Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the
Blue Cross Blue Shield Association

Title: Immunoglobulin 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	**Institutional**
Original Effective Date: June 1, 1998	Original Effective Date: January 1, 2005
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; March 15, 2021; April 1, 2021; August 1, 2022	Revision Date(s): 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; March 15, 2021; April 1, 2021; August 1, 2022
Current Effective Date: August 1, 2022	Current Effective Date: August 1, 2022

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.

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

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

Populations	Interventions	Comparators	Outcomes
			• 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: • Who are preterm and low birth weight infants with sepsis	Interventions of interest are: • Intravenous immunoglobulin therapy (treatment)	Comparators of interest are: • Standard of care	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Hospitalizations • Treatment-related mortality

Populations	Interventions	Comparators	Outcomes
			• 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:	Comparators of interest are: • Standard of care	Relevant outcomes include: • Disease-specific survival • Change in disease status

Populations	Interventions	Comparators	Outcomes
	• Intravenous immunoglobulin therapy		• 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: • Subcutaneous 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 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

Populations	Interventions	Comparators	Outcomes
			• 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

Populations	Interventions	Comparators	Outcomes
			• Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With dermatomyositis or polymyositis	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 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

Populations	Interventions	Comparators	Outcomes
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 warm antibody 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
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

Populations	Interventions	Comparators	Outcomes
			• 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:	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms

Populations	Interventions	Comparators	Outcomes
	• Intravenous immunoglobulin therapy		• 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
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

Populations	Interventions	Comparators	Outcomes
			• 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 to treat an array of disorders, including primary and secondary immune deficiency states and various autoimmune and inflammatory disorders. Human immunoglobulin therapy provides a broad spectrum of opsonizing and neutralizing immunoglobulin G antibodies against a wide variety of bacterial and viral antigens. This evidence review addresses the use of human immunoglobulin therapy for preventing and/or treating disorders in inpatient and outpatient settings. Both intravenous immunoglobulin (IVIG) infusion and subcutaneous immunoglobulin (SCIG) infusion are addressed. However, the review 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 evidence review is to determine whether intravenous and subcutaneous immunoglobulin therapies as treatments for various autoimmune and nonautoimmune conditions improve net health outcomes.

BACKGROUND

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

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

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

REGULATORY STATUS

Several IVIG products have been approved by the U.S. Food and Drug Administration (FDA). These products include Asceniv® (ADMA Biologics), Bivigam® (ADMA Biologics), Flebogamma DIF® (Instituto Grifols), Gammagard Liquid® (Takeda), Gammagard S/D® (Takeda), Gammaked® (Kedrion Biopharma), Gammaplex® (Bio Products Lab), Gamunex-C® (Grifols Therapeutics), Octagam® (Octapharma), PANZYGA® (Pfizer), and Privigen® (CSL Behring).[3,] Several SCIG products have been approved by the FDA. They include Cutaquig® (Octapharma), CUVITRU® (Takeda), Gammagard Liquid (Takeda), Gammaked (Kedrion Biopharma),Gamunex-C (Grifols Therapeutics), Hizentra® (CSL Behring AG), Hyqvia® (Takeda), and Xembify® (Grifols Therapeutics).[3,]

At least 1 IVIG product is FDA approved to treat the following conditions[3,]:

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

TARGET DRUGS

Preferred Immune Globulin Agents	Nonpreferred Immune Globulin Agents
▪ Bivigam® 10% IVIG ▪ Carimune® NF IVIG ▪ Cutaquig 16.5% SCIG ▪ Cuvitru™ 20% SCIG ▪ Flebogamma® 5% DIF IVIG ▪ Flebogamma® 10% DIF IVIG ▪ Gammagard® S/D 5% IVIG ▪ Gammagard™ Liquid 10% SCIG/IVIG ▪ Gammaked™ Liquid 10% SCIG/IVIG ▪ Gammaplex® 5% Liquid IVIG ▪ Gammaplex® 10% Liquid IVIG ▪ Gamunex®-C 10% SCIG/IVIG ▪ Hizentra® 20% SCIG ▪ HyQvia™ 10% SCIG ▪ Octagam® 5% IVIG ▪ Octagam® 10% IVIG ▪ Panzyga 10% IVIG ▪ Privigen™ 10% IVIG ▪ Xembify 20% SCIG	▪ Asceniv™ 10% IVIG

POLICY

A. Immune Globulin therapy using a preferred agent 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. **Catastrophic Antiphospholipid Syndrome**

4. **Warm Antibody 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. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** with progressive symptoms for at least 2 months.

8. **Dermatomyositis, Polymyositis** intolerant or refractory to:
   a. Corticosteroids; **AND**
   b. Immuno-suppressants (e.g., methotrexate, azathioprine, cyclophosphamide, and cyclosporine).

9. **Erythrovirus (formerly Parvovirus) B19 Infection, chronic, with Severe Anemia**

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

11. **Guillain-Barré Syndrome (GBS)** as an equivalent alternative to plasma exchange.

12. **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).

13. **Hemolytic Disease of the Newborn**

14. **HIV Associated Polyneuropathy**

15. **HIV Associated Thrombocytopenia**

16. **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.

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

18. **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.

19. **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.

20. **Kawasaki Disease**

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

22. **Moersch-Woltmann (Stiff-Man) Syndrome** not controlled by other therapies.

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

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

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

26. **Myasthenia Gravis**
    a. Patients with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine.
    b. Patients with myasthenic exacerbation (ie, an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated.

27. **Primary Immunodeficiencies** (to include congenital agammaglobulinemia, 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 (e.g., 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 (e.g., 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.

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. **Toxic Shock Syndrome (Staphylococcal or Group A Streptococcus)**

35. **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).

36. **Toxic Necrotizing Fasciitis due to Group A Streptococcus**

37. **Wegener Granulomatosis**

B. Immune Globulin therapy using a nonpreferred agent may be considered **medically necessary** if:
   1. The condition and associated criteria otherwise meet section A (see above) **AND**
   2. One of the following has been met
      a. The patient has tried and had an inadequate response to **TWO** preferred agents (medical records required)**OR**
      b. The patient has an intolerance or hypersensitivity to **TWO** preferred agents that is NOT expected to occur with the requested agent (medical records required), **OR**
      c. The patient has an FDA labeled contraindication to ALL preferred that is NOT expected to occur with the requested agent (medical records required), **OR**
      d. Information has been provided in support of the use of the non-preferred agent over **TWO** preferred agents for the requested indication.

C. Intramuscular Immune Globulin is **not medically necessary** for the indications listed in this policy.

D. IVIG is considered **not medically necessary** as a treatment of relapsing / remitting **Multiple Sclerosis**.

E. **Subcutaneous Immunoglobulin Therapy**

1. Subcutaneous immunoglobulin therapy (SCIG) may be considered **medically necessary** for the following indications: Patients with primary immunodeficiencies, including congenital agammaglobulinemia, hypogammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich syndrome, and X-linked agammaglobulinemia.

2. Other applications of SCIG therapy are considered **experimental / investigational**, including but not limited to CIDP.

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

1. Acquired Factor VIII Inhibitors
2. Acute Myocarditis
3. Acute Lymphoblastic Leukemia
4. Adrenoleukodystrophy
5. Alzheimer's Disease
6. Aplastic Anemia
7. Asthma
8. Autism
9. Behcet's Syndrome
10. Birdshot Retinopathy
11. Chronic Fatigue Syndrome
12. Chronic Progressive Multiple Sclerosis
13. Chronic Sinusitis
14. Complex Regional Pain Syndrome
15. Crohn's Disease
16. Cystic Fibrosis
17. Immune Optic Neuritis
18. Demyelinating Polyneuropathy Associated With Igm Paraproteinemia
19. Diabetes Mellitus
20. Diamond-Blackfan Anemia
21. Epilepsy
22. Fisher Syndrome
23. Hemolytic Uremic Syndrome
24. Hemophagocytic Lymphohistiocytosis
25. Igg Sub-Class Deficiency
26. Immune-Mediated Neutropenia
27. Inclusion-Body Myositis
28. Necrotizing Fasciitis Not Due To Group A Streptococcus
29. Nonimmune Thrombocytopenia
30. Other Vasculitides Besides Kawasaki Disease and Wegener's Granulomatosis, including Polyarteritis Nodosa, Goodpasture's Syndrome, and Vasculitis Associated With Other Connective Tissue Diseases
31. Opsoclonus-Myoclonus

32. Paraneoplastic Syndromes
33. Paraproteinemic Neuropathy
34. Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)
35. Polyradiculoneuropathy (Other Than Chronic Inflammatory Demyelinating Polyneuropathy)
36. Postpolio Syndrome
37. Dilated Cardiomyopathy
38. Recurrent Otitis Media
39. Recurrent Spontaneous Abortion
40. Red Cell Aplasia
41. Refractory Recurrent Pericarditis
42. Refractory Rheumatoid Arthritis And Other Connective Tissue Diseases
43. Sepsis, including Neonatal Sepsis
44. Thrombotic Thrombocytopenic Purpura
45. Toxic Epidermal Necrolysis (Lyell's Syndrome) Or Stevens-Johnson Syndrome
46. Noninfectious Uveitis

G. **Continuation of therapy** may be approved up to 12 months if **ALL** of the following are met:
1. Documentation of positive clinical response to immune globulin therapy; **AND**
2. Statement of expected frequency and duration of proposed immune globulin treatment; **AND**
3. For long term treatment, documentation of titration to the minimum effective dose **AND**
4. Frequency needed to maintain a sustained clinical response; **AND**
5. Patient has no documented contraindications

POLICY GUIDELINES

Black Box Warnings and Precautions

For intravenous immunoglobulin (IVIG):

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

- For individuals at risk of renal dysfunction or renal failure, administer IVIG at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration.

Additional warnings and precautions include:

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

The subcutaneous immunoglobulin (SCIG) product information labels note that reactions similar to other immunoglobulin products may occur. The most common adverse events with subcutaneous injections include local reactions (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 prior immunization history. The following parameters are examples of criteria for the diagnosis of the primary immunodeficiency syndromes.

- Laboratory evidence of immunoglobulin deficiency may include the following definitions:
    - Agammaglobulinemia (total immunoglobulin G (IgG) <200 mg/dL)
    - Persistent hypogammaglobulinemia (total IgG <400 mg/dL, or at least 2 standard deviations below normal, on at least 2 occasions)
    - Absence of B lymphocytes.

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

Chronic Inflammatory Demyelinating Polyneuropathy

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) should have an established diagnosis based on criteria like those established by the American Academy of Neurology in 1991[1,] or those described in guidelines from the European Federation of Neurological Societies and the Peripheral Nerve Society, published in 2006 and updated in 2010.[2,] There is currently no criterion standard set of clinical or electrophysiologic criteria for the diagnosis of CIDP and its variants.

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

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.

RATIONALE

This evidence review has been updated regularly with a search of the PubMed database. The most recent literature update was performed through August 31, 2021

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

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

IMMUNODEFICIENCY STATES

Primary Humoral Immune Deficiencies

Clinical Context and Therapy Purpose

The purpose of intravenous immunoglobulin (IVIG) therapy and subcutaneous immunoglobulin (SCIG) therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary humoral immunodeficiency. Primary humoral immune deficiencies refer to diseases resulting from impaired antibody production because of a molecular defect intrinsic to B cells or a failure of interactions between B and T cells. Antibody deficiency characteristically leads to recurrent, often severe upper and lower respiratory tract infections. Findings associated with severe primary humoral immunodeficiencies include failure to thrive, chronic diarrhea, recurrent fever, nodular lymphoid hyperplasia in the gut, and hepatosplenomegaly.

Interventions

The therapies being considered are IVIG and SCIG.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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

For individuals with immunodeficiencies, both IVIG and SCIG are effective.[5,6,7,] Use of SCIG for the treatment of primary immunodeficiencies was approved by the U.S. Food and Drug Administration based on an open-label, nonrandomized, prospective, multicenter study.[5,] Generally, many 10% IVIG solutions can be administered subcutaneously or intravenously, but more concentrated products (e.g., 20%) should not be given intravenously. The subcutaneous route is associated with fewer systemic adverse events and provides more stable serum immunoglobulin G (IgG) levels. In contrast, SCIG has not been studied as extensively in autoimmune and inflammatory disorders.

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

HEMATOPOIETIC CELL TRANSPLANTATION (PROPHYLAXIS)

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

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

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

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

Interventions
The therapy being considered is IVIG therapy.

Comparators
Comparators of interest include standard of care.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews

A systematic review and meta-analysis by Raanani et al (2009) included 30 trials with 4223 patients undergoing HCT.[8,] There was no difference in all-cause mortality between IVIG and cytomegalovirus-IVIG compared with controls (relative risk [RR], 0.99; 95% confidence interval [CI], 0.88 to 1.12; RR, 0.86; 95% CI, 0.63 to 1.16, respectively). There was no difference in clinically documented infections with IVIG compared with control (RR, 1.00; 95% CI, 0.90 to 1.10). Reviewers concluded that routine IVIG prophylaxis in patients undergoing HCT was not associated with survival benefit or reduction in infection and therefore routine use of IVIG prophylaxis in patients undergoing HCT was not recommended.

Section Summary: Hematopoietic Cell Transplantation (Prophylaxis)

The evidence for IVIG for routine prophylaxis of infection in HCT consists of a systematic review and meta-analysis. Compared with the standard of care, IVIG for routine prophylaxis of infection in patients undergoing HCT was not associated with survival benefit or reduction in infection.

ACUTE ANTIBODY-MEDIATED REJECTION AFTER SOLID ORGAN TRANSPLANT

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are at risk of acute antibody-mediated rejection (ABMR) after a 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 PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

Comparators of interest include standard of care.

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

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

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

REVIEW OF EVIDENCE

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

Systematic Review
In 2019, Bourasssa-Blanchette and colleagues published a systematic review involving 18 trials (with 8 RCTs) investigating the impact of IVIG prophylaxis on infection, rejection, graft loss, and death following kidney transplantation.[9,] Results revealed that IVIG administration did not reduce cytomegalovirus infection (odds ratio [OR], 0.68; 95% CI: 0.39 to 1.21; 6 studies, n=295), rejection (OR, 0.96; 95% CI: 0.50 to 1.82; 4 studies, n=187), or graft loss (OR, 1.03; 95% CI: 0.46 to 2.30; 6 studies, n=265) in the RCTs. Among the included nonrandomized studies, IVIG administration was associated with a reduction in rejection and graft loss but not cytomegalovirus infection or death. The authors noted that the quality of included studies was variable with a high to very high risk of bias and that additional adequately powered RCTs are needed in order to determine if IVIG is an effective intervention.

Randomized Controlled Trials
In the National Institutes of Health (NIH)-sponsored IG02 study, 101 adults with a PRA screen of 50% or higher were randomized to IVIG 2 g/kg monthly for 4 months or placebo.[10,] If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reductions in PRA levels compared with placebo (35% vs. 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80% IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than a placebo in reducing anti-human leukocyte antigen antibody levels and improving transplantation rates in highly sensitized patients with end-stage renal disease. In a follow-up study, the combination of high-dose IVIG and B-cell depletion therapy reduced PRA from 77% to 44% at the time of transplantation.[11,]

Nonrandomized Studies

More recent studies have failed to show a reduction in PRA levels, specifically in patients with a PRA greater than 80%.[12,13,14,] Nonrandomized clinical observations have suggested that a combination of plasmapheresis plus low-dose IVIG and interleukin-2 blockade or rabbit anti-thymocyte globulin for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients.[15,16,17,]

Section Summary: Prophylaxis for Acute Antibody-Mediated Rejection After Solid Organ Transplant

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

TREATMENT

Systematic 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 the use of IVIG in the treatment of ABMR.[18,] A RCT by Casadei et al (2011) demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection[19,]; 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.[18,] According to Roberts et al (2012), 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 and a systematic review. According to a 2012 systematic review, the evidence for IVIG treatment of ABMR is very low (GRADE criteria). Compared with the standard of care, IVIG treatment for ABMR has shown potential benefits in retrospective or small prospective studies; however, larger RCTs with longer follow-up are needed to demonstrate improved health outcomes.

Chronic Lymphocytic Leukemia

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who have chronic lymphocytic leukemia (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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who have CLL with recurrent bacterial infections associated with hypogammaglobulinemia. Chronic lymphocytic leukemia is a disorder characterized by progressive accumulation of functionally incompetent lymphocytes; most patients develop hypogammaglobulinemia at some point in the course of their disease. Patients experiencing recurrent bacterial infections associated with hypogammaglobulinemia are likely to benefit from monthly infusions of IVIG.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Randomized Controlled Trials
Multiple trials and a meta-analysis comparing IVIG with placebo have shown decreased bacterial infections, but not decreased mortality.[20,21,22,23,24,25,] Use of IVIG has not been directly compared with prophylactic antimicrobials. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. Treatment with IVIG has not been shown to increase QOL or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both.[20,] Although minor or moderate bacterial infections were significantly less common in patients receiving IVIG, there was no impact on the incidence of major infections, mortality, or nonbacterial infections.

Section Summary: Chronic Lymphocytic Leukemia
The evidence for the use of IVIG therapy for prophylaxis of infection in CLL consists of multiple RCTs and a meta-analysis. Compared with placebo, IVIG treatment for recurrent bacterial infections associated with hypogammaglobulinemia in CLL patients has shown reductions in minor

and moderate infections without a reduction in other clinically important outcomes, including mortality.

INFECTIONS

HIV-INFECTED CHILDREN

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in children who have human immunodeficiency virus (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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is children with HIV infection and recurrent bacterial infections associated with hypogammaglobulinemia. Prevention of opportunistic infections remains a critical component of care for HIV-infected children even though the availability of combination antiretroviral therapies has substantially and dramatically decreased HIV-related opportunistic infections and deaths.

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

Randomized Controlled Trials

A 1991 double-blind RCT allocated 372 HIV-infected children to IVIG or placebo every 28 days.[26,] 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; $p<.05$); reduced overall the number of serious and minor bacterial infections (RR, 0.68; $p<.05$); and reduced the number of hospitalizations for acute care (RR, 0.65; $p<.05$). The effect was less marked in children with CD4-positive counts less than 0.2×10^9/L.

Subsection Summary: HIV-Infected Children
The evidence for the use of IVIG for prophylaxis of opportunistic infections in children with HIV consists of a single RCT. Compared with placebo, IVIG therapy for the prevention of opportunistic infections in HIV-infected children has shown reductions in minor and serious infections without a reduction in other clinically important outcomes, including mortality.

NEONATAL SEPSIS

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is infants who are preterm, low birth weight, and at risk for sepsis or who have sepsis. Preterm and low birth weight infants are prone to infection because of an immature immune system as well as increased exposure to nosocomial pathogens.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

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

REVIEW OF EVIDENCE

Prophylaxis

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 (e.g., lack of caregiver blinding in 10 studies). In a meta-analysis of 10 studies, IVIG was associated with a statistically significant reduction in sepsis (≥1 episodes; RR, 0.85; 95% CI, 0.75 to 0.98). Moreover, a meta-analysis of 16 studies showed a significant reduction in serious infection (≥1 episodes) with IVIG (RR, 0.82; 95% CI, 0.74 to 0.92). However, IVIG was not associated with a significant reduction in mortality. A meta-analysis of 15 studies that reported all-cause mortality found a RR of 0.89 (95% CI, 0.75 to 1.05), and a meta-analysis of 10 studies that reported mortality due to infection found a RR of 0.83 (95% CI, 0.56 to 1.22). Reviewers noted that a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without a reduction in other clinically important outcomes, including mortality, were of marginal clinical importance. No major adverse events related to IVIG administration were reported.

Subsection Summary: Prophylaxis of Neonatal Sepsis

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

TREATMENT

Systematic Reviews

A Cochrane review by Ohlsson and Lacy (2020) identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or confirmed infection. [28,] Studies included a total of 3,973 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 versus the control therapy (RR, 0.95; 95% CI, 0.80 to 1.13). Meta-analysis of 3 trials found that IVIG significantly reduced the length of the hospital stay compared with a control intervention (mean difference [MD], -4.08; 95% CI, -6.47 to -1.69). Results were not pooled for other outcomes.

Randomized Controlled Trials

The trial with a large sample size was published by the International Neonatal Immunotherapy Study group (2011); it was conducted in 9 countries.[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 (e.g., birthweight, gestational age at birth, sex) were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIG group (including 2 deaths) versus 10 in the placebo group (including 4 deaths).

Section Summary: Treatment of Neonatal Sepsis
The evidence for the use of IVIG treatment for suspected or confirmed infection in neonates consists of a systematic review and multiple RCTs. Compared with placebo, IVIG treatment for neonatal sepsis did not differ significantly in the rates of death or major disability.

SEPSIS IN ADULTS

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

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

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

Populations
The relevant population of interest is adults with sepsis.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
A meta-analysis by Busani et al (2016), which pooled 18 RCTs, showed that the use of IVIG reduced the mortality risk of septic patients by half (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 the widespread use of IVIG as adjunctive therapy for sepsis in adults.

Section Summary: Sepsis in Adults
The evidence for the use of IVIG treatment for sepsis in adults consists of a meta-analysis of 18 RCTs. Compared with placebo, IVIG treatment for adult sepsis showed reductions in mortality in the meta-analysis. However, multiple factors preclude recommending the routine use of IVIG to treat sepsis. These factors include the preponderance of small low-quality studies, the use of heterogeneous dosing regimens, types of IVIG preparations used, and changes over time in the management of sepsis.

SEVERE ANEMIA ASSOCIATED WITH HUMAN PARVOVIRUS B19

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

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

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

Populations
The relevant population of interest is individuals with 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.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Case Series

No controlled trials have evaluated IVIG for severe anemia associated with parvovirus B19. Only small case series and case reports are available.[31,32,33,] 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. Although observed improvements in outcomes have suggested potential benefits with IVIG therapy, data are retrospective. Randomized controlled trials are needed to demonstrate improved health outcomes.

TOXIC SHOCK SYNDROME

Clinical Context and Therapy Purpose

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

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

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

Populations

The relevant population of interest is patients with toxic shock syndrome. Toxic shock syndrome is also called Streptococcal toxic shock syndrome. Streptococcal toxins induce the release of inflammatory cytokines, which cause capillary leakage and tissue damage resulting in shock, multiorgan failure, and death.

Interventions

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

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

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

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

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

REVIEW OF EVIDENCE

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.[36,37,38,39,] The RCT by Darenberg et al (2003) allocated 21 adults with toxic shock syndrome to IVIG or 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 a placebo.[36,] The odds for survival were 5.6 for IVIG versus placebo (p=.03). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls.[37,38,] While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups poses difficulties when interpreting the results. A retrospective study by Shah et al (2009), which included 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG.[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. Compared with placebo, IVIG treatment for toxic shock syndrome in patients has shown reductions in mortality in a small RCT and in multiple observational studies.

AUTOIMMUNE AND INFLAMMATORY CONDITIONS

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with idiopathic thrombocytopenia purpura (ITP).

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

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

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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, the mean number of days with a platelet count greater than $50x10^9$/L at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG versus corticosteroids)[42,] and 1 randomized (IVIG alone versus oral prednisone alone versus IVIG plus oral

prednisone)[43,] found no differences in platelet counts greater than $50x10^9$/L at 48 hours or in response rates between groups, respectively.

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

GUILLAIN-BARRÉ SYNDROME

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Guillain-Barré syndrome (GBS).

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

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

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

REVIEW OF EVIDENCE

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 (1 compared IVIG plus immunoabsorption with immunoabsorption only). Four trials included adults only, 5 included children only, 1 included both, and 2 included adults and possibly children. The primary outcome of the review was change in disability level (using a 7-grade disability scale) after 4 weeks. A pooled analysis of 7 trials comparing IVIG with plasma exchange did not find significant differences between groups in change in the number of disability grades at 4 weeks (MD, -0.02; 95% CI, -0.25 to 0.20). There were also no significant differences in other outcome measures for IVIG versus plasma exchange (e.g., number of patients who improved by ≥1 grades). There were insufficient data to pool results for comparisons of IVIG with other interventions or for subgroup analysis by age. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR, 0.14; 95% CI, 0.05 to 0.36).

Most trials in this review had small sample sizes. The largest was a 1997 multicenter, randomized trial of 383 adults that compared IVIG, plasma exchange, and combination IVIG plus plasma exchange.[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 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
For individuals who have GBS who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes.

KAWASAKI DISEASE

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

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

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

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

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

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

REVIEW OF EVIDENCE

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 MD 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 symptom onset.

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

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER GRANULOMATOSIS)

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG for maintenance therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
The success of IVIG therapy for Kawasaki disease led to a study of IVIG therapy for other vasculitides such as Wegener granulomatosis. A Cochrane review by Fortin et al (2013) identified 1 RCT on IVIG for Wegener granulomatosis.[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)
For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes a systematic review with a single relevant RCT. This small trial found significantly more responders in the IVIG treatment group at 3 months, but no significant differences after 3 months, or in the frequency of relapse or use of other medications.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Clinical Context and Therapy Purpose
The purpose of IVIG and SCIG therapies is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

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

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

Populations
The relevant population of interest is individuals with CIDP. Chronic inflammatory demyelinating polyneuropathy is an acquired neurologic disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder is caused by damage to the myelin sheath of the peripheral nerves. The disease is difficult to diagnose due to its heterogeneous presentation (both clinical and electrophysiological).

Interventions
The therapies being considered are IVIG and SCIG.

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

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

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

REVIEW OF EVIDENCE

INTRAVENOUS IMMUNOGLOBULIN 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, corticosteroids, or plasma exchange. Three trials compared IVIG with another active

treatment,[51,52,53,] and the other 5 were placebo-controlled (n=235).[54,55,56,57,58,] 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<.001). When data were pooled from 3 studies on IVIG versus placebo in which the disability measures could be converted to the Rankin Scale, the RR was similar (2.40), but not statistically significant (95% CI, 0.98 to 5.83; p=.054). Pooled analyses of data from these 3 placebo-controlled trials found a statistically higher rate of any adverse event with IVIG, but no serious adverse events. Data from studies comparing IVIG with active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

Randomized Controlled Trials

The ICE study reported by Hughes et al (2008), the largest included in the meta-analysis, was a double-blind, multicenter trial that randomized 117 patients to IVIG or placebo.[58,] The primary outcome measure was the proportion of patients showing clinically meaningful reductions in disability at week 24. Results showed that the proportion of patients meeting the primary endpoint was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase were 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: Intravenous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy

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

Subcutaneous Immunoglobulin Therapy

In the randomized, double-blind, placebo-controlled, phase 3 PATH trial, van Schaik et al (2018) studied relapse rates in 172 patients with CIDP given SCIG and placebo.[59,] Patients were randomized in a 1:1:1 ratio to a placebo group (n=57 [33%]), a low-dose group (n=57 [33%]), and a high-dose group (n=57 [33%]). The trial found that both SCIG doses were effective and well-tolerated, suggesting that SCIG can be used as maintenance treatment for CIDP. Seventy-seven patients withdrew from the trial due to relapse or other reasons: 36 (63%; 95% CI, 50% to 74%) placebo patients, 22 (39%; 95% CI, 27% to 52) low-dose SCIG patients, and 19 (33%; 95% CI, [22% to 46) high-dose patients (p<.001). The trial was limited by missing patient data and inadequate follow-up of those who withdrew.

One crossover RCT comparing IVIG and SCIG for CIDP was identified; this trial by Markvardsen et al (2017) included 20 patients.[60,] 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: Subcutaneous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy
For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Only 1 RCT has directly compared SCIG with IVIG in patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (e.g., 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIDP might be effective, with relatively low adverse events, but this trial also had a number of limitations (e.g., small sample, 30% dropout rate).

MULTIFOCAL MOTOR NEUROPATHY

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with multifocal motor neuropathy (MMN).

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

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

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

Interventions

The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
Van Schaik et al (2005) included 4 RCTs (N=34 patients) in a meta-analysis to assess the efficacy and safety of IVIG in MMN.[61,] Strength improved in 78% of patients treated with IVIG versus 4% in placebo-treated patients. Disability was reduced by 39% and 11%, respectively (p value nonsignificant). 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 (N=53 patients).[62,63,64,65,] 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 score in 28 muscles; a responder was defined as at least 1 more Medical Research Council 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
For individuals who have MMN who receive IVIG therapy, the evidence includes multiple RCTs and a meta-analysis. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength.

EATON-LAMBERT MYASTHENIC SYNDROME

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with 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.

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

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

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

REVIEW OF EVIDENCE

Randomized Controlled Trials
A crossover RCT by Bain et al (1996) evaluating 9 patients treated with IVIG therapy (1 g/kg/d for 2 days) or placebo showed statistically significant improvements in serial measurements of limb, respiratory, and bulbar muscle strength associated with treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude.[66,]

Observational Studies
A number of noncomparative studies have substantiated clinical benefits.[67,68,69,70,]

Section Summary: Eaton-Lambert Myasthenic Syndrome
For individuals who have Eaton-Lambert myasthenic syndrome who receive IVIG therapy, the evidence includes a RCT and multiple observational studies. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in outcomes assessing muscle strength and activity.

NEUROMYELITIS OPTICA

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

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

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

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

Interventions

The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Observational Studies
A retrospective review by Elsone et al (2014) of 10 patients treated with IVIG for acute relapses after lack of response to steroids with or without plasma exchange showed improvement in about 50% of patients.[71,] 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.[72,]

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

SEVERE REFRACTORY MYASTHENIA GRAVIS OR MYASTHENIC EXACERBATION

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant populations of interest are individuals with severe refractory myasthenia gravis or myasthenic exacerbation. Myasthenia gravis is a relatively rare autoimmune disorder in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular

junction of skeletal muscles resulting in characteristic patterns of progressively reduced muscle strength with repeated use and recovery of muscle strength after a period of rest.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
A Cochrane review by Gadjos et al (2012) assessed IVIG therapy for acute exacerbations or for chronic long-term myasthenia gravis.[73,] Reviewers identified 7 RCTs including an unpublished trial, all of which investigated short-term benefit. The trials varied in inclusion criteria, comparator interventions, and outcome measures and, thus, trial findings were not pooled. Five trials evaluated IVIG for treating myasthenia gravis worsening or exacerbation, and 2 evaluated IVIG for treatment of moderate or severe myasthenia gravis. Several trials were small, with insufficient statistical power. Reviewers concluded that there was some evidence for efficacy in exacerbations of myasthenia gravis, and that evidence for treating chronic myasthenia gravis was insufficient to form conclusions about efficacy.

Randomized Controlled Trials
Zinman et al (2007) conducted the only RCT that compared IVIG with placebo in 51 patients who had myasthenia gravis with progressive weakness.[74,] 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.[75,] 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.[76,] 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.[77,] The trial also did not find a statistically significant difference in the efficacy between the 2 treatments; however, the trial did report that IVIG was better tolerated. Nine patients experienced adverse events (8 in the plasma exchange group, 1 in the IVIG group).

Section Summary: Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation
For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Compared with placebo, IVIG therapy has shown clinically meaningful reductions in disability and improvements in muscle strength. Compared with plasma exchange, IVIG therapy did not show significantly improved outcomes but was better tolerated.

RELAPSING-REMITTING MULTIPLE SCLEROSIS

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with relapsing-remitting multiple sclerosis (RRMS).

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

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

Populations
The relevant population of interest is individuals with RRMS. Relapsing-remitting multiple sclerosis is an immune-mediated inflammatory disease that attacks and destroys myelinated axons in the central nervous system, resulting in variable degrees of physical disability characterized by symptomatic episodes that occur months or years apart and affect different anatomic locations.

Interventions
The therapy being considered is IVIG therapy.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

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

REVIEW OF EVIDENCE

Systematic Reviews
Based on a technology assessment by Goodin et al (2002), the American Academy of Neurology (AAN) recommended the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation) for the treatment of RRMS.[78,] The AAN suggested that IVIG was no longer considered a drug of choice for RRMS.

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

AUTOIMMUNE MUCOCUTANEOUS BLISTERING DISEASES

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with autoimmune mucocutaneous blistering diseases. Autoimmune mucocutaneous blistering diseases are a group of conditions that manifest with blisters on the skin or mucous membranes and include pemphigus vulgaris, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, and linear IgA dermatosis.

Interventions
The therapy being considered is IVIG therapy.

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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).[79,] 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.[80,] The IVIG group received 400 mg/kg/d for 5 days and the placebo group received saline for 5 days. The primary endpoint was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant (p=.089). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15 (p=.041). In patients with severe disease, there were significantly lower DAS scores in the IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.

Another RCT by the same research group was published by Amagai et al (2009); this study was multicenter, placebo-controlled and double-blind in design and included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥20 mg/d).[81,] Patients were randomized to a single cycle of IVIG 400 mg/kg/d for 5 days, IVIG 200 mg/kg/d for 5 days or a placebo infusion for 5 days. The primary endpoint was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (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

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

TOXIC EPIDERMAL NECROLYSIS AND STEVENS-JOHNSON SYNDROME

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with toxic epidermal necrolysis (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 PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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.[82,] Three of the studies had control groups and 2 of these included historical controls. Intravenous immunoglobulin was not found to reduce mortality in TEN or SJS. The pooled standardized mortality ratio in the 10 studies was 1.00 (95% CI, 0.76 to 1.32, p=.67). A meta-analysis by Barron et al (2015) also did not demonstrate a survival advantage of IVIG for TEN and/or SJS.[83,]

Section Summary: Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

For individuals who have TEN or SJS who receive IVIG therapy, the evidence includes systematic reviews of observational studies. No RCTs 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.

IDIOPATHIC INFLAMMATORY MYOPATHIES

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with dermatomyositis, 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 PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with dermatomyositis, polymyositis, or inclusion body myositis. Polymyositis and dermatomyositis involve weakness of the proximal muscles such as the muscles of the hips and thighs, upper arms, and neck. Dermatomyositis is associated with various characteristic skin manifestations. In inclusion body myositis, the muscles most affected are those of the wrists and fingers and the front of the thigh.

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

DERMATOMYOSITIS AND POLYMYOSITIS

Systematic Reviews

Wang et al (2012) published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis.[84,] Reviewers identified 14 studies including 2 RCTs, 9 prospective case series, and 3 retrospective case series. Eleven of the 14 studies included patients with refractory disease. For example, a trial by Dalakas et al (1993) compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis.[85,] At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified Medical Research Council scale (84.6 IVIG versus 78.6 placebo) and the Neuromuscular Symptom Scale (51.4 IVIG versus 45.7 placebo). Repeated transfusions every 6 to 8 weeks can be required to maintain a benefit.

Randomized Controlled Trials

Miyasaka et al (2012) in Japan conducted a RCT of 26 patients with corticosteroid-resistant polymyositis or dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month.[86,] Patients were randomized to IVIG (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary endpoint 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.

Section Summary: Dermatomyositis and Polymyositis

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes a systematic review and RCTs. In a RCT, compared with placebo, IVIG therapy showed significant improvements in muscle strength.

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.[87,] There was no statistically significant improvement in overall muscle strength in the IVIG group compared with the placebo group. Two more RCTs published in 2000 and 2001 (58 IVIG patients) also found no significant functional improvement when IVIG treatment was compared with placebo.[88,89,]

Section Summary: Inclusion Body Myositis

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

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Context and Therapy Purpose

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

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

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

Populations
The relevant population of interest is individuals with SLE. Systemic lupus erythematosus is a chronic autoimmune inflammatory disease and follows a relapsing and remitting course. It is characterized by an autoantibody response to nuclear and cytoplasmic antigens and can affect any organ system, but mainly attacks the skin, joints, kidneys, blood cells, and nervous system.

Interventions
The therapy being considered is IVIG therapy. Intravenous immunoglobulin 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, QOL, and treatment-related mortality and morbidity. Follow-up at 6, 12, and 24 months is of interest to monitor outcomes.

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

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

REVIEW OF EVIDENCE

Systematic Reviews
A systematic review by Sakthiswary et al (2014) identified 13 studies on IVIG for the treatment of SLE.[90,] Three studies had control groups, and only 1 was an RCT.[91,] Most studies were small; only 3 had more than 50 patients, and the single RCT included only 14 patients. In a meta-analysis of 6 studies (N=216 patients), there was a statistically significant difference in SLE disease activity in IVIG-treated groups (standardized mean difference=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.[92,]

Section Summary: Systemic Lupus Erythematosus

For individuals who have SLE who receive IVIG therapy, the evidence includes a systematic review of multiple studies. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are mainly retrospective. More RCTs are needed to demonstrate improved health outcomes.

IMMUNE OPTIC NEURITIS

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

Randomized Controlled Trials

Two RCTs have evaluated the potential benefit of IVIG for immune optic neuritis. Roed et al (2005) randomized 68 patients in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34).[93,] The authors found no differences in the visual outcome measure or disease activity as measured by magnetic resonance imaging after 6 months.

Noseworthy et al (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo.[94,] 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=.766).

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

CROHN DISEASE

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with 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.

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

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

REVIEW OF EVIDENCE

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.[95,] 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
For individuals who have Crohn disease who receive IVIG therapy, the evidence includes multiple case reports of single patients summarized in a systematic review.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with hemophagocytic lymphohistiocytosis. Hemophagocytic lymphohistiocytosis is an uncommon but potentially fatal syndrome of excessive immune activation resulting from overactive histiocytes and lymphocytes. It may be inherited or acquired.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

REVIEW OF EVIDENCE

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.[96,] Steroids were the most common treatment. Intravenous immunoglobulin 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.[97,98,99,]

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

WARM ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIA

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with warm antibody hemolytic anemia, refractory to prednisone and splenectomy. Also known as autoimmune hemolytic anemia, warm antibody autoimmune hemolytic anemia occurs commonly due to IgG antibodies that react with protein antigens on the red blood cell surface at body temperature.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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[100,] and a case report.[101,] 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

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data and a case report. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select patients with refractory autoimmune hemolytic anemia. Randomized controlled trials are needed to demonstrate improved health outcomes.

ANTIPHOSPHOLIPID SYNDROME

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with antiphospholipid syndrome. Antiphospholipid syndrome is an autoimmune disease that results from the development of an antibody against phospholipid proteins, which causes venous or arterial thromboses and/or pregnancy morbidity.

Interventions

The therapy being considered is IVIG therapy.

Comparators

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

Outcomes

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

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

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

REVIEW OF EVIDENCE

Case Reports
Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry.[102,] Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received therapy with anticoagulants, corticosteroids, plasma exchange, and/or IVIG compared with combinations that did not use plasma exchange, IVIG, or both.

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

ALLOIMMUNE PROCESSES

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is neonates with alloimmune thrombocytopenia. Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet-antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage (ICH) occurs in 10% to 30% of affected neonates. Currently, 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.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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.[103,] Reviewers concluded that the optimal management of fetomaternal alloimmune thrombocytopenia remains unclear. Lack of complete data sets for 2 trials and differences in interventions precluded the pooling of data from these trials.

Randomized Controlled Trials
Paridaans et al (2015) evaluated the effectiveness of a lower dose of IVIG (0.5 g/kg/wk versus 1 g/kg/wk) in an RCT of 23 women.[104,] The primary outcome was fetal or neonatal ICH. The median newborn platelet count was 81×10^9/L in the 0.5-g/kg group and 110×10^9/L in the 1-g/kg group (p=.644).

Berkowitz et al (2007) showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies.[105,] 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.[106,]

Bussel et al (1996) did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids.[107,] Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because the natural history of the disease suggests that subsequent births should be similar, if not more severely, affected with thrombocytopenia. The trial reported a mean increase in platelet count of 69,000/mL. There were no instances of ICH, although hemorrhage had occurred previously in 10 untreated siblings.

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

Section Summary: Neonatal Alloimmune Thrombocytopenia
For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple RCTs and a systematic review. Compared with combination use with corticosteroids, IVIG alone did not show any additional increases in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy.

RECURRENT SPONTANEOUS ABORTION

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

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

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

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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.[108,] Meta-analyses published in 2015 and 2016 that included 11 RCTs also found no significant difference in the number of live births with IVIG versus placebo or treatment as usual.[109,110,]

Randomized Controlled Trials

An RCT by Christiansen et al (2002) evaluated 58 women with at least 4 unexplained miscarriages and compared IVIG with placebo.[111,] Using an intention to treat analysis, the live birth rate was similar for both groups; also, there were no differences in neonatal data (e.g., birth weight, gestational age at delivery).

Likewise, a multicenter RCT by Branch et al (2000) compared heparin plus low-dose aspirin with or without IVIG in women with a lupus anticoagulant, anticardiolipin antibody, or both, and found no significant differences.[112,]

A blinded RCT by Jablonowska et al (1999) assessing 41 women treated with IVIG or saline placebo also found no differences in live birth rates.[113,]

Section Summary: Recurrent Spontaneous Abortion

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

MISCELLANEOUS INDICATIONS

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

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

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

Populations

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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.[114,] After a 6-week double-blind treatment phase, nonresponders could continue treatment on an open-label basis. The primary outcome at 6 weeks, the Children's Yale-Brown Obsessive Compulsive Scale total score, did not differ significantly between groups. There was a mean decrease in the Children's Yale-Brown Obsessive Compulsive Scale of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvements in other outcomes (e.g., mean Clinical Global Impressions improvement scores) also did not differ significantly between groups. A total of 24 participants met the criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the Children's Yale-Brown Obsessive Compulsive Scale improved significantly compared with 6 weeks; however, the 12-week analysis did not include a placebo comparison.

An RCT by Perlmutter et al (1999) included 30 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections.[115,] Patients were randomized to IVIG, plasma exchange, or placebo (10 per group). At the 1-month follow-up, IVIG and plasma exchange showed statistically significant improvements in obsessive-compulsive symptoms, anxiety, and overall functioning.

Section Summary: Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections
For individuals who have PANDAS who receive IVIG therapy, the evidence includes 2 small RCTs. The trials had mixed findings and both had small sample sizes and short intervention duration.

AUTISM SPECTRUM DISORDER

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with an 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with an autism spectrum disorder. Autism spectrum disorder is a neurodevelopmental disorder characterized by deficits in social communication and interaction and restricted repetitive patterns of behavior, interests, and activities.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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.[116,] 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.[117,] No improvements were observed in the third series.[118,]

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

Section Summary: Autism Spectrum Disorder

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

COMPLEX REGIONAL PAIN SYNDROME

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with complex regional pain syndrome (CRPS).

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

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

Populations
The relevant population of interest is individuals with CRPS. Complex regional pain syndrome is defined as a disorder of the extremities characterized by regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesions.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

REVIEW OF EVIDENCE

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.[119,] Intravenous immunoglobulin 0.5 g/kg of body weight or saline placebo on days 1 and 22 were administered after 111 patients were randomized. An 11-point (0- to 10-point) rating scale was used to measure the primary outcome of 24-hour average pain intensity. Mean pain scores were 6.9 points for placebo and 7.2 points for IVIG at 6 weeks

demonstrating that low-dose immunoglobulin treatment was not effective in relieving pain in moderate-to-severe CRPS.

Goebel et al (2010) reported on the use of IVIG treatment for CRPS in a crossover, double-blind RCT conducted at an academic pain management center in the U.K.[120,] The trial randomized 13 patients refractory to standard treatment to IVIG or normal saline. Median daily pain intensity score for each 14-day period was 6.21 after IVIG infusion versus 7.35 after saline infusion, a difference of 1.14 points. Trialists reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; p<.001).

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

ALZHEIMER DISEASE

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

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

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

Populations
The relevant population of interest is individuals with AD.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trials

Three placebo-controlled, double-blind, randomized trials in patients with AD were identified. Two included patients with mild-to-moderate AD. Relkin et al (2017) reported on 390 patients treated with 1 of 2 doses of IVIG (0.2 or 0.4 g/kg every 2 weeks for 18 months) or placebo.[121,] The primary outcomes were a change from baseline to 18 months on the cognitive subscale of the Alzheimer Disease Assessment scale and on the Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory. Neither outcome was significantly improved in either IVIG group compared with the placebo group.

Kile et al (2017) assessed 50 patients with mild cognitive impairment (MCI) related to AD.[122,] 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 2 g/kg over 5 sessions, or placebo. The primary outcome was brain atrophy, defined as annualized percent change in the ventricular volume measured by MRI. In unadjusted analyses, annualized percent change in the ventricular volume did not differ significantly between groups at 12 or 24 months. In a subgroup analysis, the annualized percent change in the ventricular volume was significantly lower in the IVIG compared with the placebo group in patients with early MCI but not late MCI at 12 months, and there was no significant difference at 12 months in either the early or late MCI groups. Secondary outcomes, cognition scores, and conversion to AD dementia did not differ between the IVIG and placebo groups at 12 or 24 months. As with the primary outcome, for several secondary outcomes, IVIG showed a significant benefit in the early MCI group at 12 months, but not 24 months.

In a trial by Dodel et al (2013) with 56 patients, the primary outcome (area under the curve of plasma amyloid β 1-40) did not differ between the IVIG and the placebo groups.[123,] Secondary outcomes, including cognitive and functional scales, also did not differ between groups.

Section Summary: Alzheimer Disease

For individuals who have AD who receive IVIG therapy, the evidence includes 3 RCTs. With the exception of a few subgroup analyses using MCI status, IVIG therapy was not significantly better than a placebo for outcomes such as brain atrophy, level of plasma amyloid β 1-40, or cognition and function. Studies differed by treatment protocols, outcomes assessed, and 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI.

PARAPROTEINEMIC NEUROPATHY

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with paraproteinemic neuropathy. Paraproteinemic neuropathy is a heterogeneous set of neuropathies characterized by the presence of paraproteins, which are immunoglobulins produced in excess by an abnormal clonal proliferation of B lymphocytes or plasma cells. Paraproteinemic neuropathy may be caused by the interaction of antibodies with specific antigenic targets on peripheral nerves or by deposition of immunoglobulins or amyloid.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Randomized Controlled Trials
An RCT by Comi et al (2002) focused on short-term outcomes at 2 weeks in 22 patients.[124,] 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) comparing IVIG with placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients.[125,]

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

CHRONIC FATIGUE SYNDROME

Clinical Context and Therapy Purpose

The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

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.[126,]

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

ACUTE MYOCARDITIS

Clinical Context and Therapy Purpose

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

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

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

Populations
The relevant population of interest is individuals with acute myocarditis. Acute myocarditis is a sudden inflammation of the myocardium that can occur in individuals of all ages. It is presumed to start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear whether the primary problem is ongoing damage from a virus, a postinfectious inflammatory reaction, or a combination of the 2.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
The literature has been summarized in a Cochrane review by Robinson et al (2015)[127,], updated in 2020[128,], that included a 2001 placebo-controlled, randomized trial of 62 adults with recent-onset dilated cardiomyopathy[129,], a randomized, multicenter trial in Japan of 41 adults with a clinical diagnosis compatible with acute myocarditis[130,], and a randomized, placebo-controlled study from Egypt in 86 children with acute onset dilated cardiomyopathy.[131,] The overall certainty of the included evidence was very low, with an unclear risk of bias in the 2 adult studies and a low risk of bias in the pediatric study. In adults, the evidence regarding the effect of IVIG on event-free and overall survival is uncertain (event free survival: risk ratio: 1.76; 95% CI, 0.48 to 6.40 and overall survival: pooled risk ratio: 0.91; 95% CI, 0.23 to 3.62). For the pediatric study, the evidence for overall survival was also uncertain (risk ratio of death: 0.48; 95% CI, 0.20 to 1.15).

Huang et al (2019) published a meta-analysis assessing IVIG for patients with acute myocarditis.[132,] Thirteen studies (1534 participants), published between 1994 and 2017, were included. In-hospital mortality rates (pooled results: OR 0.44, 95% CI 0.17-0.71, p<.001) were significantly reduced for the IVIG group compared with patients who did not receive IVIG, and left ventricular ejection fraction (OR 1.73, 95% CI 1.34–2.13, p<.001) was significantly increased for IVIG. The study was limited by the IVIG doses not being uniformly predefined and by the limited follow-up durations (mainly between 6 and 12 months) across the included studies.

Retrospective Studies
Heidendael et al (2017) reported on 94 children with new-onset dilated cardiomyopathy in a retrospective cohort study with a median follow-up of 33 months.[133,] 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=.045), however, the HR for recovery with IVIG was not significant (HR=2.1; 95% CI, 1.0 to 4.6; p=.056) after correction for possible cofounders. The authors concluded that IVIG treatment was associated with better improvement of systolic left ventricular function and better recovery, but did not influence transplant-free survival.

Section Summary: Acute Myocarditis
For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes a meta-analysis, RCTs, and a retrospective study. Results from a Cochrane review concluded that, after pooling the available data, there was uncertain evidence of the effect of IVIG in preventing deaths. More RCT evidence is required before IVIG can be routinely recommended in the setting of myocarditis.

REFRACTORY RECURRENT PERICARDITIS

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with refractory recurrent pericarditis. Refractory recurrent pericarditis is defined as recurrent pericarditis not responding to conventional anti-inflammatories such as aspirin, nonsteroidal inflammatory drugs, corticosteroids, and colchicine.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
Imazio et al (2016) conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports).[134,] Approximately 47% of patients had idiopathic recurrent pericarditis, 10% had an infective cause, and the remainder had a systemic inflammatory disease. Intravenous immunoglobulin was generally administered at a dose of 400 to 500 mg/kg/d for 5 consecutive days, with repeated cycles according to clinical response. Overall, recurrence occurred in 26.6% of cases after the first IVIG cycle, and 22 (73.3%) of the 30 patients were recurrence-free after a mean follow-up of approximately 33 months.

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

STIFF-PERSON SYNDROME

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Randomized Controlled Trial
The benefit of IVIG in stiff-person syndrome was confirmed in a small randomized crossover study by Dalakas et al (2001), which compared IVIG with placebo in 16 patients who had stiff-person syndrome and anti-GAD65 autoantibodies, who were maintained on current doses of benzodiazepines throughout the study.[135,] 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
For individuals who have stiff-person syndrome who receive IVIG therapy, the evidence includes a small randomized crossover study. Compared with placebo, IVIG therapy has shown decreases in stiffness scores and improvements in functional outcomes.

NONINFECTIOUS UVEITIS

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Case Series
Two small case series of 18 and 10 patients, respectively, have reported measurable improvements in visual acuity after IVIG therapy.[136,137,] Collectively, these 2 studies represent insufficient evidence to draw conclusions about efficacy.

Section Summary: Noninfectious Uveitis
For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. The case series reported measurable improvements in visual acuity after IVIG therapy, but controlled studies are needed to draw conclusions about the efficacy of IVIG for this population.

POSTPOLIO SYNDROME

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is IVIG therapy.

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

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

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

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

REVIEW OF EVIDENCE

Systematic Reviews
Huang et al (2015) published a systematic review and meta-analysis of RCTs and nonrandomized prospective studies on IVIG treatment of the postpolio syndrome.[138,] Reviewers identified 3 RCTs (n=241 patients) and 5 prospective studies (n=267 patients). The primary outcomes of interest were the severity of pain, fatigue, and change in muscle strength 2 to 3 months after IVIG administration. Meta-analyses of RCT data found no statistically significant differences between IVIG- and placebo-treated groups for any of these outcomes. For example, the pooled MD 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 MD of 0.28 (95% CI, -1.56 to 1.12). The small number of RCTs and the negative findings of this systematic review represent insufficient evidence of the efficacy of IVIG for the postpolio syndrome.

Section Summary: Postpolio Syndrome
For individuals who have postpolio syndrome who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs and nonrandomized prospective studies. Compared with

placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength.

NECROTIZING FASCIITIS

Clinical Context and Therapy Purpose
The purpose of IVIG therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with necrotizing fasciitis.

Interventions
The therapy being considered is IVIG therapy.

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

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

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

REVIEW OF EVIDENCE

Randomized Controlled Trials
Madsen et al (2017) published a placebo-controlled, randomized trial evaluating IVIG for patients with necrotizing soft tissue infection (e.g., necrotizing fasciitis).[139,] The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admission to the intensive care unit. The primary outcome was patient-reported physical function at 6 months, assessed using the Physical Component Summary score of the 36-Item Short-Form Health Survey. The mean Physical Component Summary score adjusted for the site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant

(p=.81). Other outcomes (ie, mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

Section Summary: Necrotizing Fasciitis
For individuals who have necrotizing fasciitis who receive IVIG therapy, the evidence includes a RCT. The RCT found that, compared with placebo, IVIG therapy did not significantly improve functional outcomes, mortality rates, or other outcomes (e.g., the use of life support in the intensive care unit). Additional controlled studies are needed to draw conclusions about the efficacy of IVIG for treating necrotizing fasciitis.

SUMMARY OF EVIDENCE

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

For individuals who are undergoing hematopoietic cell transplantation who receive IVIG therapy (prophylaxis), the evidence includes a systematic review and meta-analysis. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG for routine prophylaxis of infection in patients undergoing hematopoietic cell transplantation was not associated with survival benefit or reduction in infection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are at risk of acute antibody-mediated rejection after solid organ transplants who receive IVIG therapy, the evidence consists of a systematic review, NIH-sponsored RCT, and nonrandomized observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. The systematic review involving variable quality studies with high to very high risk of bias concluded that there is insufficient data to support or advise against the use of IVIG prophylaxis in solid organ transplant. More adequately powered RCTs are needed. Additionally, studies have shown conflicting results that prophylaxis with IVIG in patients with high PRA levels prior to solid organ transplant leads to a significant reduction in PRA levels. Compared with the standard of care, IVIG for prophylaxis of infection in patients with high PRA levels was not consistently associated with a survival benefit or reduction in infection. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute antibody-mediated rejection after solid organ transplants who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, hospitalizations, and treatment-related mortality and morbidity. Compared with the standard of care, IVIG treatment for antibody-mediated rejection has shown potential benefits in retrospective or small prospective studies; however, larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who are preterm and low birth weight infants and at risk for sepsis who receive IVIG therapy (prophylaxis), the evidence includes a Cochrane review involving multiple RCTs. Relevant outcomes are OS, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prophylaxis of neonatal sepsis has shown a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection (considered of marginal clinical importance) with no improvement in any of the other clinically important outcomes, including mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who have severe anemia associated with human parvovirus B19 who receive IVIG therapy, the evidence includes case series. Relevant outcomes are a change in disease status, treatment-related mortality, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefits with IVIG therapy, data are retrospective. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence

is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Autoimmune and Inflammatory Conditions
For individuals who have ITP who receive IVIG therapy, the evidence includes multiple RCTs and noncomparative studies. Relevant outcomes are DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with corticosteroids, IVIG therapy improved platelet counts. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have GBS who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs. Relevant outcomes are OS, DSS, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with plasma exchange or combination therapy with plasma exchange, IVIG therapy showed similar outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

For individuals who have CIDP who receive SCIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Only 1 RCT has directly compared SCIG with IVIG in

patients who had CIDP and conclusions about the relative efficacy of the treatments cannot be drawn due to methodologic limitations (e.g., 45% of patients withdrew from the trial). The other RCT demonstrated that the use of SCIG for the maintenance of CIDP might be effective, with relatively low adverse events, but this trial also had a number of limitations (e.g., small sample, 30% dropout rate). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

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

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

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

For individuals who have toxic epidermal necrolysis or Stevens-Johnson syndrome who receive IVIG therapy, the evidence includes systematic reviews of observational studies. Relevant outcomes are DSS, symptoms, change in disease status, morbid events, QOL, and treatment-related mortality and morbidity. No RCTs have evaluated IVIG for toxic epidermal necrolysis or Stevens-Johnson syndrome; most trials that have, have been uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes a systematic review and RCTs. Relevant outcomes are a change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. In 1 of the RCTs, compared with placebo, IVIG therapy showed significant improvements in muscle strength. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have SLE who receive IVIG therapy, the evidence includes a systematic review of multiples studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are mainly retrospective. More RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who have hemophagocytic lymphohistiocytosis who receive IVIG therapy, the evidence includes multiple case reports summarized in a systematic review and case series. Relevant outcomes are OS, DSS, change in disease status, QOL, and treatment-related mortality

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

For individuals who have warm antibody autoimmune hemolytic anemia, refractory to prednisone and splenectomy, who receive IVIG therapy, the evidence includes pooled observational data and a case report. Relevant outcomes are a change in disease status, QOL, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested potential benefits with IVIG therapy in select patients with refractory autoimmune hemolytic anemia. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have antiphospholipid syndrome who receive IVIG therapy, the evidence includes pooled data from a registry. Relevant outcomes are OS, change in disease status, QOL, and treatment-related mortality and morbidity. Observed improvements in outcomes have suggested a potential mortality benefit with IVIG therapy in catastrophic antiphospholipid syndrome. Randomized controlled trials are needed to demonstrate improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Miscellaneous Indications
For individuals who have 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 that the technology results in an improvement in the net health outcome.

For individuals who have autism spectrum disorder who receive IVIG therapy, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Although improvements were observed in 1 case series, the other 2 reported negative findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CRPS who receive IVIG therapy, the evidence includes 2 RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related mortality and morbidity. In 1

trial, compared with placebo, IVIG therapy was associated with improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from data on 13 patients. In the other RCT, low-dose IVIG was ineffective in relieving pain in CRPS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have Alzheimer disease who receive IVIG therapy, the evidence includes 3 RCTs. Relevant outcomes are OS, DSS, symptoms, change in disease status, QOL, and treatment-related mortality and morbidity. With the exception of a few subgroup analyses using mild cognitive impairment status, IVIG therapy was not significantly better than a placebo for outcomes such as brain atrophy, level of plasma amyloid β 1-40, or cognition and function. Studies differed by treatment protocols, outcomes assessed, and 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early mild cognitive impairment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes a meta-analysis, RCTs, and a retrospective study. Results from a Cochrane review concluded that, after pooling the available data, there was uncertain evidence of the effect of IVIG in preventing deaths. More RCT evidence is required before IVIG can be routinely recommended in the setting of myocarditis. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have stiff-person syndrome who receive IVIG therapy, the evidence includes a small randomized crossover study. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown decreases in stiffness scores and improvements in functional outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have noninfectious uveitis who receive IVIG therapy, the evidence includes 2 small case series. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-

related mortality and morbidity. The case series reported measurable improvements in visual acuity after IVIG therapy, but controlled studies are needed to draw conclusions about the efficacy of IVIG for this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have postpolio syndrome who receive IVIG therapy, the evidence includes a systematic review of multiple RCTs and nonrandomized prospective studies. Relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show reductions in the severity of pain and fatigue or improvements in muscle strength. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

Additional clinical input was obtained in June 2013, focusing on severe anemia due to parvovirus B19. Input was received from 3 reviewers (all hematologists), and there was a 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
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US

representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Allergy, Asthma, and Immunology Work Group Report
In 2017, the American Academy of Allergy, Asthma, and Immunology (AAAAI) published an updated Work Group Report on the use of immunoglobulin in human disease that evaluated published data through June 2015.[140,] Table 1 summarizes the conclusions of the Work Group regarding the potential benefit of immune globulin therapy for various disease states.

Table 1. AAAAI Work Group Report Immune Globulin Recommendations[140,]

Benefit of Immune Globulin Therapy	Disease State
Definitely beneficial	• Primary immune defects with absent B cells • Primary immune defects with hypogammaglobulinemia and impaired specific antibody production • Distinct genetically defined primary immunodeficiencies with variable defects in antibody quality and quantity • Graves ophthalmopathy • ITP • Kawasaki disease • Reduction of secondary infections in pediatric HIV infection • CMV pneumonitis in solid organ transplants • CIDP • Multifocal motor neuropathy • Guillain-Barré syndrome
Probably beneficial	• Chronic lymphocytic leukemia with reduced IgG and history of infections • Prevention of bacterial infection in HIV-infected children • Primary immune defects with normal IgG and impaired specific antibody production • Dermatomyositis • Birdshot retinopathy • Henoch-Schonlein purpura • Neonatal sepsis • Rotaviral enterocolitis • Bacterial infections in lymphoproliferative disease • Toxic shock syndrome • Enteroviral meningoencephalitis • IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy • Lambert-Eaton myasthenia syndrome • Myasthenia gravis • Stiff-person syndrome • Toxic epidermal necrolysis and Stevens-Johnson syndrome
May provide benefit	• Rasmussen syndrome • Acute disseminated encephalomyelitis • Human T-lymphotropic virus I-associated myelopathy • Cerebral infarctions with anti-phospholipid antibodies • Demyelinative brain stem encephalitis

Benefit of Immune Globulin Therapy	Disease State
	• Lumbosacral or brachial plexitis • Paraproteinemic neuropathy • Autoimmune encephalitides • Opsoclonus myoclonus syndrome • Postinfectious cerebellar ataxia • Acute idiopathic dysautonomia • Autoimmune optic neuropathy • Paraneoplastic cerebellar degeneration • Brown-Vialetto-Van Laere syndrome • Alzheimer disease • Narcolepsy with cataplexy • Limbic encephalitis • Prevention of infection and acute GVHD post-BMT • Prevention of acute humoral rejection in renal transplantation • PANDAS • Delayed pressure urtictimes • Severe persistent high-dose steroid-dependent asthma • Treatment of acute humoral rejection in renal transplantation • Autoimmune blistering skin diseases and manifestation of systemic diseases • Chronic urtictimes • Autoimmune liver disease • Acute myocarditis • Atopic dermatitis • Prevention of unexplained spontaneous recurrent abortion • Prevention of neonatal sepsis • Transient hypogammaglobulinemia of infancy • Other immune mechanism driving recurrent infections that affect B-cell function • Selective antibody deficiency "memory phenotype" • Isolated IgG subclass deficiency (IgG_1, IgG_2, IgG_3) with recurrent infections • Juvenile idiopathic arthritis • Anti-phospholipid antibody syndrome in pregnancy • Severe rheumatoid arthritis • Still disease • Felty syndrome • Macrophage activation syndrome • Polyarteritis nodosa • Post-transfusion purpura • Thrombotic thrombocytopenic purpura • ANCA syndromes • Autoimmune neutropenia • Autoimmune hemolytic anemia/Evan syndrome • Autoimmune hemophilia • Systemic lupus erythematosus • Neonatal alloimmune thrombocytopenia • Neonatal isoimmune hemolytic jaundice • Cystic fibrosis with hypogammaglobulinemia • Postoperative sepsis

Benefit of Immune Globulin Therapy	Disease State
	• Respiratory syncytial virus lower respiratory tract infection (proven for palivizumab) • Pseumdomembranous colitis • Camplylobacter enteritis • Chronic parvovirus B19 • Relapsing-remitting multiple sclerosis • Intractable childhood epilepsy • Postpolio syndrome
Unlikely to be beneficial	• Isolated IgE deficiency • Isolated IgG_4 deficiency • Selective IgA deficiency • Isolated IgM deficiency • Inclusion body myositis • Autoimmune diabetes mellitus • Inflammatory bowel disease • Chronic fatigue syndrome • Cystic fibrosis without hypogammaglobulinemia • Acute rheumatic fever • Viral load in HIV infection • Demyelinating neuropathy associated with monoclonal IgM • Adrenoleukodystrophy • Amyotrophic lateral sclerosis • POEMS syndrome • Paraneoplastic cerebellar degeneration, sensory neuropathy or encephalopathy • Brachial plexopathy • Autism • Non-steroid dependent asthma • Dilated cardiomyopathy

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

DISEASE STATE GUIDELINES

IMMUNODEFICIENCY STATES

PRIMARY HUMORAL IMMUNE DEFICIENCIES

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

In 2010, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services (CBS) published guidelines on the use of immunoglobulin therapy for patients with primary immune deficiency.[4,] The guidelines reported that there was sufficient evidence that immunoglobulin therapy reduces the rate of infection and hospitalization in patients with primary immune deficiency, lowers mortality, and improves quality of life. Treatment should

be started at a dose of 400 to 600 mg/kg per 4 weeks for IVIG or 100 to 150 mg/kg per week for subcutaneous immunoglobulin (SCIG) infusion.

American Academy of Allergy, Asthma, and Immunology
In 2015, AAAAI published practice parameters for the diagnosis and management of primary immunodeficiency.[141,] The Academy advised that treatment of these conditions include antibiotic prophylaxis and immunoglobulin G (IgG) replacement.

Hematopoietic Cell Transplantation (Prophylaxis)
In 2007, the 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.[142,] The following conclusions were issued on non-kidney solid organ transplantation:

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

Chronic Lymphocytic Leukemia
The National Comprehensive Cancer Network guidelines (v.4.2021) 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).[143,] The guidelines recommend monitoring IVIG levels and administering monthly SCIG or IVIG (0.3 to 0.5 g/kg) to maintain levels of 500 mg/dL.

INFECTIONS

Infections in HIV-Infected Children
In 2020, updated joint guidelines on the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children were published.[144,] The guidelines, endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and other agencies and societies, included the following statements:

- "Intravenous immune globulin is recommended to prevent serious bacterial infections in HIV-infected children who have hypogammaglobulinemia."

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

Neonatal Sepsis
In 2018, the American Academy of Pediatrics published guidelines on the management of neonates with suspected or proven early-onset bacterial sepsis.[145,] The guidelines did not address the use of IVIG to treat neonatal sepsis.

AUTOIMMUNE AND INFLAMMATORY CONDITIONS

Idiopathic Thrombocytopenic Purpura
In 2007, the NAC and CBS issued guidelines on the use of IVIG for hematologic conditions, including idiopathic thrombocytopenic purpura (ITP).[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 American Academy of Neurology (AAN; 2012) 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).[146,] The guidelines indicated that there was insufficient evidence to support or refute the use of IVIG in children. Of note, the AAN website states this is a "retired" guideline.

Kawasaki Syndrome and Other Vasculitides
The American Academy of Family Physicians (2015)[147,] and the American Heart Association (2017)[148,] have supported the use of IVIG in the treatment of Kawasaki syndrome.

Chronic Inflammatory Demyelinating Polyneuropathy
The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is effective and should be offered as a long-term treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) (level A).[146,] The guidelines indicated that data are insufficient to compare the efficacy of prednisone and IVIG in the treatment of CIDP. Of note, the AAN website states this is a "retired" guideline.

The European Academy of Neurology and the Peripheral Nerve Society published updated guidelines on the management of CIDP in 2021.[149,]ecommendations regarding immunoglobulin therapy included:

- "Both IVIG and oral or intravenous corticosteroids are first-line treatments for CIDP. Based on the level of evidence, the task force did not recommend an overall preference for either treatment modality and weakly recommended either IVIG or corticosteroid treatment. "
- "Both short- and long-term effectiveness, risks, ease of implementation, and cost should be considered:
    - IVIG may be preferable when it comes to short-term treatment effectiveness, or when (relative) contraindications for corticosteroids exist.
    - There is some indication that pulsed corticosteroids may be preferable for long-term treatment effectiveness, because of a possible higher rate and longer duration of remission, or when IVIG is unaffordable or unavailable."
- "Although the evidence from studies is limited, the task force weakly recommended treatment with IVIG compared with plasma exchange, mainly based on the ease of administration of IVIG.
    - In some patients with good vascular access, plasma exchange my be an acceptable option for chronic treatment."
- "The task force strongly recommended using SCIG for maintenance treatment in CIDP."
- "The task force recommended no preference for either IVIG or SCIG for maintenance treatment in CIDP."
- "During follow-up, the dose should be tailored according to individual treatment response."
- "The task force weakly recommended against using SCIG for induction treatment in CIDP."

Multifocal Motor Neuropathy
The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is probably effective and should be considered for the treatment of multifocal motor neuropathy (level B).[146,] There were insufficient data to determine the optimal treatment interval, dosing, and duration. Of note, the AAN website states this is a "retired" guideline.

Eaton-Lambert Myasthenic Syndrome
The AAN (2012) guidelines on the treatment of neuromuscular disorders stated that IVIG is possibly effective and may be considered for treating Lambert-Eaton myasthenic syndrome (level C).[146,]Of note, the AAN website states this is a "retired" guideline.

Neuromyelitis Optica
According to the Neuromyelitis Optica's (2014) updated guidelines, high-dose IVIG is potentially beneficial in the long-term treatment of neuromyelitis optica and may be used as an alternative for patients with a contraindication to 1 of the other treatments or, particularly, in children.[150,]

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation
In 2013, the Myasthenia Gravis Foundation of America appointed a task force to develop an international consensus guidance that focused on the appropriate management of myasthenia gravis.[151,] The authors of this guidance recommended the use of IVIG or plasma exchange for short-term treatment in patients with myasthenia gravis with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. Additionally, the guidance notes that the choice between plasma exchange and IVIG depends on individual patient factors and availability and that each therapy is probably equally effective in the treatment of severe generalized myasthenia gravis. For milder myasthenia gravis or ocular myasthenia gravis, the efficacy of IVIG is less certain. The use of IVIG

as maintenance therapy can be considered for patients with refractory myasthenia gravis or for those in whom immunosuppressive agents are relatively contraindicated.

The AAN (2012) guidelines on the treatment of neuromuscular disorders concluded that IVIG therapy is probably effective in treating patients with severe myasthenia gravis and should be considered in the treatment plan (level B).[146,] There was insufficient evidence to compare IVIG and plasmapheresis in the treatment of these patients. Of note, the AAN website states this is a "retired" guideline.

Relapsing-Remitting Multiple Sclerosis
In 2002, the AAN published a technology assessment on therapies for multiple sclerosis.[78,] The assessment was reviewed and reaffirmed in 2018. The assessment offered the following recommendations on IVIG:

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

Autoimmune Mucocutaneous Blistering Diseases
In 2003, a consensus statement on the use of immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases was published.[152,] The authors of this statement recommended that immune globulin products be administered in the following situations:

- failure of conventional therapy
- contraindications to, or significant adverse effects of, standard treatment
- progressive disease while receiving appropriate therapy
- uncontrolled rapidly progressive disease.

Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome
The British Association of Dermatologists (2016) published guidelines on the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in adults.[153,] These guidelines are accredited by the National Institute for Health and Care Excellence. The guidelines indicated that evidence for the use of IVIG in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome was not of sufficient quality or consistency.

The British Association of Dermatologists (2019) published guidelines for the management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children and young people, which said, "There is no reliable evidence on the benefits or lack of benefit of any systemic treatments including prednisolone, IVIG, anti-tumor necrosis factor (TNF) biologics or ciclosporin."[154,]

Idiopathic Inflammatory Myopathies
The AAN (2012) guidelines on IVIG for treating neuromuscular disorders have stated that IVIG is possibly effective and may be considered as a treatment for nonresponsive dermatomyositis (an idiopathic inflammatory condition) in adults (level C).[146,]Of note, the AAN website states this is a "retired" guideline.

Immune Optic Neuritis

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

ALLOIMMUNE PROCESSES

Antiphospholipid syndrome

In 2014, the Task Force on Catastrophic Antiphospholipid Syndrome concluded that triple therapy involving anticoagulation with heparin, glucocorticoids, plus either plasma exchange, IVIG, or both "has affected mortality compared to other strategies that did not use plasma exchange, IVIG, or both."[155,] This is a Grade B recommendation.

Neonatal Alloimmune Thrombocytopenia

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

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

Recurrent Spontaneous Abortion

The Royal College of Obstetricians and Gynecologists (2011; reviewed in 2017) issued guidelines on the treatment of recurrent first- and second-trimester miscarriages.[156,] The guidelines, accredited by the National Institute for Health and Care Excellence, concluded that IVIG does not improve the live birth rate in women with recurrent miscarriages (level A).

MISCELLANEOUS

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

In 2007, the NAC and CBS convened a panel of national experts to develop evidence-based practice guidelines on the use of IVIG for neurologic conditions.[157,] The panel recommended the use of IVIG for the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The optimal dose and duration of treatment are uncertain.

Autism Spectrum Disorder

The NAC and CBS (2007) guidelines on neurologic conditions did not recommend IVIG for autism.[157,]

The American Academy of Child and Adolescent Psychiatry (2014) published practice parameters on the assessment and treatment of autism spectrum disorder.[158,] The Academy parameters did not address the use of IVIG for the treatment of autism spectrum disorder.

Chronic Fatigue Syndrome

The National Institute for Health and Care Excellence (2007; currently undergoing an update development) issued guidance on the diagnosis and management of chronic fatigue syndrome.[159,] The guidance indicated that there is no cure for chronic fatigue syndrome and that symptoms (pain, sleep disturbances, physical limitations, and debilitating fatigue) should be managed under the supervision of a specialist. The use of IVIG was not addressed.

Viral Myocarditis

The American College of Cardiology Foundation and the American Heart Association issued joint guidelines in 2013, updated in 2017, on the management of heart failure.[160,] The guidelines did not address the use of IVIG for the treatment of viral myocarditis.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02176863[a]	A Multicenter, Prospective, Randomized, Placebo-controlled, Double-blind, Parallel-Group Clinical Trial to Assess the Efficacy and Safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in Patients With Post-Polio Syndrome	210	Sep 2023
NCT03194815	IVIG and Rituximab in Antibody-associated Psychosis - SINAPPS2 (SINAPPS2)	80	Mar 2024
Unpublished			
NCT03065244	KIDCARE (Kawasaki Disease Comparative Effectiveness Trial)	105	Nov 2020

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. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

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 (e.g., liquid), 500 mg
J1551	Injection, immune globulin (cutaquig), 100 mg
J1554	Injection, immune globulin (asceniv), 500 mg
J1555	Injection, immune globulin, (cuvitru) 100mg
J1556	Injection, immune globulin (bivigam), 500 mg
J1557	Injection, immune globulin (Gammaplex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1558	Injection, immune globulin (xembify), 100 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1562	Injection, immune globulin (vivaglobin)
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin (Octagam) intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin (Gammagard liquid) intravenous, nonlyophilized (e.g., liquid), 500 mg

CPT/HCPCS	
J1572	Injection, immune globulin (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase (Hyqvia), 100 mg
J1599	Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg

ICD-10 DIAGNOSES	
A40.0-A40.9	Streptococcal sepsis, code range
A41.01-A41.9	Other sepsis, code range
A48.3	Toxic shock syndrome
B20	Human immunodeficiency virus [HIV] disease
B34.3	Parvovirus infection, unspecified
B95.0-B95.8	Streptococcus, staphylococcus and enterococcus as the cause of diseases classified elsewhere code range
B97.6	Parvovirus as the cause of diseases classified elsewhere
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D59.1	Other autoimmune hemolytic anemias
D68.61	Antiphospholipid syndrome
D69.6	Thrombocytopenia, unspecified
D80.0-D80.9	Immunodeficiency with predominantly antibody defects
D82.0-D82.9	Immunodeficiency associated with other major defects (includes Wiskott-Aldrich syndrome)
D83.0-D83.9	Common variable immunodeficiency
G11.3	Telangiectasia (cerebellar) (Louis-Bar)
G25.82	Stiff-man syndrome
G35	Multiple sclerosis
G60.0-G60.9	Hereditary and idiopathic neuropathy
G61.0	Guillain-Barré syndrome
G61.82	Multifocal motor neuropathy
G70.01	Myasthenia gravis with (acute) exacerbation
G73.3	Myasthenic syndromes in other diseases classified elsewhere
I44.0-I45.9	Other conduction disorders
L12.0-L12.9	Pemphigoid code range
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M31.30-M31.31	Wegener's granulomatosis
M33.20-M33.29	Polymyositis code range
M33.90-M33.99	Dermatopolymyositis unspecified
P07.00-P07.39	Disorders of newborn related to short gestation and low birth weight, not elsewhere classified code range

ICD-10 DIAGNOSES	
P36.0-P36.9	Bacterial sepsis of newborn, code range
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

REVISIONS	
	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) (e.g. 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, e.g., 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.

REVISIONS	
	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"

REVISIONS	
	○ "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 "(e.g. 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;

REVISIONS	
	6. myasthenia gravis in patients responsive to immunosuppressive treatment; 7. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; e.g., 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:

REVISIONS	
	▪ 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."

REVISIONS	
	▪ 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.
03-15-2021	Updated Description section.

REVISIONS	
	Updated Rationale section.
	In Coding section • Added HCPCS codes: J1558 and J1562
	Updated References section.
04-01-2021	Added HCPCS code J1554
08-01-2022	Changed Policy Title to "Immunoglobulin Therapy"
	Updated Description section
	Policy Section Updated (based on policy with effective date March 15, 2021) ▪ Added Target Drug Chart ▪ Current section A moved to section C ▪ Current section B will now be section A o B added "using a preferred agent" o B3 changed to read "Catastrophic" antiphospholipid syndrome o B4 Changed to read "Warm antibody" Hemolytic Anemia o B7 Birdshot Retinopathy was removed and moved to E/I section o B8 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) added "with progressive symptoms for at least 2 months o B9 Omitted "includes Juvenile" and "or" in B9a o B10 Removed Enteroviral Meningoencephalitis o B13 Moved Fisher syndrome to E/I sections and changed statement to ready "as an equivalent alternative to plasmas exchange" o B23 Changed to read "and/or" o B24 deleted (positive anti-GAD antibody) when benzodiazepines (e.g., Valium) and/or baclofen, phenytoin, clonidine, tizanidine have failed and added "not controlled by other therapies" o B28 Myasthenia gravis added sections A and B: o A. Patients with severe refractory myasthenia gravis with chronic debilitating disease despite treatment with cholinesterase inhibitors, or complications from or failure of corticosteroids and/or azathioprine. o B. Patients with myasthenic exacerbation (ie, an acute episode of respiratory muscle weakness) in whom plasma exchange is contraindicated. o B29 Removed Neonatal Hemochromatosis o B30 Removed Neuroblastoma Associated Paraneoplastic Opsoclonus-Myoclonus-Ataxia Syndrome o B31 Removed Post-Transfusion Purpura (PTP) o B32 Removed "Humoral", added "congenital agammaglobulinemia" o B34 Removed Rasmussen Encephalitis o B35 Refractory Opsoclonus-Myoclonus moved to E/I o B38 Toxic Epidermal Necrolysis (Lyell's syndrome) or Stevens-Johnson Syndrome moved to E/I o B36 Changed to read "Toxic Shock Syndrome (Staphylococcal or Group A Streptococcus)" o B 39 changed to read "Toxic Necrotizing Fasciitis due to Group A Streptococcus" ▪ Added "Wegener Granulomatosis" to medically necessary section ▪ Added New section B B. Immune Globulin therapy using a nonpreferred agent may be considered medically necessary if: 1.The condition and associated criteria otherwise meet section A (see above) AND

REVISIONS	
	2. One of the following has been met a. The patient has tried and had an inadequate response to TWO preferred agents (medical records required)OR b. The patient has an intolerance or hypersensitivity to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required), OR c. The patient has an FDA labeled contraindication to ALL preferred that is NOT expected to occur with the requested agent (medical records required), OR d. Information has been provided in support of the use of the non-preferred agent over TWO preferred agents for the requested indication ▪ Section C: "IVIG is considered not medically necessary as a treatment of relapsing / remitting Multiple Sclerosis" changed to section D ▪ Added Section E Subcutaneous Immunoglobulin therapy ▪ Experimental / Investigational Section Changed to section F o Added: Acute Myocarditis, Birdshot Retinopathy, Fisher Syndrome, Necrotizing Fasciitis not due to Group A Streptococcus, Opsoclonus-Myoclonus, Paraproteinemic Neuropathy, Polyradiculoneuropathy (other than chronic inflammatory demyelinating polyneuropathy), Postpolio Syndrome, Refractory Recurrent Pericarditis, Toxic Epidermal Necrolysis (Lyell's syndrome) or Stevens-Johnson Syndrome o Changed: Demyelinating Optic Neuritis to Immune Optic Neuritis, Hemophagocytic Syndrome to Hemophagocytic Lymphohistiocytosis, Recent Onset Dilated Cardiomyopathy to Dilated Cardiomyopathy, Uveitis to Noninfectious Uveitis. o Removed: Myasthenia Gravis in patients responsive to immunosuppressive treatment and "Other Than Lambert-Eaton Myasthenic Syndrome" from Paraneoplastic Syndromes ▪ Added Section G Continuation of Therapy criteria
	Updated Rationale Section
	Updated Coding Section ▪ Added HCPCS code J1551 ▪ Added ICD-10 codes A40.0-A40.9, A41.01- A41.9, B34.3, B97.6, D82.0-D82.9, G25.82, G61.82, M31.30-M31.31, M33.20-M33.29, ▪ Converted ICD-10 codes to ranges
	Updated References

REFERENCES

1. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from an Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Neurology. May 1991; 41(5): 617-8. PMID 2027473
2. Van den Bergh PYK, Hadden RDM, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - First Revision. Eur J Neurol. 2010;17:356-363. doi: 10.1111/j.1468-1331.2009.02930.x. https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1468-1331.2009.02930.x. Accessed August 23, 2021

3. Food and Drug Administration (FDA). Vaccines, Blood & Biologics: Immune Globulins. 2020; https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/immune-globulins. Accessed August 30, 2021
4. Shehata N, Palda V, Bowen T, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev. Jan 2010; 24 Suppl 1: S28-50. PMID 19962579
5. Ochs HD, Gupta S, Kiessling P, et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J Clin Immunol. May 2006; 26(3): 265-73. PMID 16783465
6. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. J Clin Immunol. Mar 2006; 26(2): 177-85. PMID 16758340
7. Lingman-Framme J, Fasth A. Subcutaneous immunoglobulin for primary and secondary immunodeficiencies: an evidence-based review. Drugs. Aug 2013; 73(12): 1307-19. PMID 23861187
8. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol. Feb 10 2009; 27(5): 770-81. PMID 19114702
9. Bourassa-Blanchette S, Knoll GA, Hutton B, et al. Clinical outcomes of polyvalent immunoglobulin use in solid organ transplant recipients: A systematic review and meta-analysis. Clin Transplant. Jun 2019; 33(6): e13560. PMID 30938866
10. Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IG02 trial. J Am Soc Nephrol. Dec 2004; 15(12): 3256-62. PMID 15579530
11. Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med. Jul 17 2008; 359(3): 242-51. PMID 18635429
12. Alachkar N, Lonze BE, Zachary AA, et al. Infusion of high-dose intravenous immunoglobulin fails to lower the strength of human leukocyte antigen antibodies in highly sensitized patients. Transplantation. Jul 27 2012; 94(2): 165-71. PMID 22735712
13. Kozlowski T, Andreoni K. Limitations of rituximab/IVIg desensitization protocol in kidney transplantation; is this better than a tincture of time?. Ann Transplant. Apr-Jun 2011; 16(2): 19-25. PMID 21716181
14. Marfo K, Ling M, Bao Y, et al. Lack of effect in desensitization with intravenous immunoglobulin and rituximab in highly sensitized patients. Transplantation. Aug 27 2012; 94(4): 345-51. PMID 22820699
15. Stegall MD, Gloor J, Winters JL, et al. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. Am J Transplant. Feb 2006; 6(2): 346-51. PMID 16426319
16. Mohan S, Palanisamy A, Tsapepas D, et al. Donor-specific antibodies adversely affect kidney allograft outcomes. J Am Soc Nephrol. Dec 2012; 23(12): 2061-71. PMID 23160511
17. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med. Jul 28 2011; 365(4): 318-26. PMID 21793744
18. Roberts DM, Jiang SH, Chadban SJ. The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. Transplantation. Oct 27 2012; 94(8): 775-83. PMID 23032865
19. Casadei DH, del C Rial M, Opelz G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for

rescue of kidney grafts with steroid-resistant rejection. Transplantation. Jan 15 2001; 71(1): 53-8. PMID 11211195
20. Gale RP, Chapel HM, Bunch C, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med. Oct 06 1988; 319(14): 902-7. PMID 2901668
21. Boughton BJ, Jackson N, Lim S, et al. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol. Mar 1995; 17(1): 75-80. PMID 7621634
22. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica. Mar-Apr 1996; 81(2): 121-6. PMID 8641639
23. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. Br J Haematol. Sep 1994; 88(1): 209-12. PMID 7803248
24. Griffiths H, Brennan V, Lea J, et al. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. Blood. Feb 1989; 73(2): 366-8. PMID 2492832
25. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma. May 2009; 50(5): 764-72. PMID 19330654
26. National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. N Engl J Med. Jul 11 1991; 325(2): 73-80. PMID 1675763
27. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database Syst Rev. Jul 02 2013; (7): CD000361. PMID 23821390
28. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database Syst Rev. Jan 29 2020; 1: CD001239. PMID 31995649
29. Brocklehurst P, Farrell B, King A, et al. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med. Sep 29 2011; 365(13): 1201-11. PMID 21962214
30. Busani S, Damiani E, Cavazzuti I, et al. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. Minerva Anestesiol. May 2016; 82(5): 559-72. PMID 26474267
31. Ito S, Oyake T, Uchiyama T, et al. Successful treatment with cyclosporine and high-dose gamma immunoglobulin for persistent parvovirus B19 infection in a patient with refractory autoimmune hemolytic anemia. Int J Hematol. Oct 2004; 80(3): 250-3. PMID 15540900
32. Koduri PR, Kumapley R, Khokha ND, et al. Red cell aplasia caused by parvovirus B19 in AIDS: use of i.v. immunoglobulin. Ann Hematol. Jul-Aug 1997; 75(1-2): 67-8. PMID 9322687
33. Chuhjo T, Nakao S, Matsuda T. Successful treatment of persistent erythroid aplasia caused by parvovirus B19 infection in a patient with common variable immunodeficiency with low-dose immunoglobulin. Am J Hematol. Mar 1999; 60(3): 222-4. PMID 10072114
34. Crabol Y, Terrier B, Rozenberg F, et al. Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus b19 infection: a retrospective study of 10 patients and review of the literature. Clin Infect Dis. Apr 2013; 56(7): 968-77. PMID 23243178
35. Darenberg J, Ihendyane N, Sjolin J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. Aug 01 2003; 37(3): 333-40. PMID 12884156

36. Linner A, Darenberg J, Sjolin J, et al. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin Infect Dis. Sep 15 2014; 59(6): 851-7. PMID 24928291
37. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome--a comparative observational study. The Canadian Streptococcal Study Group. Clin Infect Dis. Apr 1999; 28(4): 800-7. PMID 10825042
38. Norrby-Teglund A, Muller MP, Mcgeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. Scand J Infect Dis. 2005; 37(3): 166-72. PMID 15849047
39. Shah SS, Hall M, Srivastava R, et al. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. Clin Infect Dis. Nov 01 2009; 49(9): 1369-76. PMID 19788359
40. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev. Apr 2007; 21(2 Suppl 1): S9-56. PMID 17397769
41. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. Lancet. Jan 05 2002; 359(9300): 23-9. PMID 11809183
42. von dem Borne AE, Vos JJ, Pegels JG, et al. High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. Br Med J (Clin Res Ed). Jan 23 1988; 296(6617): 249-50. PMID 2449258
43. Jacobs P, Wood L. The comparison of gammaglobulin to steroids in treating adult immune thrombocytopenia. An interim analysis. Blut. Jul 1989; 59(1): 92-5. PMID 2752179
44. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev. Sep 19 2014; (9): CD002063. PMID 25238327
45. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Lancet. Jan 25 1997; 349(9047): 225-30. PMID 9014908
46. Overell JR, Hsieh ST, Odaka M, et al. Treatment for Fisher syndrome, Bickerstaff's brainstem encephalitis and related disorders. Cochrane Database Syst Rev. Jan 24 2007; (1): CD004761. PMID 17253522
47. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2003; (4): CD004000. PMID 14584002
48. Fortin PM, Tejani AM, Bassett K, et al. Intravenous immunoglobulin as adjuvant therapy for Wegener's granulomatosis. Cochrane Database Syst Rev. Jan 31 2013; (1): CD007057. PMID 23440811
49. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM. Jul 2000; 93(7): 433-9. PMID 10874052
50. Eftimov F, Winer JB, Vermeulen M, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. Dec 30 2013; (12): CD001797. PMID 24379104
51. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. Dec 1994; 36(6): 838-45. PMID 7998769

52. Hughes R, Bensa S, Willison H, et al. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol. Aug 2001; 50(2): 195-201. PMID 11506402
53. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurol. Jun 2012; 11(6): 493-502. PMID 22578914
54. Vermeulen M, van Doorn PA, Brand A, et al. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry. Jan 1993; 56(1): 36-9. PMID 8429321
55. Hahn AF, Bolton CF, Zochodne D, et al. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. Brain. Aug 1996; 119 (Pt 4): 1067-77. PMID 8813271
56. Thompson N, Choudhary P, Hughes RA, et al. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol. Mar 1996; 243(3): 280-5. PMID 8936360
57. Mendell JR, Barohn RJ, Freimer ML, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. Neurology. Feb 27 2001; 56(4): 445-9. PMID 11222785
58. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol. Feb 2008; 7(2): 136-44. PMID 18178525
59. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. Jan 2018; 17(1): 35-46. PMID 29122523
60. Markvardsen LH, Sindrup SH, Christiansen I, et al. Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study. Eur J Neurol. Feb 2017; 24(2): 412-418. PMID 28000311
61. van Schaik IN, van den Berg LH, de Haan R, et al. Intravenous immunoglobulin for multifocal motor neuropathy. Cochrane Database Syst Rev. Apr 18 2005; (2): CD004429. PMID 15846714
62. Azulay JP, Blin O, Pouget J, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. Neurology. Mar 1994; 44(3 Pt 1): 429-32. PMID 8145910
63. Federico P, Zochodne DW, Hahn AF, et al. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. Neurology. Nov 14 2000; 55(9): 1256-62. PMID 11087764
64. Leger JM, Chassande B, Musset L, et al. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. Brain. Jan 2001; 124(Pt 1): 145-53. PMID 11133794
65. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry. Sep 1995; 59(3): 248-52. PMID 7673950
66. Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology. Sep 1996; 47(3): 678-83. PMID 8797464

67. Muchnik S, Losavio AS, Vidal A, et al. Long-term follow-up of Lambert-Eaton syndrome treated with intravenous immunoglobulin. Muscle Nerve. Jun 1997; 20(6): 674-8. PMID 9149073
68. Rich MM, Teener JW, Bird SJ. Treatment of Lambert-Eaton syndrome with intravenous immunoglobulin. Muscle Nerve. May 1997; 20(5): 614-5. PMID 9140371
69. Takano H, Tanaka M, Koike R, et al. Effect of intravenous immunoglobulin in Lambert-Eaton myasthenic syndrome with small-cell lung cancer: correlation with the titer of anti-voltage-gated calcium channel antibody. Muscle Nerve. Sep 1994; 17(9): 1073-5. PMID 8065398
70. Bird SJ. Clinical and electrophysiologic improvement in Lambert-Eaton syndrome with intravenous immunoglobulin therapy. Neurology. Jul 1992; 42(7): 1422-3. PMID 1620360
71. Elsone L, Panicker J, Mutch K, et al. Role of intravenous immunoglobulin in the treatment of acute relapses of neuromyelitis optica: experience in 10 patients. Mult Scler. Apr 2014; 20(4): 501-4. PMID 23986097
72. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia. Mar 2013; 28(2): 65-72. PMID 22841880
73. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev. Dec 12 2012; 12: CD002277. PMID 23235588
74. Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. Neurology. Mar 13 2007; 68(11): 837-41. PMID 17353471
75. Barth D, Nabavi Nouri M, Ng E, et al. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. Jun 07 2011; 76(23): 2017-23. PMID 21562253
76. Gajdos P, Tranchant C, Clair B, et al. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. Arch Neurol. Nov 2005; 62(11): 1689-93. PMID 16286541
77. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Ann Neurol. Jun 1997; 41(6): 789-96. PMID 9189040
78. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology. Jan 22 2002; 58(2): 169-78. PMID 11805241
79. Gurcan HM, Jeph S, Ahmed AR. Intravenous immunoglobulin therapy in autoimmune mucocutaneous blistering diseases: a review of the evidence for its efficacy and safety. Am J Clin Dermatol. 2010; 11(5): 315-26. PMID 20642294
80. Amagai M, Ikeda S, Hashimoto T, et al. A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid. J Dermatol Sci. Feb 2017; 85(2): 77-84. PMID 27876358
81. Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. J Am Acad Dermatol. Apr 2009; 60(4): 595-603. PMID 19293008
82. Huang YC, Chien YN, Chen YT, et al. Intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. G Ital Dermatol Venereol. Oct 2016; 151(5): 515-24. PMID 27248150
83. Barron SJ, Del Vecchio MT, Aronoff SC. Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. Int J Dermatol. Jan 2015; 54(1): 108-15. PMID 24697283

84. Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol. May 2012; 31(5): 801-6. PMID 22274797
85. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. Dec 30 1993; 329(27): 1993-2000. PMID 8247075
86. Miyasaka N, Hara M, Koike T, et al. Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial. Mod Rheumatol. Jun 2012; 22(3): 382-93. PMID 21971943
87. Dalakas MC, Sonies B, Dambrosia J, et al. Treatment of inclusion-body myositis with IVIg: a double-blind, placebo-controlled study. Neurology. Mar 1997; 48(3): 712-6. PMID 9065553
88. Walter MC, Lochmuller H, Toepfer M, et al. High-dose immunoglobulin therapy in sporadic inclusion body myositis: a double-blind, placebo-controlled study. J Neurol. Jan 2000; 247(1): 22-8. PMID 10701893
89. Dalakas MC, Koffman B, Fujii M, et al. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. Feb 13 2001; 56(3): 323-7. PMID 11171896
90. Sakthiswary R, D'Cruz D. Intravenous immunoglobulin in the therapeutic armamentarium of systemic lupus erythematosus: a systematic review and meta-analysis. Medicine (Baltimore). Oct 2014; 93(16): e86. PMID 25310743
91. Boletis JN, Ioannidis JP, Boki KA, et al. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. Lancet. Aug 14 1999; 354(9178): 569-70. PMID 10470708
92. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. Apr 2006; 117(4 Suppl): S525-53. PMID 16580469
93. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology. Mar 08 2005; 64(5): 804-10. PMID 15753413
94. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. Neurology. Jun 12 2001; 56(11): 1514-22. PMID 11402108
95. Rogosnitzky M, Danks R, Holt D. Intravenous immunoglobulin for the treatment of Crohn's disease. Autoimmun Rev. Dec 2012; 12(2): 275-80. PMID 22579561
96. Rajagopala S, Singh N. Diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics: systematic review from the Indian subcontinent. Acta Med Acad. 2012; 41(2): 161-74. PMID 23331391
97. Hot A, Madoux MH, Viard JP, et al. Successful treatment of cytomegalovirus-associated hemophagocytic syndrome by intravenous immunoglobulins. Am J Hematol. Feb 2008; 83(2): 159-62. PMID 17849465
98. Ostronoff M, Ostronoff F, Coutinho M, et al. Hemophagocytic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma; successful treatment with high-dose intravenous immunoglobulin. Bone Marrow Transplant. Apr 2006; 37(8): 797-8. PMID 16518425
99. Arlet JB, Le TH, Marinho A, et al. Reactive haemophagocytic syndrome in adult-onset Still's disease: a report of six patients and a review of the literature. Ann Rheum Dis. Dec 2006; 65(12): 1596-601. PMID 16540551

100. Flores G, Cunningham-Rundles C, Newland AC, et al. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. Am J Hematol. Dec 1993; 44(4): 237-42. PMID 8237993
101. Macintyre EA, Linch DC, Macey MG, et al. Successful response to intravenous immunoglobulin in autoimmune haemolytic anaemia. Br J Haematol. Jun 1985; 60(2): 387-8. PMID 4005186
102. Bucciarelli S, Espinosa G, Cervera R, et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. Aug 2006; 54(8): 2568-76. PMID 16868979
103. Rayment R, Brunskill SJ, Soothill PW, et al. Antenatal interventions for fetomaternal alloimmune thrombocytopenia. Cochrane Database Syst Rev. May 11 2011; (5): CD004226. PMID 21563140
104. Paridaans NP, Kamphuis MM, Taune Wikman A, et al. Low-Dose versus Standard-Dose Intravenous Immunoglobulin to Prevent Fetal Intracranial Hemorrhage in Fetal and Neonatal Alloimmune Thrombocytopenia: A Randomized Trial. Fetal Diagn Ther. 2015; 38(2): 147-53. PMID 25896635
105. Berkowitz RL, Lesser ML, McFarland JG, et al. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomized controlled trial. Obstet Gynecol. Aug 2007; 110(2 Pt 1): 249-55. PMID 17666597
106. Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol. Jan 2006; 107(1): 91-6. PMID 16394045
107. Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol. May 1996; 174(5): 1414-23. PMID 9065105
108. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. Cochrane Database Syst Rev. Apr 19 2006; (2): CD000112. PMID 16625529
109. Egerup P, Lindschou J, Gluud C, et al. The Effects of Intravenous Immunoglobulins in Women with Recurrent Miscarriages: A Systematic Review of Randomised Trials with Meta-Analyses and Trial Sequential Analyses Including Individual Patient Data. PLoS One. 2015; 10(10): e0141588. PMID 26517123
110. Wang SW, Zhong SY, Lou LJ, et al. The effect of intravenous immunoglobulin passive immunotherapy on unexplained recurrent spontaneous abortion: a meta-analysis. Reprod Biomed Online. Dec 2016; 33(6): 720-736. PMID 27720163
111. Christiansen OB, Pedersen B, Rosgaard A, et al. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. Hum Reprod. Mar 2002; 17(3): 809-16. PMID 11870141
112. Branch DW, Peaceman AM, Druzin M, et al. A multicenter, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The Pregnancy Loss Study Group. Am J Obstet Gynecol. Jan 2000; 182(1 Pt 1): 122-7. PMID 10649166
113. Jablonowska B, Selbing A, Palfi M, et al. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. Hum Reprod. Mar 1999; 14(3): 838-41. PMID 10221723
114. Williams KA, Swedo SE, Farmer CA, et al. Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With

Streptococcal Infections. J Am Acad Child Adolesc Psychiatry. Oct 2016; 55(10): 860-867.e2. PMID 27663941
115. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet. Oct 02 1999; 354(9185): 1153-8. PMID 10513708
116. Gupta S, Aggarwal S, Heads C. Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. J Autism Dev Disord. Aug 1996; 26(4): 439-52. PMID 8863094
117. Plioplys AV. Intravenous immunoglobulin treatment of children with autism. J Child Neurol. Feb 1998; 13(2): 79-82. PMID 9512308
118. DelGiudice-Asch G, Simon L, Schmeidler J, et al. Brief report: a pilot open clinical trial of intravenous immunoglobulin in childhood autism. J Autism Dev Disord. Apr 1999; 29(2): 157-60. PMID 10382136
119. Goebel A, Bisla J, Carganillo R, et al. Low-Dose Intravenous Immunoglobulin Treatment for Long-Standing Complex Regional Pain Syndrome: A Randomized Trial. Ann Intern Med. Oct 03 2017; 167(7): 476-483. PMID 28973211
120. Goebel A, Baranowski A, Maurer K, et al. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. Ann Intern Med. Feb 02 2010; 152(3): 152-8. PMID 20124231
121. Relkin NR, Thomas RG, Rissman RA, et al. A phase 3 trial of IV immunoglobulin for Alzheimer disease. Neurology. May 02 2017; 88(18): 1768-1775. PMID 28381506
122. Kile S, Au W, Parise C, et al. IVIG treatment of mild cognitive impairment due to Alzheimer's disease: a randomised double-blinded exploratory study of the effect on brain atrophy, cognition and conversion to dementia. J Neurol Neurosurg Psychiatry. Feb 2017; 88(2): 106-112. PMID 26420886
123. Dodel R, Rominger A, Bartenstein P, et al. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol. Mar 2013; 12(3): 233-43. PMID 23375965
124. Comi G, Roveri L, Swan A, et al. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. J Neurol. Oct 2002; 249(10): 1370-7. PMID 12382151
125. Dalakas MC, Quarles RH, Farrer RG, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. Ann Neurol. Nov 1996; 40(5): 792-5. PMID 8957021
126. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. Am J Med. Jul 1997; 103(1): 38-43. PMID 9236484
127. Robinson J, Hartling L, Vandermeer B, et al. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. Cochrane Database Syst Rev. May 20 2015; (5): CD004370. PMID 25992494
128. Robinson J, Hartling L, Vandermeer B, et al. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. Cochrane Database Syst Rev. Aug 19 2020; 8: CD004370. PMID 32835416
129. McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation. May 08 2001; 103(18): 2254-9. PMID 11342473
130. Kishimoto C, Shioji K, Hashimoto T, et al. Therapy with immunoglobulin in patients with acute myocarditis and cardiomyopathy: analysis of leukocyte balance. Heart Vessels. May 2014; 29(3): 336-42. PMID 23702697

131. El-Saiedi SA. Randomized controlled trial on the use of intravenous immune globulin in acute pediatric myocarditis. J Clin Res Bioethics. 2013;5(1):1-5. https://www.longdom.org/open-access/randomized-controlled-trial-on-the-use-of-intravenous-immune-globulin-2155-9627-5-170.pdf. Accessed September 2, 2021
132. Huang X, Sun Y, Su G, et al. Intravenous Immunoglobulin Therapy for Acute Myocarditis in Children and Adults. Int Heart J. Mar 20 2019; 60(2): 359-365. PMID 30745539
133. Heidendael JF, Den Boer SL, Wildenbeest JG, et al. Intravenous immunoglobulins in children with new onset dilated cardiomyopathy. Cardiol Young. Jan 2018; 28(1): 46-54. PMID 28797313
134. Imazio M, Lazaros G, Picardi E, et al. Intravenous human immunoglobulins for refractory recurrent pericarditis: a systematic review of all published cases. J Cardiovasc Med (Hagerstown). Apr 2016; 17(4): 263-9. PMID 26090917
135. Dalakas MC, Fujii M, Li M, et al. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med. Dec 27 2001; 345(26): 1870-6. PMID 11756577
136. LeHoang P, Cassoux N, George F, et al. Intravenous immunoglobulin (IVIg) for the treatment of birdshot retinochoroidopathy. Ocul Immunol Inflamm. Mar 2000; 8(1): 49-57. PMID 10806434
137. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. Am J Ophthalmol. May 1999; 127(5): 545-9. PMID 10334347
138. Huang YH, Chen HC, Huang KW, et al. Intravenous immunoglobulin for postpolio syndrome: a systematic review and meta-analysis. BMC Neurol. Mar 22 2015; 15: 39. PMID 25886512
139. Madsen MB, Hjortrup PB, Hansen MB, et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial. Intensive Care Med. Nov 2017; 43(11): 1585-1593. PMID 28421246
140. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol. Mar 2017; 139(3S): S1-S46. PMID 28041678
141. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. Nov 2015; 136(5): 1186-205.e1-78. PMID 26371839
142. Shehata N, Palda VA, Meyer RM, et al. The use of immunoglobulin therapy for patients undergoing solid organ transplantation: an evidence-based practice guideline. Transfus Med Rev. Jan 2010; 24 Suppl 1: S7-S27. PMID 19962580
143. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 4.2021. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed August 31, 2021
144. Centers for Disease Control (CDC). Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: bacterial infections. 2013; https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed August 31, 2021
145. Polin RA, Committee on Fetus Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. https://pediatrics.aappublications.org/content/pediatrics/142/6/e20182894.full.pdf. Accessed August 31, 2021
146. Patwa HS, Chaudhry V, Katzberg H, et al. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. Mar 27 2012; 78(13): 1009-15. PMID 22454268

147. Saguil A, Fargo M, Grogan S. Diagnosis and management of kawasaki disease. Am Fam Physician. Mar 15 2015; 91(6): 365-71. PMID 25822554
148. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. Apr 25 2017; 135(17): e927-e999. PMID 28356445
149. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force - second revision. J Peripher Nerv Syst. 2021;1-27. https://onlinelibrary.wiley.com/doi/10.1111/jns.12455. Accessed September 1, 2021
150. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. Jan 2014; 261(1): 1-16. PMID 24272588
151. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. Jul 26 2016; 87(4): 419-25. PMID 27358333
152. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol. Aug 2003; 139(8): 1051-9. PMID 12925395
153. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. Jun 2016; 174(6): 1194-227. PMID 27317286
154. McPherson T, Exton LS, Biswas S, et al. British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people, 2018. Br J Dermatol. 2019;181:37-54. doi: 10.1111/bjd.17841. https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.17841. Accessed September 1, 2021
155. Cervera R, Rodriguez-Pinto I, Cervera R, et al. Catastrophic antiphospholipid syndrome: task force report summary. Lupus. Oct 2014; 23(12): 1283-5. PMID 25228727
156. Royal College of Obstetricians and Gynecologists. The Investigation and Treatment of Couples with Recurrent Firsttrimester and Second-trimester Miscarriage. Royal Colleg of Obstetricians and Gynecologists Green-Top Guidelines No. 17. 2011; https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf. Accessed September 1, 2021
157. Feasby T, Banwell B, Benstead T, et al. Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev. Apr 2007; 21(2 Suppl 1): S57-107. PMID 17397768
158. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. Feb 2014; 53(2): 237-57. PMID 24472258
159. National Institute for Health and Care Excellence (NICE). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management [CG53]. 2007; https://www.nice.org.uk/guidance/cg53. Accessed September 1, 2021
160. Writing Committee Members, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. https://www.jacc.org/doi/full/10.1016/j.jacc.2013.05.019?_ga=2.248107975.1773510622.1630531729-1275499959.1630531729 Accessed September 1, 2021
161. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination for intravenous immune globulin for the treatment of autoimmune mucocutaneous blistering

diseases (250.3). 2002; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=158. Accessed August 31, 2021

OTHER REFERENCES

1. BCBSKS Medical Consultant, Practicing Board-Certified Internist / Medical Oncologist with special training as a Hospitalist and Hematologist (2015-57929), March 30, 2015.
2. BCBSKS Medical Consultant, Practicing Board-Certified Hematologist / Oncologist (9268970), March 30, 2015.
3. Blue Cross and Blue Shield of Kansas Family Practice Liaison Committee, July 2008, July 2010; July 2012; February 2018.
4. Blue Cross and Blue Shield of Kansas OB/GYN Liaison Committee; July 2010, July 2013.
5. Blue Cross and Blue Shield of Kansas Pediatrics Liaison Committee; August 2007, July 2008, July 2010, July 2011, July 2014, July 2015, January 2019, January 2022.
6. Blue Cross and Blue Shield of Kansas Internal Medicine Liaison Committee; CB October 2010, August 2013, August 2014, August 2015, February 2022.
7. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee; CB October 2010, February 2014; February 2015; CB May 2015, August 2017, June 2022.