering diseases	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With toxic epidermal necrosis or Stevens-Johnson syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals:	Interventions of interest are:	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status

Populations	Interventions	Comparators	Outcomes
• With dermatomyositis or polymyositis	• Intravenous immunoglobulin therapy		• Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With inclusion body myositis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With systemic lupus erythematosus	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With immune optic neuritis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Crohn's disease	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With hemophagocytic lymphohistiocytosis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Supportive care alone • Chemotherapy • Allogeneic cell transplantation	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With autoimmune hemolytic anemia, refractory to prednisone and splenectomy	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Prednisone • Splenectomy • Cytotoxic medications	Relevant outcomes include: • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With antiphospholipid syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Anticoagulant therapy • Antiplatelet therapy	Relevant outcomes include • Overall survival • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With neonatal alloimmune thrombocytopenia	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Platelet transfusion and supportive care alone	Relevant outcomes include: • Disease-specific survival • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With recurrent spontaneous abortion	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Supportive care	Relevant outcomes include: • Disease-specific survival • Treatment-related mortality • Treatment-related morbidity
Individuals: • With pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Antibiotic therapy alone	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related mortality • Treatment-related morbidity
Individuals: • With autism spectrum disorder	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With complex regional pain syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Alzheimer disease	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Disease-specific survival • Symptoms • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With paraproteinemic neuropathy	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic fatigue syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With acute myocarditis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Heart failure therapy alone	Relevant outcomes include: • Overall survival • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With refractory recurrent pericarditis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Heart failure therapy alone	Relevant outcomes include: • Overall survival • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With stiff person syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Benzodiazepines • Baclofen	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With noninfectious uveitis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Topical glucocorticoids • Difluprednate • Intraocular glucocorticoids • Systemic glucocorticoids • Systemic immunomodulating agents	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With postpolio syndrome	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Supportive care alone	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With necrotizing fasciitis	Interventions of interest are: • Intravenous immunoglobulin therapy	Comparators of interest are: • Antibiotics • Surgical removal of tissue	Relevant outcomes include: • Overall survival • Symptoms • Functional outcomes • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

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

OBJECTIVE

The objective of this policy is to determine whether intravenous and subcutaneous immunoglobulin therapies are an effective treatment for various autoimmune and nonautoimmune conditions.

BACKGROUND

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

a wide variety of bacterial and viral antigens. Two formulations of human IgG are available: intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin. Intramuscular immunoglobulin depot injections have been largely abandoned.

IVIG is an antibody-containing solution obtained from the pooled plasma of healthy blood donors that contains antibodies to greater than 10 million antigens. IVIG has been used to correct immune deficiencies in patients with either inherited or acquired immunodeficiencies and has also been investigated as an immunomodulator in diseases thought to have an autoimmune basis. Several IVIG products are available for clinical use in the United States. A variety of off-label indications have been investigated; some of the most common are inflammatory myopathies, neuropathies (eg, Guillain-Barré syndrome), myasthenia gravis, multiple sclerosis, and solid organ transplantation.

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

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

REGULATORY STATUS

Several intravenous immunoglobulin (IVIG) products have been approved by the U.S. Food and Drug Administration (FDA). They include Bivigam® (Biotest) Carimune® (CSL Behring AG), Flebogamma DIF® (Instituto Grifols), GammaSTAN S/D® (Grifols Therapeutics), Gammagard Liquid® (Baxter), Gammagard S/D® (Baxter), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), and Privigen® (CSL Behring).[1]

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

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

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

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

POLICY

A. Intramuscular immune globulin is **not medically necessary** for the indications listed in this policy.

B. Immune Globulin therapy may be **medically necessary** in the following conditions when the associated criteria are met:

1. **Acute Disseminated Encephalomyelitis** when response to intravenous corticosteroid treatment is insufficient.

2. **Antibody-Mediated Rejection**, following solid organ transplant.

3. **Antiphospholipid Syndrome**

4. **Autoimmune Hemolytic Anemia,** refractory to corticosteroids or splenectomy.

5. **Autoimmune Mucocutaneous Blistering Diseases** (includes pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [a.k.a. cicatricial pemphigoid], and epidermolysis bullosa acquisita) when corticosteroids and immuno-suppressive agents have failed.

6. **B Cell Chronic Lymphocytic Leukemia (CLL)** in patients with:
   a. Hypogammaglobulinemia (total IgG <400 mg/dL), **AND**
   b. Recurrent or persistent bacterial infections.

7. **Birdshot (vitiliginous) Retinochoroidopathy** not responsive to immunosuppressives (eg, corticosteroids, cyclosporine).

8. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

9. **Dermatomyositis, Polymyositis (includes Juvenile)** intolerant or refractory to:
   a. Corticosteroids; **AND/OR**
   b. Immuno-suppressants (eg, methotrexate, azathioprine, cyclophosphamide, and cyclosporine).

10. **Enteroviral Meningoencephalitis**

11. **Erythrovirus (formerly Parvovirus) B19 Infection, chronic, with severe anemia**

12. **Fetal Alloimmune Thrombocytopenia (FAIT) or previous pregnancy affected by FAIT**

13. **Guillain-Barré Syndrome (GBS)** (includes GBS variants: Miller Fisher syndrome [MFS], panautonomic polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy [AMAN], and acute motor and sensory axonal neuropathy [AMSAN]). IVIG should usually be initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms.

14. **Hematopoietic Stem Cell Transplant (HSCT) or Bone Marrow Transplant (BMT)**
    a. For prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for treatment of recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL) or who have CMV or RSV infection; **OR**
    b. IVIG is considered medically necessary for steroid-resistant graft-versus-host disease in BMT recipients 20 years of age or older, in the first 100 days post transplant, and who are hypogammaglobinemic (IgG level less than 400 mg/dL).

15. **Hemolytic Disease of the Newborn**

16. **HIV Associated Polyneuropathy**

17. **HIV Associated Thrombocytopenia**

18. **HIV Infected Children**- who meet the following criteria:
    a. Serum IgG concentration less than 250 mg/dL; **AND**
    b. Recurrent serious bacterial infections; **AND**
    c. Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine; **OR**
    d. Single dose for HIV-infected children who are exposed to measles; **OR**
    e. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.

19. **Hyperimmunoglobulin E Syndrome** with recurrent staphylococcal abscesses.

20. **Immune Thrombocytopenia (idiopathic thrombocytopenic purpura [ITP])**
    a. Unresponsive to corticosteroid therapy; **OR**
    b. To defer or avoid splenectomy; **OR**
    c. Platelet counts less than 20,000 u/l (risk of intracerebral hemorrhage); **OR**
    d. Management of acute bleeding with platelet counts less than 30,000 u/l; **OR**

e. To increase platelet counts, prior to major surgical procedures.

21. **Immunosuppressed Patients** associated immunosuppression (IgG < 400 mg/dL) with one of the following:
    a. Solid organ transplants or extensive surgery with immunosuppression; **OR**
    b. Hematological malignancy; **OR**
    c. Extensive burns; **OR**
    d. Collagen-vascular disease.

22. **Kawasaki disease**

23. **Lambert-Eaton Myasthenic Syndrome (LEMS)** and inadequate response to anticholinesterases and diaminopyridine).

24. **Moersch-Woltmann (Stiff-man) Syndrome** (positive anti-GAD antibody) when benzodiazepines (eg, Valium) and/or baclofen, phenytoin, clonidine, tizanidine have failed.

25. **Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) Variant**

26. **Multifocal Motor Neuropathy with Conduction Block**-diagnosed on the basis of electrophysiologic findings.

27. **Multiple Myeloma (MM)**
    a. IgG level < 600 mg/dL; **AND**
    b. Recurrent or persistent bacterial infections.

28. **Myasthenia gravis** when other treatments have been unsuccessful or are contraindicated (eg, azathioprine, cyclosporine, cyclophosphamide, and myasthenic crisis).

29. **Neonatal Hemochromatosis**

30. **Neuroblastoma Associated Paraneoplastic Opsoclonus-Myoclonus-Ataxia Syndrome**

31. **Post-Transfusion Purpura (PTP)**

32. **Primary Humoral Immunodeficiencies** (to include X-linked agammaglobulinemia [Bruton] X-linked hyper-IgM syndrome, severe combined immunodeficiency [SCID], common variable immunodeficiency [CVID], Wiskott-Aldrich syndrome, and ataxia telangiectasia) with a history of significant recurrent infections and one of the following:

a. A very low level of IgG (eg, 200 mg/dL or less). Assessing vaccine response is not necessary; **OR**
b. Nonprotective levels of antibodies to pneumococcal vaccine serotypes documented with a 14-serotype panel. If antibodies are at nonprotective levels, a pneumococcal vaccine challenge is required.

For a pneumococcal vaccine challenge, a 14-serotype panel should be done prior to the vaccine and repeated no earlier than one month after vaccination.

The interpretation of response to polyvalent pneumococcal polysaccharide vaccine is as follows:
- In children 2 to 5 years of age, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 50% of the serotypes tested.
- In children > 5 years of age and in adults, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 70% of the serotypes tested.

Immunoglobulin replacement should be reserved for patients who have failed the following treatments:
- Immunization with conjugate vaccines.
- Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (eg, asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures).
- Prophylactic antibiotics such as amoxicillin-clavulanate or cefdinir.
- Increased vigilance and appropriate antibiotic therapy for infections.

Note: SCIg, instead of IVIG may be considered **medically necessary** for the treatment of primary immunodeficiencies when policy requirements are met.

33. **Prior to solid organ transplant,** treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ.

34. **Rasmussen Encephalitis** refractory to antiepileptic drugs and corticosteroids.

35. **Refractory Opsoclonus-Myoclonus**

36. **Staphylococcal Toxic Shock Syndrome**

37. **Systemic Lupus Erythematosus such as** severe active SLE for whom first- and second-line therapies have been unsuccessful (non-steroidal anti-inflammatory drugs, corticosteroids, antimalarial compounds, methotrexate, azathioprine, or cyclophosphamide).

38. **Toxic Epidermal Necrolysis (Lyell's syndrome) or Stevens-Johnson Syndrome**

39. **Toxic Shock Syndrome or Toxic Necrotizing Fasciitis due to Group A Streptococcus**

C. IVIG is considered **not medically necessary** as a treatment of relapsing / remitting multiple sclerosis.

D. Other application of IVIG therapy are considered **experimental / investigational**, including, but not limited to, the following conditions:

1. acquired factor VIII inhibitors
2. acute lymphoblastic leukemia
3. adrenoleukodystrophy
4. Alzheimer's disease
5. aplastic anemia
6. asthma
7. autism
8. Behcet's syndrome
9. chronic fatigue syndrome
10. chronic progressive multiple sclerosis
11. chronic sinusitis
12. complex regional pain syndrome
13. Crohn's disease
14. cystic fibrosis
15. demyelinating optic neuritis
16. demyelinating polyneuropathy associated with IgM paraproteinemia
17. diabetes mellitus
18. Diamond-Blackfan anemia
19. epilepsy
20. hemolytic uremic syndrome
21. hemophagocytic syndrome
22. IgG sub-class deficiency
23. immune-mediated neutropenia
24. inclusion-body myositis
25. myasthenia gravis in patients responsive to immunosuppressive treatment
26. nonimmune thrombocytopenia
27. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; eg, Wegener's granulomatosis, polyarteritis nodosa), Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases
28. paraneoplastic syndromes, other than Lambert-Eaton myasthenic syndrome
29. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

30. recent-onset dilated cardiomyopathy
31. recurrent otitis media
32. recurrent spontaneous abortion (see below for related laboratory tests)
33. red cell aplasia
34. refractory rheumatoid arthritis and other connective tissue diseases
35. sepsis, including neonatal sepsis
36. thrombotic thrombocytopenic purpura
37. uveitis

Policy Guidelines

Black Box Warnings and Precautions

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

Additional warnings and precautions include:

- 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 development of fever, chills, nausea, and vomiting.
- IVIG is made from human plasma and may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent).

- Passive transfer of antibodies may confound serologic testing.

The subcutaneous immunoglobulin product information labels note reactions similar to other immunoglobulin products may occur. The most common adverse reactions with subcutaneous injections include local reactions (ie, 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 patient and may vary depending on the type of vaccine given and the prior immunization history of the patient. The following parameters are examples of criteria for diagnosis of the primary immunodeficiency syndromes.

- Laboratory evidence of immunoglobulin deficiency may include the following definitions:
  - Agammaglobulinemia (total 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

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

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

RATIONALE

Updated literature reviews were conducted most recently through September 6, 2018. The key published literature is summarized below.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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 immunodeficiency deficiencies refer to diseases resulting from impaired antibody production because of a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Antibody deficiency characteristically leads to recurrent, often severe upper and lower respiratory tract infections. Findings associated with severe primary humoral immunodeficiencies include failure to thrive, chronic diarrhea, recurrent fever, nodular lymphoid hyperplasia in the gut, and hepatosplenomegaly.

➢Primary Humoral Immune Deficiencies

Clinical Context and Test 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 patients with primary humoral immunodeficiency.

The question addressed in this evidence review is: Are IVIG and SCIG therapies effective treatments for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients

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

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, symptoms, change in disease status, morbid events, functional outcomes, hospitalizations, and treatment-related mortality and morbidity.

Timing

Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with primary humoral immunodeficiency are actively managed by a primary care providers and immunologists in an outpatient setting.

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 longer 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.[2] The search identified 3 RCTs, several cohort studies, and numerous case series.

Clinical immunologists have questioned whether having a low serum immunoglobulin G (IgG) subclass is a true immunodeficiency disease. The rationale is that low serum IgG subclass levels may be found with more sensitive assays available today, and these individuals may be otherwise healthy.

For individuals with immunodeficiencies, both IVIG and SCIG are effective.[3-5] Use of SCIG for the treatment of primary immunodeficiencies was approved by the Food and Drug Administration (FDA) based on an open-label, nonrandomized, prospective, multicenter study.[3] Generally, many 10% IVIG solutions can be administered subcutaneously or intravenously, but more concentrated products (eg, 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse events and provides more stable serum IgG levels. In contrast, SCIG has not been studied as extensively in autoimmune and inflammatory disorders.

Section Summary: Primary Humoral Immune Deficiencies
The evidence for the use of IVIG and SCIG therapy in primary humoral immune deficiencies consists of multiple RCTs and noncomparative studies. The literature was summarized in a series of evidence-based guidelines (102 studies) initiated by the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products.

➢Hematopoietic Cell Transplantation (Prophylaxis)
Hematopoietic cell transplantation (HCT) is the intravenous infusion of hematopoietic stem and progenitor cells designed to establish marrow and immune function in patients with various acquired and inherited malignant and nonmalignant disorders.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are undergoing HCT.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals who are undergoing HCT.

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, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients who are undergoing HCT are actively managed by stem cell transplant specialists in an inpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
A systematic review and meta-analysis by Raanani et al (2009) included 30 trials with 4223 patients undergoing HCT.[6] 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.

Randomized Controlled Trials
The initial use of immunoglobulin for prophylaxis in HCT was based on the RCT by Sullivan et al (1990) in 369 patients undergoing HCT.[7] The trial showed that neither survival nor risk of relapse was altered by IVIG. However, IVIG treatment was associated with a reduction in the incidence of acute graft-versus-host disease compared with controls (51% vs 34%) and deaths due to transplant-related causes after transplantation of human leukocyte antigen (HLA)–identical marrow (46% vs 30%). There were many methodologic flaws in the trial, including lack of control for type I error for multiple comparisons, the inclusion of a heterogeneous group of patients, and a lack of a placebo control. Subsequent to this pivotal trial, multiple trials have been conducted and

systematic reviews have assessed the efficacy of immunoglobulin prophylaxis in HCT to prevent infection and prolong survival.

Section Summary: Hematopoietic Cell Transplantation (Prophylaxis)
The evidence for IVIG for routine prophylaxis of infection in HCT consists of multiple RCTs. The most recent systematic review and meta-analysis published in 2009 included 30 trials and concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection.

➢Acute Antibody-Mediated Rejection After Solid Organ Transplant
Acute rejection after transplant can be broadly divided into 2 categories: the more common acute cellular rejection related to activation of T cells, and the less common acute antibody-mediated rejection (ABMR) related to the presence of antidonor 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.

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals who are at risk of acute ABMR after solid organ transplant or who have acute ABMR after solid organ transplant.

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, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity.

Timing
Follow-up at 2 years is of interest to monitor outcomes.

Setting
Patients who are at risk of acute ABMR after solid organ transplant or who acute ABMR after solid organ transplant are actively managed by organ transplant surgeons and specialists in an inpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.

Randomized Controlled Trials
In the National Institutes of Health–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.[8] If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reductions in PRA levels compared with placebo (35% vs 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80% IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than placebo in reducing anti-HLA 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.[9]

Nonrandomized Studies
More recent studies have failed to show reduction in PRA levels, specifically in patients with PRA greater than 80%.[10-12] Nonrandomized clinical observations have suggested that a combination of plasmapheresis plus low-dose IVIG and interleukin-2 blockade or rATG for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients.[13-15]

Subsection Summary: Prophylaxis for Acute Antibody-Mediated Rejection After Solid Organ Transplant: The evidence for the use of IVIG for prophylaxis in patients with high PRA levels prior to solid organ transplant consists of multiple RCTs and noncomparative observational studies. RCTs have shown conflicting results that prophylaxis with IVIG in patients with high PRA levels prior to solid organ transplant leads to significant reduction in PRA levels.

Treatment
Systematic Reviews
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 use of IVIG in the treatment of ABMR.[16] The RCT by Casadei et al (2011) demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection[17]; however, it should be noted that IVIG was ineligible for inclusion in the Roberts review because 83% of the patients had Banff 1 (pure cellular) rejection on biopsy.[16] According to Roberts, the evidence to support the use of IVIG to treat ABMR is very low (GRADE criteria).

Section 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. According to a 2012 systematic review, the evidence for IVIG treatment of ABMR is very low (GRADE criteria).

➢Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes and most patients develop hypogammaglobulinemia at some point in the course of their disease. Patients experiencing recurrent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of IVIG.

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia.

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 overall survival, symptoms, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity.

Timing

Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting

Patients who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia are actively managed by oncologists in an inpatient setting.

Study Selection Criteria

Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials

Multiple trials and a meta-analysis comparing IVIG with placebo have shown decreased bacterial infections but not decreased mortality.[18-23] 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 quality of life or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both.[18] 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 that have generally shown reductions in rates of minor and moderate, but not major, bacterial infections. No benefit in quality of life and mortality has been shown.

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

Clinical Context and Test 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 question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is children with HIV infection and recurrent bacterial infections associated with hypogammaglobulinemia.

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 overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity.

Timing
Follow-up at 18 months is of interest to monitor outcomes.

Setting
HIV-infected children with recurrent bacterial infections associated with hypogammaglobulinemia are actively managed by infectious disease specialist and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
A 1991 double-blind RCT allocated 372 HIV-infected children to IVIG or placebo every 28 days.[24] The median length of follow-up was 17 months. Results were stratified by CD4-positive counts ($\geq 0.2\times10^9$/L or $<0.2\times10^9$/L). After 24 months, for children with CD4-positive counts of 0.2×10^9/L or greater, IVIG treatment compared with placebo significantly increased infection-free rates (67% vs 48% respectively; $p<0.05$); reduced overall the number of serious and minor bacterial infections (RR=0.68; $p<0.05$); and reduced the number of hospitalizations for acute care (RR=0.65; $p<0.05$). The effect was less marked in children with CD4-positive counts less than 0.2×10^9/L.

Guidelines
Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children have recommended IVIG to prevent serious bacterial infections in HIV-infected children who have IgG levels less than 400 mg/dL.[25] The guidelines for the prevention and treatment of serious opportunistic infections in HIV-infected adults and adolescents do not give such recommendations.[26]

Subsection Summary: HIV-Infected Children
The evidence for the use of IVIG for prophylaxis of opportunistic infections in children with HIV consists of an RCT that showed a reduction in serious and minor bacterial infections and hospitalization. A reduction in mortality has not yet been demonstrated.

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

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

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

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 overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Infants who are preterm, low birth weight, and at risk for or who have sepsis are actively managed by pediatricians in an inpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Prophylaxis of Neonatal Sepsis
A Cochrane review by Ohlsson and Lacy(2013) assessed IVIG for the prevention of infection in preterm and/or low birth weight infants.[27] 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 (eg, 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. Meta-analysis of 15 studies that reported all-cause mortality found a RR of 0.89 (95% CI, 0.75 to 1.05), and 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 multiple RCTs that have generally shown reductions in the rates of sepsis but no benefit in mortality. A meta-analysis of 10 studies assessing the use of IVIG for prophylaxis of infection in preterm and/or low birth weight infants concluded that a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without reduction in other clinically important outcomes, including mortality, was of marginal clinical importance.

Treatment of Neonatal Sepsis
Systematic Reviews
A Cochrane review by Ohlsson and Lacy (2015) identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or confirmed infection.[28] Studies included a total of 3973 infants; the largest trial had a sample size of 3493 and contributed 90% of the data. Meta-analysis of all 9 trials found no statistically significant difference in mortality rates with IVIG vs 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.[29] 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, 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 (eg, birthweight, gestational age at birth, sex) were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIG group (including 2 deaths) vs 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 multiple RCTs. The largest RCTs in 3493 neonates showed that there was no difference in the rates of death or major disability between IVIG-treated neonates and placebo-treated neonates. A meta-analysis (9 studies) also did not find a significant difference in mortality rates or major disability with IVIG vs control.

➢Sepsis in Adults
Clinical Context and Test 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 question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
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 overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Adults with sepsis are actively managed by primary and emergency care providers in an inpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
A meta-analysis by Busani et al (2016), which pooled 18 RCTs, showed that use of IVIG reduced the mortality risk of septic patients by half (OR=0.50; 95% CI, 0.34 to 0.71).[30] However, there was a preponderance of small low quality studies in the evidence base, which was further complicated by heterogeneous dosing regimens and types of IVIG preparations used across studies that were conducted over a long time horizon. Reviewers concluded that the evidence did not support widespread use of IVIG as adjunctive therapy for sepsis in adults.

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. Though the meta-analysis demonstrated reductions in mortality risk, most studies included were small, of low quality, and employed heterogeneous dosing regimens and types of IVIG preparations.

➢Severe Anemia Associated with Human Parvovirus B19
Human parvovirus B19 is a common single-stranded DNA virus. Infections are usually mild or asymptomatic and do not require treatment. In some cases, the infection can lead to sufficiently severe complications such as transient aplastic crisis, in which case treatment is indicated and may be lifesaving.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with severe anemia associated with human parvovirus B19.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for human parvovirus infection?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with severe anemia associated with human parvovirus B19.

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 change in disease status, treatment-related mortality, and treatment-related morbidity.

Timing
Follow-up at 12 months is of interest to monitor outcomes.

Setting
Patients with severe anemia associated with human parvovirus B19 are actively managed by primary care providers and infectious disease specialists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Case Series
No controlled trials have evaluated IVIG for severe anemia associated with parvovirus B19. Only small case series and case reports are available.[31-33] One larger case series, by Crabol et al (2013), retrospectively reported on 10 patients with documented human parvovirus B19 and pure red cell aplasia.[34] 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 and case reports. The largest case series (10 patients) showed that IVIG treatment was associated with correction of anemia in most patients. Controlled trials are lacking.

➢Toxic Shock Syndrome
Toxic shock syndrome is also called as Streptococcal toxic shock syndrome. Streptococcal toxins induce the release of inflammatory cytokines, which cause capillary leakage and tissue damage resulting in shock, multiorgan failure, and death.

Clinical Context and Test 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 toxic shock syndrome.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for toxic shock syndrome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is women with toxic shock syndrome.

Interventions
The therapy being considered is IVIG therapy. IVIG is used for the treatment of septic 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 overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Women with toxic shock syndrome are actively managed by primary care providers in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
The evidence for the use of IVIG treatment for toxic shock syndrome is limited and includes a small RCT[35] and multiple observational studies.[36-39] The RCT by Darenberg et al (2003) allocated 21 adults with toxic shock syndrome to IVIG or to placebo.[35] 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 placebo.[36] The odds for survival was 5.6 for IVIG vs placebo (p=0.03). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls.[37,38] While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups pose difficulties when interpreting the results. A retrospective study by Shah et al (2009), which included 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG.[39]

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. Most studies demonstrated a beneficial effect of treatment on mortality.

Autoimmune and Inflammatory Conditions

➢ Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenia, is an acquired thrombocytopenia caused by autoantibodies against platelet antigens. It is a more common cause of thrombocytopenia in otherwise asymptomatic adults.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with ITP.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with ITP.

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 disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with ITP are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[40] 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.[41] The primary outcome, mean number of days with a platelet count greater than 50×10^9/L at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG vs corticosteroids)[42] and 1 randomized (IVIG alone vs oral prednisone alone vs IVIG plus oral prednisone)[43] found no differences in platelet counts greater than 50×10^9/L at 48 hours or in response rates between groups, respectively.

Section Summary: Idiopathic Thrombocytopenic Purpura
The evidence for the use of IVIG treatment for ITP consists of multiple RCTs and noncomparative studies. The largest RCT (122 patients) showed IVIG treatment increased platelet levels to a greater extent than corticosteroids. However, 1 RCT trial found no difference in platelet counts compared with corticosteroids.

➢Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a heterogeneous condition with several variant forms and encapsulates many acute immune-mediated polyneuropathies. It is characterized by a rapid-onset of muscle weakness caused by the immune system damaging the peripheral nervous system.

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with GBS.

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity.

Timing

Follow-up at 4 weeks is of interest to monitor outcomes.

Setting

Patients with GBS are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews

An updated Cochrane review by Hughes et al (2014) evaluated results from randomized trials of immunotherapy for GBS.[44] Reviewers identified 12 randomized trials; none was 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 (one compared IVIG plus immunoabsorption with immunoabsorption only). Four trials included adults only, five included children only, one included both, and two included adults and possibly children. The primary outcome of the review was change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIG with plasma exchange did not find significant differences between groups in change in the number of disability grades at 4 weeks (MD = -0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIG vs plasma exchange (eg, number of patients who

improved by ≥1 grades). There were insufficient data to pool results for comparisons of IVIG with other interventions or for a subgroup analysis by age. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR=0.14; 95% CI, 0.05 to 0.36).

Most trials 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.[45] 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 group and plasma exchange group was 0.09 grade (95% CI, -0.23 to 0.42); this met the predefined criterion for equivalence of these treatments. Differences were 0.29 grade (95% CI, -0.04 to 0.63) between the IVIG plus plasma exchange group and the IVIG only group, and 0.20 grade (95% CI, -0.14 to 0.54) between the IVIG plus plasma exchange group and the plasma exchange only group. Thus, neither combined treatment 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.[46] No RCTs were identified.

Section Summary: Guillain-Barré Syndrome
The evidence for IVIG treatment for GBS patients consists of multiple RCTs that compared IVIG therapy with other modalities such as plasma exchange and immunoabsorption but not placebo. A Cochrane meta-analysis of 7 trials comparing IVIG therapy with plasma exchange did not find a significant difference in disability scores. The largest RCT (383 GBS patients) showed noninferiority between IVIG and plasma exchange.

➢Kawasaki Disease
Kawasaki disease is among the most common vasculitides of childhood; it is characterized by fever and manifestations of acute inflammation lasting for an average of 12 days without therapy. It is typically self-limiting but may cause cardiovascular complications, particularly coronary artery aneurysms, which can lead to coronary occlusion and cardiac ischemia ultimately leading to significant morbidity and even death. Therefore, early treatment is essential. Although the mechanism of action of IVIG is not understood, its use early in the course of disease has reduced the prevalence of coronary artery abnormalities.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Kawasaki disease.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with Kawasaki disease.

Interventions
The therapy being considered is IVIG therapy.

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

Outcomes
The general outcomes of interest are disease-specific survival, change in disease status, and treatment-related mortality and morbidity.

Timing
Follow-up at 30 days is of interest to monitor outcomes.

Setting
Patients with Kawasaki disease are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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 Oates-Whitehead et al (2003) identified 59 trials in the initial search and selected 16 trials for meta-analysis using RR for dichotomous data or weighted mean difference for continuous data.[47] Results showed a significant decrease in new coronary artery abnormalities in favor of IVIG compared with placebo at 30 days (RR=0.74; 95% CI, 0.61 to 0.90). Reviewers concluded that children fulfilling the diagnostic criteria for Kawasaki disease should be treated with IVIG (2 g/kg single dose) within 10 days of onset of symptoms

Section Summary: Kawasaki Disease
The evidence for the use of IVIG treatment for Kawasaki disease consists of multiple RCTs and noncomparative studies. A Cochrane meta-analysis of 16 trials comparing IVIG with placebo in children with Kawasaki disease showed that treatment with IVIG decreased the incidence of new coronary artery abnormalities.

Granulomatosis with Polyangiitis (Wegener Granulomatosis)
Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with granulomatosis with polyangiitis (Wegener granulomatosis).

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG therapy.

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

Outcomes
The general outcomes of interest are disease-specific survival, change in disease status, and treatment-related mortality and morbidity.

Timing
Follow-up at 3 months is of interest to monitor outcomes.

Setting
Patients with granulomatosis with polyangiitis (Wegener granulomatosis) are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
The success of IVIG therapy for Kawasaki disease led to 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.[48] 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.[49]

Section Summary: Granulomatosis with Polyangiitis (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.

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

Clinical Context and Test 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 patients with CIDP.

The question addressed in this evidence review is: Are IVIG and SCIG therapies effective treatments for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with CIDP.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 48 weeks is of interest to monitor outcomes.

Setting
Patients with CIDP are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

IVIG Therapy
Systematic Reviews
Eftimov et al (2013) published a Cochrane review of RCTs on IVIG for treating CIDP.[50] Reviewers identified 8 RCTs that enrolled 332 patients with definite or probable CIDP and that compared IVIG with placebo, corticosteroid, or plasma exchange. Three trials compared IVIG with another active treatment,[51-53] and the other 5 were placebo-controlled (n=235).[54-58] 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<0.001). When data were pooled from 3 studies on IVIG vs 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=0.054). Pooled analyses of data from these 3 placebo-controlled trials found a statistically higher rate of any adverse event with IVIG, but not serious adverse events. Data from studies comparing IVIG with an active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

An evidence-based guideline on IVIG for treating neuromuscular disorders, prepared by Patwa et al (2012) for the American Academy of Neurology (AAN), stated that IVIG should be offered for the long-term treatment of CIDP.[59]

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.[58] The primary outcome measure was proportion of patients showing clinically meaningful reductions in disability at week 24. Results showed that the proportion of patients meeting the primary end point was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase were rerandomized to IVIG or placebo. Relapse rates were significantly lower for patients treated with IVIG (13% vs 45%; hazard ratio [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
The evidence for the use of IVIG treatment for CIDP consists of multiple RCTs. The largest trial (117 patients) found that IVIG treatment led to clinically meaningful reductions in disability compared with placebo. A Cochrane meta-analysis of 5 RCTs comparing IVIG with placebo found that IVIG reduced disability.

SCIG Therapy
In the randomized, double-blind, placebo-controlled, phase 3 PATH trial, van Schaik et al (2018) studied the relapse rates in 172 patients with CIDP given SCIG and placebo.[60] 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 can be used as maintenance treatment for CIDP. Seventy-seven patients withdrew from the trial due to relapse- or other reasons: 36 (63%; 95% CI, 50% to 74%) placebo patients, 22 (39%; 95% CI, 27% to 52) low-dose SCIG patients, and 19 (33%; 95% CI, [22% to 46) high-dose patients ($p<0.001$). The trial was limited by missing patient data and inadequate follow-up of those who withdrew.

One crossover RCT comparing IVIG and SCIG for CIDP was identified; this trial by Markvardsen et al (2017) included 20 patients.[61] Patients underwent 10 weeks of treatment with SCIG and IVIG, in random order, for a total intervention duration of 20 weeks. The primary efficacy outcome was change in isokinetic muscle strength. Fourteen (20%) of 20 patients completed the trial. Isokinetic muscle strength increased by 7.4% with SCIG and 14% with IVIG; the difference between groups was not statistically significant. Conclusions about the relative efficacy of SCIG and IVIG cannot be drawn from this trial due to the small sample size, high dropout rate, short-term follow-up, and the crossover design without a washout period.

Section Summary: SCIG Therapy for CIDP
Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (eg, 45% of patients withdrew from the trial). Another RCT demonstrated that the use of SCIG for the maintenance of CIPD might be effective, with relatively low adverse events, but this trial also had a number of limitations (eg, small sample, 30% dropout rate). Additional direct comparisons, particularly in parallel-group RCTs, are needed.

➢Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities, a presentation similar to that of motor neuron disease.

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with MMN.

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, quality of life, and treatment-related mortality and morbidity.

Timing

Follow-up at 4 months is of interest to monitor outcomes.

Setting

Patients with MMN are actively managed by neurologists and primary care providers in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews

Van Schaik et al (2005) included 4 RCTs (total N=34 patients) in a meta-analysis to assess the efficacy and safety of IVIG in MMN.[62] Strength improved in 78% of patients treated with IVIG vs 4% in placebo-treated patients. Disability was reduced in 39% and 11%, respectively (p=*NS*). Mild, transient side effects were reported in 71% of IVIG-treated patients. Serious side effects were not encountered.

Randomized Controlled Trials

The benefit of IVIG for MMN has been evaluated in 4 RCTs (total N=53 patients).[63-66] The largest of the 4 RCTs randomized 19 patients with MMN with persistent conduction block to IVIG or placebo. Response to treatment was assessed using the Medical Research Council (MRC) score in 28 muscles; a responder was defined as at least 1 more MRC point in 2 affected muscles plus 1

point less in 2 activities of daily life compared with baseline. At 4 months, 7 of 9 patients who received IVIG responded compared with 2 of 9 patients treated with placebo.

Section Summary: Multifocal Motor Neuropathy
The evidence for use IVIG therapy for MMN consists of multiple RCTs. A Cochrane meta-analysis of 4 RCTs comparing IVIG with placebo found that IVIG treatment led to significant improvements in muscle strength but not reductions in disability levels. The largest trial of 19 patients found that IVIG treatment with IVIG improved muscle strength compared with placebo.

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

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with Eaton-Lambert myasthenic syndrome.

Interventions
The therapy being considered is IVIG therapy.

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

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

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with Eaton-Lambert myasthenic syndrome are actively managed by neurologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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 IVIG treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude.[67]
A number of noncomparative studies have substantiated clinical benefits.[68-71]

Section Summary: Eaton-Lambert Myasthenic Syndrome
The evidence for IVIG therapy for Eaton-Lambert myasthenic syndrome consists of a single RCT and multiple noncomparative studies. In the RCT (9 patients), IVIG treatment demonstrated significant improvement in muscle strength compared with placebo.

➢Neuromyelitis Optica
Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Previously considered a variant of multiple sclerosis, it is now recognized as a distinct clinical entity.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with NMO.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with NMO.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 2 years is of interest to monitor outcomes.

Setting
Patients with NMO are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Retrospective Studies
A retrospective review by Elsone et al (2014) of 10 patients treated with IVIG for acute relapses after lack of response to steroids with or without plasma exchange showed improvement in about 50% of patients.[72] 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.[73]

Section Summary: Neuromyelitis Optica
The evidence for IVIG therapy for NMO consists of multiple noncomparative studies. Results of these studies have shown that IVIG treatment may benefit patients who are refractory to first-line treatment.

➢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.

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

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

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 overall survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Treatment of 2 weeks is of interest to monitor outcomes.

Setting
Patients with severe refractory myasthenia gravis or myasthenic exacerbation are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
A Cochrane review by Gadjos et al (2012) assessed IVIG therapy for acute exacerbations or for chronic long-term myasthenia gravis.[74] 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 two 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.[75] 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.[76] The trial did not find a statistically significant difference in the efficacy between treatments. Gajdos et al (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of myasthenia gravis.[77] Mean improvement in the myasthenic muscular scores did not differ significantly between doses after 2 weeks. Gajdos et al (1997) compared IVIG with plasma exchange in 87 patients with myasthenia gravis exacerbations.[78] 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 (eight in the plasma exchange group, one in the IVIG group).

Section Summary: Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation
The evidence for IVIG treatment for severe refractory myasthenia gravis or myasthenic exacerbation consists of multiple small trials. The largest trial (51 myasthenia gravis patients) showed a clinically meaningful improvement in disease severity with IVIG compared with placebo. Two other RCTs (n>80 patients) assessing myasthenia gravis exacerbations showed noninferiority between IVIG and plasm exchange. A Cochrane review evaluating 7 RCTs did not pool the results because of study heterogeneity; reviewers concluded that there was limited evidence for efficacy in exacerbations of myasthenia gravis.

➢Relapsing-Remitting Multiple Sclerosis
Relapsing-remitting multiple sclerosis (RRMS) is an immune-mediated inflammatory disease that attacks and destroys myelinated axons in the central nervous system, resulting in variable degrees of physical disability characterized by symptomatic episodes that occur months or years apart and affect different anatomic locations.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with RRMS.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with RRMS.
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 overall survival, disease-specific survival, symptoms, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity.

Timing
Treatment of 2 weeks is of interest to monitor outcomes.

Setting
Patients with RRMS are actively managed by neurologists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
Based on a technology assessment by Goodin et al (2002), AAN recommended the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation) for the treatment of RRMS.[79] AAN suggested that IVIG was no longer considered a drug of choice for RRMS.

Section Summary: Relapsing-Remitting Multiple Sclerosis
The evidence for the use of IVIG treatment for RRMS consists of multiple RCTs that were summarized in a technology assessment. Since then, multiple new treatments have become available for treatment of RRMS with demonstrable efficacy and safety.

➢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.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with autoimmune mucocutaneous blistering diseases.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with autoimmune mucocutaneous blistering diseases.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with autoimmune mucocutaneous blistering diseases are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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).[80] 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.[81] The IVIG group received 400 mg/kg/d for 5 days and the placebo group received saline for 5 days. The primary end point was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant (p=0.089). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15

(p=0.041). In patients with severe disease, there were significantly lower DAS scores in the IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.

Another RCT by the same research group was published by Amagai et al (2009); it was multicenter, placebo-controlled and double-blind that included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥20 mg/d).[82] 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 end point was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (ie, time to escape protocol). Time to escape protocol was significantly longer for patients in the IVIG 400-mg group than for patients in the placebo group but not between the IVIG 200-mg group and the placebo group. Furthermore, a significant decrease in a pemphigus activity score was detected at all study observation points for patients in the IVIG 400-mg group and at all study observation points after day 15 in the IVIG 200-mg group. The pemphigus activity score did not decrease significantly at any time point in the placebo group.

Section Summary: Autoimmune Mucocutaneous Blistering Diseases
The evidence for IVIG treatment for autoimmune mucocutaneous blistering diseases consists of 2 RCTs and multiple noncomparative studies. The RCT in glucocorticoid-resistant pemphigus patients demonstrated that IVIG treatment decreased disease activity and the need for additional treatment compared with placebo. The RCT in patients with bullous pemphigoid found that IVIG was effective in the subgroup of patients with severe disease. A systematic review pooled data of 260 patients across 23 studies and showed improvements in most patients.

➢Toxic Epidermal Necrosis and Stevens-Johnson Syndrome
Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with toxic epidermal necrosis (TEN) or Stevens-Johnson syndrome (SJS).

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
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 disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with TEN or SJS are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[83] Three of the studies had control groups and two 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=0.67). A meta-analysis by Barron et al (2015) also did not demonstrate a survival advantage of IVIG for TEN and/or SJS.[84]

Section Summary: Toxic Epidermal Necrosis and Stevens-Johnson Syndrome
No RCTs identified evaluated IVIG for TEN or SJS. There are several systematic reviews of observational studies, controlled and uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality.

➢ Idiopathic Inflammatory Myopathies
Idiopathic inflammatory myopathies are a group of disorders characterized by inflammation of skeletal muscles and include dermatomyositis, polymyositis, and inclusion body myositis. Polymyositis and dermatomyositis involve weakness of the proximal muscles such as the muscles of the hips and thighs, upper arms, and neck. Dermatomyositis is associated with various characteristic skin manifestations. In inclusion body myositis, the muscles most affected are those of the wrists and fingers and the front of the thigh.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with dermatomyositis or polymyositis or inclusion body myositis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with dermatomyositis, polymyositis, or inclusion body myositis.

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 are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity.

Timing
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.

Setting
Patients with dermatomyositis, polymyositis, or inclusion body myositis are actively managed by primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Dermatomyositis and Polymyositis
Systematic Reviews
Wang et al (2012) published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis.[85] Reviewers identified 14 studies including 2 RCTs, 9 prospective case series, and 3 retrospective case series. Eleven of 14 studies included patients with refractory disease. For example, a trial by Dalakas et al (1993) compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis.[86] At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified MRC 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.

Randomized Controlled Trials
Miyasaka et al (2012) in Japan conducted an RCT of 26 patients with corticosteroid-resistant polymyositis or dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month.[87] Patients were randomized to IVIG (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary end point was change from baseline mean manual muscle test scores at 8 weeks. Change in mean manual muscle test was 11.8 points in the IVIG group and 9.9 points in the placebo group. This 1.9-point difference was not statistically significant (95% CI, -4.8 to 8.5). Other outcomes also did not differ significantly between groups.

Case Series
A case series by Cherin et al (2002) assessed 35 patients with polymyositis, all of whom had disease that required ongoing glucocorticoid therapy and none could be weaned from glucocorticoids despite trials of 1 or more additional therapies, showed some clinical benefit; 33 patients with initially elevated serum creatine kinase levels showed biochemical improvement; 25 of 35 showed improvement in muscle strength, which returned to near-normal in 10 of the 25 responders; 8 of 11 patients with esophageal dysfunction showed resolution of dysphagia; 12 of the 25 responders had complete clinical responses (absence of myositis activity) while receiving

not more than prednisone 6 mg/d.[88] Mean follow-up for these patients was 39 months. Five patients discontinued all other medical treatments for myositis.

Section Summary: Dermatomyositis and Polymyositis
The evidence for IVIG treatment of dermatomyositis and polymyositis consists of multiple RCTs and noncomparative studies. A systematic review of 12 studies concluded that IVIG therapy is effective for adults with refractory polymyositis or dermatomyositis. However, a recent RCT failed to show significant differences in muscle test scores between IVIG and placebo.

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.[89] There was no statistically significant improvement in overall muscle strength in the IVIG group compared with the control (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.[90,91]

Section Summary: Inclusion Body Myositis
Three RCTs of IVIG therapy for inclusion body myositis failed to show any improvements in overall muscle strength or functional status compared with placebo.

➢Systemic Lupus Erythematosus
Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has protean manifestations and follows a relapsing and remitting course. It is characterized by an autoantibody response to nuclear and cytoplasmic antigens. SLE can affect any organ system, but it mainly attacks the skin, joints, kidneys, blood cells, and nervous system.

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with SLE.

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 patients 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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with SLE are actively managed by rheumatologists, cardiologists, pulmonologists, nephrologists, and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
A systematic review by Sakthiswary et al (2014) identified 13 studies on IVIG for treatment of SLE.[92] Three studies had control groups, and only one was an RCT.[93] 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 (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.

There has been limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE.[94]

Section Summary: Systemic Lupus Erythematosus
The evidence for IVIG treatment of SLE consists of a single RCT and multiple noncomparative studies. In a meta-analysis (6 studies), IVIG treatment was associated with reduced disease activity. However, most studies included in the meta-analysis were observational, and good quality RCTs are lacking. Therefore, results were limited by methodologic limitations and the effect of IVIG therapy on health outcomes remain to be established.

➢ 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.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with immune optic neuritis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with immune optic neuritis.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6 months is of interest to monitor outcomes.

Setting
Patients with immune optic neuritis are actively managed by ophthalmologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
Two RCTs have evaluated the potential benefit of IVIG for immune optic neuritis. Roed et al (2005) randomized 68 in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34).[95] They found no differences in the visual outcome measure or disease activity as measured by magnetic resonance imaging after 6 months.

Noseworthy et al (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo.[96] The trial was terminated early after 55 patients were enrolled because investigators did not find a difference in the logMAR visual scores at 6 months (p=0.766).

Section Summary: Immune Optic Neuritis
The evidence for IVIG treatment of immune optic neuritis consists of 2 RCTs, both of which failed to demonstrate any benefit in visual outcomes measures with IVIG.

➢Crohn Disease
Crohn disease is an inflammatory condition of unknown etiology that can affect any portion of the gastrointestinal tract, from the mouth to the perianal area, with a wide spectrum of clinical presentations.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Crohn disease.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with Crohn disease.

Interventions
The therapy being considered is IVIG therapy.

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

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with Crohn disease are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
A systematic review by Rogosnitzky et al (2012) of IVIG therapy for Crohn disease did not identify any randomized or nonrandomized controlled trials.[97] Reviewers found 5 case reports of IVIG used for single patients with Crohn disease, and the remaining literature identified included conference papers, abstracts only, or a nonsystematic review.

Section Summary: Crohn Disease
The evidence for IVIG treatment of Crohn disease consists of multiple case reports, which is not sufficiently robust to determine the efficacy of IVIG for this population.

➢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.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with hemophagocytic lymphohistiocytosis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with hemophagocytic lymphohistiocytosis.

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 overall survival, disease-specific survival, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with hemophagocytic lymphohistiocytosis are actively managed by immunologists and hematologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[98] 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.[99-101]

Section Summary: Hemophagocytic Lymphohistiocytosis
The evidence for IVIG treatment of hemophagocytic lymphohistiocytosis consists of multiple case series and reports, which is not sufficiently robust to determine the efficacy of IVIG for this population.

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

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

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

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 change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 3 weeks is of interest to monitor outcomes.

Setting
Patients with warm antibody hemolytic anemia, refractory to prednisone and splenectomy, are actively managed by hematologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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[102] and a case report.[103] Overall, 29 (39.7%) of 73 patients responded to IVIG therapy. Because of limited therapeutic value, it is used in patients refractory to conventional therapy with prednisone and splenectomy or as a conjunctive therapy in patients with very severe disease. Further, the effect is usually transient, unless repeated courses are given every 3 weeks.

Section Summary: Warm Antibody Autoimmune Hemolytic Anemia
The evidence for IVIG treatment of warm antibody autoimmune hemolytic anemia consists of pooled case series and a single case report, which is not sufficiently robust to determine the efficacy of IVIG for this population.

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

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with antiphospholipid syndrome.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with antiphospholipid syndrome.

Interventions
The therapy being considered is IVIG therapy.

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

Outcomes
The general outcomes of interest are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with antiphospholipid syndrome are actively managed by hematologists, rheumatologists, and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Case Reports
Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry.[104] Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received triple 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
The evidence for IVIG treatment of antiphospholipid syndrome consists of pooled case series from a registry, which is not sufficiently robust to determine the efficacy of IVIG for this population.

Alloimmune Processes
Neonatal Alloimmune Thrombocytopenia
Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet-antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage (ICH) occurs in 10% to 30% of affected neonates. Currently, screening for this

condition is unavailable and, thus, thrombocytopenia is only identified at birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia, and the severity of thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIG.

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is neonates with alloimmune thrombocytopenia.

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 disease-specific survival, change in disease status, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Neonates with alloimmune thrombocytopenia are actively managed by pediatricians and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[105] 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.[106] The primary outcome was fetal or neonatal ICH. The median

newborn platelet count was 81×10^9/L in the 0.5-g/kg group and 110×10^9/L in the 1-g/kg group (p=0.644).

Berkowitz et al (2007) showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies.[107] 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.[108]

Bussel et al (1996) did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids.[109] Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because the natural history of the disease suggests that subsequent births should be similarly, if not more severely, affected with thrombocytopenia. The trial reported a mean increase in platelet count of 69,000/mL. There were no instances of ICHs, although hemorrhage had occurred previously in 10 untreated siblings.

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

Section Summary: Neonatal Alloimmune Thrombocytopenia
The evidence for IVIG treatment of neonatal alloimmune thrombocytopenia consists of multiple RCTs summarized in a Cochrane review; the review showed that optimal management with IVIG with or without corticosteroids remains unclear. IVIG has been shown to increase platelet counts in standard-risk pregnancies in individual studies.

➢Recurrent Spontaneous Abortion
Recurrent spontaneous abortion is defined as 3 or more pregnancies resulting in a spontaneous abortion before 16 to 20 weeks of gestational age. Women with recurrent spontaneous abortion frequently have immunologic abnormalities, particularly antiphospholipid antibodies whose incidence may increase with each subsequent pregnancy loss.

Clinical Context and Test 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 question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is women with recurrent spontaneous abortion.

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 disease-specific survival, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Women with recurrent spontaneous abortion are actively managed by obstetricians or gynecologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[110] Meta-analyses published in 2015 and 2016 that included 11 RCTs also found no significant difference in the number of live births with IVIG vs placebo or treatment as usual.[111,112]

Randomized Controlled Trials
An RCT by Christiansen et al (2002) evaluated 58 women with at least 4 unexplained miscarriages and compared IVIG with placebo.[113] Using intention to treat analysis, the live birth rate was similar for both groups; also, there were no differences in neonatal data (eg, 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 lupus anticoagulant, anticardiolipin antibody, or both, and found no significant differences.[114]

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.[115]

Section Summary: Recurrent Spontaneous Abortion
The evidence for IVIG treatment of recurrent spontaneous abortion consists of multiple RCTs summarized in a Cochrane review; it concluded that IVIG therapy provides no significant beneficial effect over placebo in preventing further miscarriages.

Miscellaneous Indications
➢Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a term used to describe a subset of children whose symptoms of obsessive-compulsive disorder (or tic disorders) are exacerbated by group A streptococcal infection. This syndrome is not well-understood, and diagnosis of PANDAS requires expert consultation.

Clinical Context and Test 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 PANAS.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is children with PANAS.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat PANAS: antibiotic therapy alone.

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

Timing
Follow-up at 1 month is of interest to monitor outcomes.

Setting
Children with PANAS are actively managed by pediatricians and neurologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[116] 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 (CY-BOCS) total score, did not differ significantly between groups. There was a mean decrease in the CY-BOCS of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvements in other outcomes (eg, mean Clinical Global Impressions improvement scores) also did not differ significantly between groups. A total of 24 participants met criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the CY-BOCS 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.[117] 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. The trial included only 10 children who were treated with IVIG.

Section Summary: Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections
Two placebo-controlled randomized trials have evaluated IVIG for PANDAS. A 2016 trial with 35 children did not find significant benefits with IVIG compared with placebo at the end of the 6-week double-blind phase. The other trial found significant benefits of IVIG over placebo at 1 month but included only 10 children with PANDAS. Due to the mixed findings of the RCTs, the small sample sizes and the short duration of double-blind interventions, the evidence is insufficient to draw conclusions about the impact of IVIG on health outcomes in children with PANDAS.

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

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with autism spectrum disorder.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with autism spectrum disorder.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6 months is of interest to monitor outcomes.

Setting
Patients with autism spectrum disorder are actively managed by primary care providers, pediatricians, occupational therapists, clinical psychologists, and neurologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[118] 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.[119] No improvements were observed in the third series.[120]

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

Section Summary: Autism Spectrum Disorder
The evidence for IVIG treatment of autism spectrum disorder consists of multiple case series with conflicted findings; 1 case series reported benefit while 2 others failed to replicate those findings.

➢Complex Regional Pain Syndrome
Complex regional pain syndrome (CRPS) is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with CRPS.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with CRPS.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 14 days is of interest to monitor outcomes.

Setting
Patients with CRPS are actively managed by physiatrists, occupational therapists, physical therapists, and neurologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[121] IVIG 0.5 g/kg of body weight or saline placebo on days 1 and 22 were administered after 111 patients were randomized. An 11-point (0- to 10-point) rating scale was used to measure the primary outcome of 24-hour average pain intensity. Mean pain scores were 6.9 points for placebo and 7.2 points for IVIG at 6 weeks demonstrating that low-dose immunoglobulin treatment was not effective in relieving pain in moderate-to-severe CRPS patients. Goebel et al (2010) reported on the use of IVIG treatment for CRPS in a crossover double-blinded RCT conducted at an academic pain management center in the U.K.[122] The trial randomized 13 patients refractory to standard treatment to IVIG or normal saline. Median daily pain intensity score for each 14-day period was 6.21 after IVIG infusion vs 7.35 after saline infusion, a difference of 1.14 points. Trialists reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; $p<0.001$).

Section Summary: Complex Regional Pain Syndrome
The evidence for IVIG treatment of CRPS consists of a small crossover RCT that showed reductions in pain scores compared with placebo. However, the evidence is insufficient to draw conclusions about the impact of IVIG on health outcomes in those who suffer with CRPS.

➢Alzheimer Disease
Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Alzheimer disease.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with Alzheimer disease.

Interventions
The therapy being considered is IVIG therapy.

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

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 12 or 24 months is of interest to monitor outcomes.

Setting
Patients with Alzheimer disease are actively managed by geriatricians, neurologists and primary care providers in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
Three placebo-controlled double-blind, randomized trials in patients with Alzheimer disease were identified. Two included patients with mild-to-moderate Alzheimer disease. 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.[123] The primary outcomes were 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 groups compared with the placebo group.

Kile et al (2017) assessed 50 patients with mild cognitive impairment (MCI) related to Alzheimer disease.[124] 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 (APCV) measured by magnetic resonance imaging. In unadjusted analyses, APCV did not differ significantly between groups at 12 or 24 months. In a subgroup analysis, the APCV was significantly lower in the IVIG compared with 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 Alzheimer disease 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.[125] Secondary outcomes, including cognitive and functional scales, also did not differ between groups.

Section Summary: Alzheimer Disease
Three double-blind placebo-controlled randomized trials have evaluated IVIG in patients with Alzheimer disease. With the exception of a few subgroup analyses by MCI status, IVIG did not show significantly better outcomes than placebo for brain atrophy, level of plasma amyloid β 1–40, or cognition and function. Studies differed in factors such as 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
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.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with paraproteinemic neuropathy.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with paraproteinemic neuropathy.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 2 weeks is of interest to monitor outcomes.

Setting
Patients with paraproteinemic neuropathy are actively managed by primary care providers and neurologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
An RCT by Comi et al (2002) focused on short-term outcomes at 2 weeks in 22 patients.[126] No significant differences were found between the treatment and placebo groups.
Results of a double-blind, placebo-controlled, randomized crossover trial by Dalakas et al (1996) compared IVIG with placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients.[127]

Section Summary: Paraproteinemic Neuropathy
The evidence for IVIG treatment of paraproteinemic neuropathy consists of 2 RCTs with conflicting findings; the first reported a small benefit while the larger failed to replicate those findings.

➢Chronic Fatigue Syndrome
Chronic fatigue syndrome (also called systemic exertion intolerance disease) is a complex and controversial disease with multiple definitions.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic fatigue syndrome.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with chronic fatigue syndrome.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is to monitor outcomes.

Setting
Patients with chronic fatigue syndrome are actively managed by primary care providers and physiatrists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

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.[128]

Section Summary: Chronic Fatigue Syndrome
The evidence for IVIG treatment of chronic fatigue syndrome consists of noncomparative studies and an RCT that failed to show a benefit of IVIG.

➢Acute Myocarditis
Acute myocarditis is a sudden inflammation of myocardium that can occur in individuals of all ages. It is presumed to start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear whether the primary problem is most commonly ongoing damage from the virus, a postinfectious inflammatory reaction, or a combination of the two.

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

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with acute myocarditis.

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 overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with acute myocarditis are actively managed by cardiologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
The literature has been summarized in a Cochrane review by Robinson et al (2015)[129] that included a 2001 placebo-controlled randomized trial of 62 adults with recent-onset dilated cardiomyopathy[130] and a 2012 quasi-randomized study of 83 children with suspected viral encephalitis and associated myocarditis with a left ventricular ejection fraction less than 0.40.[131] Both trials were rated as very low quality and had high risk of bias. In the RCT of adults, event-free survival did not differ significantly but favored the control group (OR=0.52; 95% CI, 0.12 to 2.30). The major limitation was that some patients did not have viral myocarditis (only 10 of 62 patients showed inflammation on cardiac biopsy). In the quasi-randomized trial in children, the incidence of event-free survival was 25 (96%) of 26 in the treated group and 44 (77%) of 57 in the control group (OR=7.39; 95% CI, 0.91 to 59.86).

Retrospective Studies
Heidendael et al (2017) reported on 94 children with new-onset dilated cardiomyopathy in a retrospective cohort study with a median follow-up of 33 months.[132] After viral tests were performed, 18 (19%) children met diagnostic criteria for "probably or definite viral myocarditis," and IVIG was administered to 21 (22%) patients. Treatment was associated with a higher recovery rate within 5 years, compared with nontreated children (70 vs 43%; p=0.045), however the HR for recovery with IVIG was not significant (HR=2.1; 95% CI, 1.0 to 4.6; p=0.056) after correction for possible cofounders. The authors concluded that IVIG treatment was associated with better improvement of systolic left ventricular function and better recovery, but did not influence transplant-free survival.

Multiple case reports have suggested that patients with acute myocarditis may benefit from high-dose IVIG.[94] Spontaneous rapid or gradual improvement is common with acute myocarditis, and improvement noted in these case series might have been part of the natural history of the disease.

Section Summary: Acute Myocarditis
The evidence for IVIG treatment of dilated cardiomyopathy syndrome consists of multiple noncomparative studies, a quasi-randomized trial, and an RCT. All studies had a high risk of bias. High-quality RCTs are needed to demonstrate benefit of IVIG for viral myocarditis.

➢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.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with refractory recurrent pericarditis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with refractory recurrent pericarditis.

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 overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up to 36 months is of interest to monitor outcomes.

Setting
Patients with refractory recurrent pericarditis are actively managed by cardiologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
Imazio et al (2016) conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports).[133] Approximately 47% of patients had idiopathic recurrent pericarditis, 10% had an infective cause, and the remainder had 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
The evidence for IVIG treatment of refractory recurrent pericarditis consists of multiple case reports and case series that reported benefit. Controlled trials are lacking.

➢Stiff Person Syndrome
Stiff person syndrome is rare acquired neurologic disorder characterized by progressive muscle stiffness, rigidity, and spasm involving the axial muscles, resulting in severely impaired ambulation. It is caused by increased muscle activity due to decreased inhibition of the central nervous system. If left untreated, stiff person syndrome can progress to cause difficulty walking and significantly impact a person's ability to perform routine, daily tasks.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with stiff person syndrome.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with stiff person syndrome.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 24 months is of interest to monitor outcomes.

Setting
Patients with stiff person syndrome are actively managed by primary care providers, neurologists and physical therapists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Case Reports
Multiple case reports have suggested that patients with stiff person syndrome may benefit from IVIG. The benefit was confirmed in a small 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.[134] 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.

Section Summary: Stiff Person Syndrome
The evidence for IVIG treatment of stiff person syndrome consists of an RCT and multiple noncomparative studies that confirmed the benefit of IVIG in terms of reductions in stiffness as well as improvements in mobility and function.

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

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with noninfectious uveitis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with noninfectious uveitis.

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, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

Setting
Patients with noninfectious uveitis are actively managed by ophthalmologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Case Series
Two small case series of 18 and 10 patients, respectively, have reported measurable improvements in visual acuity after IVIG therapy.[135,136] Collectively, these 2 studies represent insufficient evidence to draw conclusions about efficacy.

Section Summary: Noninfectious Uveitis
The evidence for IVIG treatment of noninfectious uveitis consists of 2 small case series that have reported measurable improvements in visual acuity after IVIG therapy. However, the evidence is insufficient to draw conclusions about the impact of IVIG on health outcomes in those who suffer with noninfectious uveitis.

➢Postpolio Syndrome
Although polio no longer poses a major public health threat in the United States, many patients live with the sequelae of paralytic polio. Many polio survivors experience a modest decline in function and muscle strength over many years that may reflect the natural history of polio.

Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with postpolio syndrome.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with postpolio syndrome.

Interventions
The therapy being considered is IVIG therapy.

Comparators
The following practice is currently being used to treat postpolio syndrome: supportive care alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, quality of life, and treatment-related mortality and morbidity.

Timing
Follow-up at 3 months is of interest to monitor outcomes.

Setting
Patients with postpolio syndrome are actively managed by primary care providers, neurologists and physical therapists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Systematic Reviews
Huang et al (2015) published a systematic review and meta-analysis of RCTs and nonrandomized prospective studies on IVIG treatment of postpolio syndrome.[137] Reviewers identified 3 RCTs (n=241 patients) and 5 prospective studies (n=267 patients). The primary outcomes of interest were severity of pain, fatigue, and change in muscle strength 2 to 3 months after IVIG administration. Meta-analyses of RCT data found no statistically significant differences between IVIG- and placebo-treated groups for any of these outcomes. For example, the pooled mean difference in pain scores (0-to-10 visual analog scale) from the 3 RCTs was -1.02 (95% CI, -2.51 to 0.47). Meta-analysis of the 2 RCTs that reported a change in fatigue scores found a weighted mean difference of 0.28 (95% CI, -1.56 to 1.12). The small number of RCTs and the negative findings of the this systematic review represent insufficient evidence of the efficacy of IVIG for postpolio syndrome.

Section Summary: Postpolio Syndrome
The evidence for IVIG treatment of postpolio syndrome consists of multiple RCTs and noncomparative studies summarized in a systematic review; it concluded that IVIG treatment was not associated with reduction in pain and fatigue or an improvement in muscle strength.

➢Necrotizing Fasciitis
Clinical Context and Test Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with necrotizing fasciitis.

The question addressed in this evidence review is: Is IVIG therapy an effective treatment for various autoimmune and nonautoimmune conditions?

The following PICOTS were used to select literature to inform this review.

Patients
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 overall survival, symptoms, functional outcomes, and treatment-related mortality and morbidity.

Timing
Follow-up at 3 months is of interest for to monitor outcomes.

Setting
Patients with necrotizing fasciitis are actively managed by general surgeons, plastic surgeons, and infectious disease doctors in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected as stated in the initial indication.

Randomized Controlled Trials
Madsen et al (2017) published a placebo-controlled randomized trial evaluating IVIG for patients with necrotizing soft issue infection (eg, necrotizing fasciitis).[138] The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admissions 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 site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant (p=0.81). Other outcomes (ie, mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

Section Summary: Necrotizing Fasciitis
The evidence for IVIG treatment of necrotizing fasciitis consists of an RCT that did not find a significant difference in outcomes between IVIG and placebo. The evidence is insufficient to draw conclusions on the impact of IVIG on health outcomes in this population.

SUMMARY OF EVIDENCE

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

For individuals who are undergoing HCT who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs, systematic reviews, and a meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG for routine prophylaxis of infection in patients undergoing HCT was not associated with

survival benefit or reduction in infection. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

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

For individuals who have acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective studies. Larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Infections

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

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

For individuals who are preterm and low birth weight infants and at risk for sepsis who receive IVIG therapy (prophylaxis), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who are preterm and low birth weight infants with sepsis who receive IVIG therapy (treatment), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and

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

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

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

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

Autoimmune and Inflammatory Conditions

For individuals who have ITP who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, a meta-analysis, and noncomparative studies. Relevant outcomes are disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with corticosteroids, IVIG therapy improved platelet counts. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes systematic reviews and an RCT. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. The success of IVIG in Kawasaki disease has led to the investigation of IVIG therapy for other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial found significantly more responders in the IVIG treatment group at 3 months—but no significant differences after 3 months, or in the frequency of relapse or use of other medications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

<u>Alloimmune Processes</u>
For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple 2 RCTs and a systematic review. Relevant outcomes are disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Compared with combination use with corticosteroids, IVIG alone did not show any additional increases in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy. The

evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Miscellaneous Indications

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

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

For individuals who have CRPS who receive IVIG therapy, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 12 patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes an RCT and anecdotal reports. Relevant outcomes are symptoms, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown no

therapeutic benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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

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

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

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers,

input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received through 3 physician specialty societies and 5 academic medical centers in March 2013 following approval of the December 2012 update of the policy. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. Input focused on IVIG treatment of 7 rare conditions. There was consensus, or near-consensus, that IVIG is investigational for 6 of these conditions: birdshot retinopathy, epidermolysis bullosa acquisita, necrotizing fasciitis, opsoclonus-myoclonus, PANDAS and polyradiculoneuropathy (other than CIPD). Clinical input was mixed overall on the seventh condition, IVIG for treating severe anemia associated with parvovirus B19.

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

Immunodeficiency States

Primary Humoral Immune Deficiencies

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

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

American Academy of Allergy, Asthma, and Immunology

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

Hematopoietic Cell Transplantation (Prophylaxis)

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

Acute Antibody-Mediated Rejection After Solid Organ Transplant

In 2010, the CBS and NAC developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation.[140] The following conclusions were issued on nonkidney 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 PP compared either to plasmapheresis or IVIG alone; and the optimum dosage of IVIG.

Chronic Lymphocytic Leukemia

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

Infections

Infections in HIV-Infected Children

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

Neonatal Sepsis

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

Autoimmune/Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

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

- Adult acute ITP with bleeding: IVIG strongly recommended as a part of multimodality therapy for major or life-threatening bleeding complications and/or clinically important mucocutaneous bleeding.
- Adult acute ITP with severe thrombocytopenia but no bleeding: IVIG not recommended as first-line therapy alone, except for patients with contraindications to corticosteroids.
- Adult ITP with no or slow response to adequate dose corticosteroids: IVIG may be considered as a possible adjunctive therapy.

- Adult chronic ITP postsplenectomy: IVIG may be considered as a possible adjunctive therapy as a corticosteroid-sparing measure. The minimal dose of IVIG should be used that maintains a safe platelet count. Patients should be reevaluated every 3 to 6 months, and alternative therapies to IVIG should be considered for patients who do not achieve a durable response for a minimum of 2 to 3 weeks.

Guillain-Barré Syndrome

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

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

Kawasaki Syndrome and Other Vasculitides

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

Chronic Inflammatory Demyelinating Polyneuropathy

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

EFNS issued guidelines on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines indicated that the efficacy of IVIG for the treatment of CIDP is proven (level A).

Multifocal Motor Neuropathy

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

EFNS issued guidelines on the use of IVIG for the treatment of neurologic disorders.[143] The guidelines indicated that the efficacy of IVIG for the treatment of multifocal motor neuropathy is proven (level A).

Eaton-Lambert Myasthenic Syndrome

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

Neuromyelitis Optica

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

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

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

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

Relapsing-Remitting Multiple Sclerosis

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

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

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

Autoimmune Mucocutaneous Blistering Diseases

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

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

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

Idiopathic Inflammatory Myopathies

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

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

Immune Optic Neuritis

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

Alloimmune Processes

Neonatal Alloimmune Thrombocytopenia

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

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

Recurrent Spontaneous Abortion

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

Miscellaneous

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

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

Autism Spectrum Disorder

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

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

Chronic Fatigue Syndrome

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

Viral Myocarditis

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

Stiff Person Syndrome

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

Postpolio Syndrome

EFNS updated its guidelines on the definition and management of postpolio syndrome in 2011.[153] The guidelines indicated that IVIG could have a modest therapeutic effect on postpolio syndrome,

though there were limitations to the study evidence (small sample size, inadequate comparators, appropriate dosage). Due to these limitations, EFNS concluded that IVIG cannot be recommended as a standard treatment.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Table 1. Summary of Key Trials

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

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

90283 Immune globulin (IgIV), human, for intravenous use
90284 Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96369 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump set-up and establishment of subcutaneous infusion site(s)
96370 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96371 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure)
J1459 Injection, immune globulin (Privigen), intravenous, nonlyophilized (eg, liquid), 500 mg
J1555 Injection, immune globulin, 100mg
J1556 Injection, immune globulin (bivigam), 500 mg

J1557 Injection, immune globulin (Gammaplex), intravenous, nonlyophilized (eg, liquid), 500 mg
J1559 Injection, immune globulin (Hizentra), 100 mg
J1561 Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), nonlyophilized (eg, liquid), 500 mg
J1566 Injection, immune globulin, intravenous, lyophilized (eg, powder), not otherwise specified, 500 mg
J1568 Injection, immune globulin (Octagam) intravenous, nonlyophilized (eg, liquid), 500 mg
J1569 Injection, immune globulin (Gammagard liquid) intravenous, nonlyophilized (eg, liquid), 500 mg
J1572 Injection, immune globulin (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (eg, liquid), 500 mg
J1575 Injection, immune globulin/hyaluronidase (Hyqvia), 100 mg
J1599 Injection, immune globulin, intravenous, nonlyophilized (eg, liquid), not otherwise specified, 500 mg

- There are CPT and HCPCS codes that describe IVIG and SCIG products: 90283, 90284, J1459, J1555, J1556, J1557, J1559, J1561, J1566, J1568, J1569, J1572, J1575, J1599.
- The following CPT drug administration codes would be used for the administration of these products: 96365, 96366, 96369, 96370, 96371.

ICD-10 Diagnoses

A48.3 Toxic shock syndrome
B20 Human immunodeficiency virus [HIV] disease
B95.0 Streptococcus, group A, as the cause of diseases classified elsewhere
B95.1 Streptococcus, group B, as the cause of diseases classified elsewhere
B95.2 Enterococcus as the cause of diseases classified elsewhere
B95.3 Streptococcus pneumoniae as the cause of diseases classified elsewhere
B95.4 Other streptococcus as the cause of diseases classified elsewhere
B95.5 Unspecified streptococcus as the cause of diseases classified elsewhere
B95.61 Methicillin susceptible Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.62 Methicillin resistant Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.7 Other staphylococcus as the cause of diseases classified elsewhere
B95.8 Unspecified staphylococcus as the cause of diseases classified elsewhere
C91.10 Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11 Chronic lymphocytic leukemia of B-cell type in remission
C91.12 Chronic lymphocytic leukemia of B-cell type in relapse
D59.1 Other autoimmune hemolytic anemias
D68.61 Antiphospholipid syndrome
D69.3 Immune thrombocytopenic purpura
D69.6 Thrombocytopenia, unspecified
D80.0 Hereditary hypogammaglobulinemia
D80.1 Nonfamilial hypogammaglobulinemia
D80.2 Selective deficiency of immunoglobulinemia
D80.3 Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4 Selective deficiency of immunoglobulin M [IgM]
D80.5 Immunodeficiency with increased immunoglobulin M [IgM]

D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominantly antibody defects
D80.9	Immunodeficiency with predominantly antibody defects, unspecified
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
G11.3	Telangiectasia (cerebellar) (Louis-Bar)
G35	Multiple sclerosis
G60.0	Hereditary motor and sensory neuropathy
G60.1	Refsum's disease
G60.2	Neuropathy in association with hereditary ataxia
G60.3	Idiopathic progressive neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified
G61.0	Guillain-Barré syndrome
G70.01	Myasthenia gravis with (acute) exacerbation
G73.3	Myasthenic syndromes in other diseases classified elsewhere
I44.0	Atrioventricular block, first degree
I44.1	Atrioventricular block, second degree
I44.2	Atrioventricular block, complete
I44.30	Unspecified atrioventricular block
I44.39	Other atrioventricular block
I44.4	Left anterior fascicular block
I44.5	Left posterior fascicular block
I44.60	Unspecified fascicular block
I44.69	Other fascicular block
I44.7	Left bundle-branch block, unspecified
I45.0	Right fascicular block
I45.10	Unspecified right bundle-branch block
I45.19	Other right bundle-branch block
I45.2	Bifascicular block
I45.3	Trifascicular block
I45.4	Nonspecific intraventricular block
I45.5	Other specified heart block
I45.6	Pre-excitation syndrome
I45.81	Long QT syndrome
I45.89	Other specified conduction disorders
I45.9	Conduction disorder, unspecified
L10.0	Pemphigus vulgaris
L10.1	Pemphigus vegetans
L10.2	Pemphigus foliaceous
L10.3	Brazilian pemphigus [fogo selvagem]
L10.4	Pemphigus erythematosus

L10.5	Drug-induced pemphigus
L10.81	Paraneoplastic pemphigus
L10.89	Other pemphigus
L10.9	Pemphigus, unspecified
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.2	Chronic bullous disease of childhood
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.91	Dermatopolymyositis, unspecified with respiratory involvement
M33.92	Dermatopolymyositis, unspecified with myopathy
M33.93	Dermatopolymyositis, unspecified without myopathy
M33.99	Dermatopolymyositis, unspecified with other organ involvement
P61.0	Transient neonatal thrombocytopenia
Z94.81	Bone marrow transplant status

REVISIONS

01-12-2007 effective 04-01-2007	In "Policy" section 1., a., added "(patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization)" based on consultant review and recommended by the Medical Director.
	In "Policy" section, added #23 "Prior to renal transplantation with high levels of panel reactive antibodies (PBA)" as recommended by the Medical Director.
	In "Coding" title deleted "NOTE: Use of any diagnosis code does not guarantee reimbursement. Medical necessity will be based on documentation in the clinical record."
	In "Coding" CPT/HCPCS section, added HCPCS codes J1562 due to the 2007 CPT changes.
	In "Reference" Government Agency; Medical Society; and Other Authoritative Publications section added #2.
09-12-2007	Revised wording of Policy #1 – Primary humoral immunodeficiencies: 1. Primary humoral immunodeficiencies a. Normal or subnormal gamma globulin and/or subclasses with recurrent significant infections. A function immune deficiency needs to be demonstrated by lack of antibody response to pneumococcal vaccine with pre-vaccine antibody titers drawn just before vaccine and post vaccination titers drawn one month after vaccine. At least a two-fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization. b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed. c. Transient hypogammaglobulinemia of childhood age less than 5 functional immune deficiency is transient, usually six months, then IVIg can be gradually withdrawn. Need testing for pneumococcal antibody response.

	Moved to Policy #24 - Chronic B Cell Lymphocytic Leukemia, multiple myeloma, or B cell lymphoma with low immunoglobulin levels
	Moved to Policy #25 - Profound neutropenia in neonatal sepsis (WBC 5,000 or below) –Allow for a single dose.
02-28-2011	Significant updates to Policy Language section. The following policy language has been updated: All immune globulin therapy will be reviewed for medical necessity prior to payment. See Utilization Section for details. Indications for immune globulin include: 1. Immunodeficiency states: One of the following six is required: a. A functional immune deficiency manifested by recurrent serious infections. Needs to be demonstrated by the lack of antibody response to pneumococcal vaccine with pre and post antibody titers (patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization) and recurrent significant infections or b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed. c. B Cell Lymphocytic Leukemia (CLL) (eg multiple myeloma, chronic lymphocytic leukemia with low immunoglobulin levels or B cell lymphoma). d. Transient hypogammaglobulinemia of childhood • Similar to a functional immune deficiency but transient, usually six months, then IVIg should be gradually withdrawn. Need testing for pneumococcal antibody response. • Consider in children less than age 5. e. Partial antibody deficiency (subclass of deficiency) • This may refer to a deficiency of one of the four subclasses. This in itself does not indicate instituting IVIg therapy even if patient presents with multiple infection (sinusitis or other upper respiratory infection). Attempts need to be made to find underlying cause and to see if patient has normal immune response. By giving Pneumovax (pneumococcal at a minimum and may include tetanus or hemophilus influenza in addition) and checking antibody levels before and after ascertain if patient has normal immune response. • If normal response is obtained, then subclass level deficiency should not be treated. The only exception to this would be in case of a life threatening hospitalization from a specific disease. f. Profound neutropenia in neonatal sepsis (WBC 5,000 or below) –Allow for a single dose. 2. Idiopathic thrombocytopenia (ITP) a. Acute Idiopathic thrombocytopenia (ITP) 1) Management of acute bleeding, due to severe thrombocytopenia (platelet counts usually less than 30,000/ul; 2) To increase platelet counts prior to invasive surgical procedures, eg, splenectomy; 3) In patients with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage b. Chronic Refractory ITP 1) Prior to treatment with corticosteroids and splenectomy and; 2) Duration of illness of greater than six months and; 3) Age of 10 years or older and; 4) No concurrent illness/disease explaining thrombocytopenia and; 5) Platelet counts persistently at or below 20,000/ul. 3. HIV associated thrombocytopenia – Allow treatment (same as ITP)

	4. Immune thrombocytopenic purpura of pregnancy – Allow for 5 days. 5. Neonatal alloimmune thrombocytopenia – Allow for 5 days. 6. Kawasaki Syndrome 7. Organ transplant – graft versus host disease. Allow treatment, but treatment should be short-term unless it is "chronic" graft versus host. 8. Guillain Barré Syndrome – Allow for no longer than 1 month. 9. Bone Marrow transplant 10. Landau-Kleffner Syndrome – Allow for six weeks with documented speech improvement, only if patient has completed a course of prednisone. Additional treatment requires prior approval. 11. Polymyositis – Allow for six months if no response to steroids and observe for relapse. 12. Dermatomyositis – Allow for six months if no response to steroids and observe for relapse. 13. HIV associated polyneuropathy. 14. Multifocal motor neuropathy. 15. Chronic inflammatory demyelinating polyneuropathy (CIDP) 16. Myasthenia gravis – Only when all other treatments fail. 17. Intractable seizure – Not recommended unless all other measures fail. 18. Rasmussen encephalitis 19. Systemic juvenile rheumatoid arthritis – Only for refractory patient cases. 20. Systemic lupus – Not recommended except for refractory cases. 21. Steroid dependent asthmatic, allow only if: a. All modalities have failed. b. Unstable patient requiring frequent hospital care. A trial should be allowed and if there is a decrease of frequency of hospital admissions and stabilization of patient's pulmonary function it should be allowed. 22. Pemphigus - only when all other treatments fail. 23. Prior to renal transplantation with high levels of panel reactive antibodies (PBA) NOTE: When it is determined IVIg is to be given for the duration of the patient's life, reviews will be conducted not for medical necessity but for patient benefits. Denied Medical Conditions: 1. Infertility and Spontaneous abortion deny experimental/investigational. 2. Frequent sinus/pulmonary infection only, deny not medically necessary. 3. Shingles deny not medically necessary. 4. Prevention of bacterial infection associated with HIV (adults), deny not medically necessary. 5. Amyotrophic Lateral Sclerosis (ALS), deny experimental/investigational.
	In Coding Section ▪ Added CPT Codes: 90284, 96365, 96366, 96369, 96370, 96371 ▪ Added HCPCS Codes: C9270, J1459, J1561, J1568, J1569, J1572, ▪ Removed CPT Codes: 90399 ▪ Removed HCPCS Codes: J1567, J3490, Q9941, Q9942, Q9943, Q9944 ▪ Added Diagnosis Codes: 041.1-041.9, 042, 204.12, 279.00, 279.04-279.05, 279.06, 279.12, 279.2, 279.3, 287.31, 287.32, 287.5, 354.0-355.9, 356.4-356.9, 426.0-426.9, 776.1, ▪ Removed Diagnosis Codes: 284.9, 357.81, 694.4, 710.4
	Reference section updated.
07-15-2011	In the Medical Policy Section: ▪ Item B, #1, a: corrected "ml" to read "(eg200 mg per dl or less)" ▪ Item B, #1, b: first bullet, corrected "mg per" to read ">1.3 micrograms/ml" ▪ Item B, #1, b, second bullet: corrected "mg per" to read ">1.3 micrograms/ml"

	In the Coding Section Added HCPCS code J1559
08-19-2011	In the Description section: Added the fourth paragraph: "One SCIg product (Vivaglobin®, ZLB Behring LLC, Kankakee, IL) has received FDA marketing approval for the treatment of patients with primary immune deficiency."
	In the Policy section: ▪ Item 16, b, added "; or "at the end. ▪ Item 16, added the following: o "c. Platelet counts less than 20,000/ul (risk of intracerebral hemorrhage; or" o "d. Management of acute bleeding with platelet counts less than 30,000/ ul; or" o "e. Increase platelet counts, prior to major surgical procedures."
	Updated the Rationale section.
	Updated the Reference section.
01-01-2012	In the Coding section: ▪ Removed HCPCS code C9270 ▪ Added HCPCS code J1561. ▪ Revised HCPCS code J1561: to include Gammaked
04-13-2012	Updated Description section.
	In the Policy section: • In Item B, #1, b, fourth paragraph, removed "with clearly impaired responses to both protein and / or polysaccharide antigens and" and inserted "who" to read "Immunoglobulin replacements should be reserved for patients who have failed the following treatments:" ▪ In Item B, #1, b, fourth paragraph, second bullet, removed "A high percentage of patients have concurrent allergic disease." and inserted "anatomic abnormalities conducive to ENT procedures" to read "(eg asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures)." ▪ In Item B, #5, removed "or the member has experienced significant complications" to read "…when corticosteroids, and immune-suppressive agents have failed." ▪ In Item B, #8, removed "with IgG level less than 600 mg/dL; and:" to read "Chronic Lymphocytic Leukemia (CLL) in Patients with Hypogammaglobulinemia" ▪ In Item B, #8, a, removed "1 server bacterial infection within preceding 6 months or 2 or more bacterial infections in one year; or" and inserted "recurrent or persistent bacterial infections" ▪ In Item B, #11, inserted "or previous pregnancy affected by FAIT" ▪ In Item B, #14, removed "Bacterial Infection" and "infected children" to read "HIV Infected Children who meet the following criteria:" ▪ In Item B, #14, b, removed "ie, defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1 year period" to read "Recurrent serious bacterial infections;" ▪ In Item B, #14, c, removed "Living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live" to read "Failure to form antibodies to common antigens, such as measles, pneumococcal, and / or Haemophilus influenza type b vaccine;" ▪ In Item B, #14, e, removed "HIV infected children with" to read "Chronic bronchiectasis that is…" ▪ In Item B, #26, inserted "diagnosed on the basis of electrophysiologic findings." ▪ In Item B, #27, b, removed "Two or more and "or a single life threatening infection" to read "Recurrent significant infections in last year;" ▪ In Item B, #33, removed "for children whose symptoms do not improve with" and inserted "refractory to" to read "Rasmussen Encephalitis refractory to antiepileptic drugs and corticosteroids."

	• In Item B, #34, removed "Sever cases of toxic shock syndrome that have not responded to fluids and vasopressors" ▪ In Item D, inserted the following conditions: 1. chronic progressive multiple sclerosis; 2. refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus; 3. recurrent spontaneous abortion (see below for related laboratory tests); 4. inclusion-body myositis; 5. polymyositis, including refractory polymyositis; 6. myasthenia gravis in patients responsive to immunosuppressive treatment; 7. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; eg, 8. Wegener's granulomatosis, polyarteritis nodosa), Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases; 9. thrombotic thrombocytopenic purpura; 10. hemolytic uremic syndrome; 11. paraneoplastic syndromes, other than Eaton-Lambert myasthenic syndrome 12. demyelinating polyneuropathy associated with IgM paraproteinemia; 13. epilepsy; 14. chronic sinusitis; 15. asthma; 16. chronic fatigue syndrome; 17. aplastic anemia; 18. Diamond-Blackfan anemia; 19. red cell aplasia; 20. acquired factor VIII inhibitors; 21. hemophagocytic syndrome; 22. acute lymphoblastic leukemia; 23. multiple myeloma; 24. immune-mediated neutropenia; 25. nonimmune thrombocytopenia; 26. cystic fibrosis; 27. recurrent otitis media; 28. diabetes mellitus; 29. Behcet's syndrome; 30. adrenoleukodystrophy; 31. stiff person syndrome; 32. organ transplant rejection; 33. uveitis; 34. demyelinating optic neuritis; 35. recent-onset dilated cardiomyopathy; 36. Fisher syndrome 37. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); 38. autism 39. complex regional pain syndrome 40. Alzheimer's disease 41. IGG sub-class deficiency 42. Sepsis
	Updated Policy Guidelines.
	Updated Coding nomenclature.
	Updated Rationale section.
	Updated Reference section.
07-30-2013	In Policy section:

	▪ In Item B, #1, b, third bullet, removed "and have not responded to polysaccharide vaccines". ▪ In Item D, #41, added ", including neonatal sepsis" to read "Sepsis, including neonatal sepsis" ▪ In Item D, added "#42. Crohn's disease"
	Updated Rationale section.
	In Coding section: ▪ Added HCPCS codes: C9130 and J1599 ▪ Removed HCPCS code J1562 ▪ Added ICD-10 diagnosis codes *(Effective October 1, 2014)*
	Updated Reference section.
01-21-2014	In Coding section: ▪ Added new code: J1556 *(Effective January 1, 2014)* ▪ Removed code: C9130 *(Deleted code, effective December 31, 2013)*
09-12-2014	In Policy section: ▪ In Item B, #1, added "(to include X-linked agammaglobulinemia (Bruton) X-linked hyper-IgM syndrome, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and ataxia telangiectasia)" ▪ In Item B, #5, added "pemphigus" ▪ In Item D, removed, "30. Stiff person syndrome;"
	Updated Rationale section.
	In Coding section: ▪ Added ICD-9 code 334.8 ▪ Added ICD-10 code G11.3
	Updated Reference section.
11-12-2014	In Description section: ▪ Added Hyqvia® (Baxter) under Regulatory Status. ▪ Removed Polygam® S/D (Baxter) [IVIg] and Vivaglobin® (ZLB Behring LLC, Kankakee, IL) [SCIg] under Regulatory Status.
	In Policy section: ▪ In Item B, diseases were alphabetized for research ease. ▪ In Item B, #5, added "B Cell", "(total IgG <400 mg/dL)", and "AND" and removed "Evidence of specific antibody deficiency to pneumococcal vaccine serotypes." to read, "B Cell Chronic Lymphocytic Leukemia (CLL) in patients with a. Hypogammaglobulinemia (total IgG <400 mg/dL), AND b. Recurrent or persistent bacterial infections." ▪ In Item B, separated "Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)" and "Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) Variant", into numbers 8 and 26. ▪ In Item B, #17, a. and b., added "AND"; c. and d., added "OR", to read, "HIV Infected Children – who meet the following criteria: a. Serum IgG concentration less than 250 mg/dL; AND b. Recurrent serious bacterial infections; AND c. Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenza type b vaccine; OR d. Single dose for HIV-infected children who are exposed to measles; OR e. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy." ▪ In Item B, #34, added "(Lyell's syndrome)" and changed "and" to "or", to read, "Toxic Epidermal Necrolysis (Lyell's syndrome) or Stevens-Johnson Syndrome." ▪ In Item D, #2, removed "including systemic lupus erythematosus." ▪ In Item D, removed #5, "polymyositis, including refractory polymyositis." ▪ In Item D, removed #22, "multiple myeloma." ▪ In Item D, removed #34, "Fisher syndrome."
02-05-2015	In Policy section: ▪ In Item B, corrected numbering of items 33-40.
07-10-2015	In Policy section:

	▪ In Item B 28 b, removed "significant: and "in last year", to read, "Recurrent or persistent infections;" ▪ Removed Item B 28 c, "Evidence of specific antibody deficiency such as those to pneumococcal vaccine serotypes." ▪ In Item B 32, added "common variable immunodeficiency [CVID]" to read "Primary Humoral Immunodeficiencies (to include X-linked agammaglobulinemia [Burton] X-linked hyper-IgM syndrome, severe combined immunodeficiency [SCID], common variable immunodeficiency [CVID], Wiskott-Aldrich syndrome, and ataxis telangiectasia) with a history of significant recurrent infections and one of the following:" ▪ In Item B 32 b, added "polyvalent" and polysaccharide" to read, "The interpretation of response to polyvalent pneumococcal polysaccharide vaccine is as follows:" ▪ Removed Item D, 28, "organ transplant rejection;"
	Updated References section.
08-20-2015	Updated Description section.
	In Policy section: ▪ In Item B, added "Immune Thrombocytopenia", to read "Immune Thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) ▪ In Item B, removed "Immune Thrombocytopenic Purpura (ITP) In Pregnancy" ▪ In Item B, revised wording from "Following solid-organ transplant, treatment of antibody-mediated rejection." to read, "Antibody-mediated rejection, following solid organ transplant." ▪ Alphabetized Item B criteria. ▪ Alphabetized Item D criteria. In Policy Guidelines section: ▪ Moved information on Primary Humoral Immune Deficiency diseases, Assessing the immunologic response to vaccination, Assessing polysaccharide responses in adults and children over two years, and IgG subclass deficiency to Rationale section.
	Updated Rationale section.
	Updated References section.
01-01-2016	In Coding section: ▪ Added HCPCS code: J1575.
01-04-2017	Updated Description section.
	Updated Rationale section.
	Updated References section.
02-15-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added coding bullets.
	Updated References section.
10-01-2017	In Coding section: ▪ Added ICD-10 code: M33.93.
11-08-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
01-01-2018	In Coding section: ▪ Added HCPCS code: J1555. ▪ Updated coding bullets.
11-07-2018	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.

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