

Medical Policy



Title: Intravenous and Subcutaneous Immune Globulin Therapy

PRE-DETERMINATION of services is required.

Predetermination Request Form:

http://www.bcbsks.com/CustomService/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

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 Revision Date(s): November 11, 1999;
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State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

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

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

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

Populations	Interventions	Comparators	Outcomes
birth weight infants with sepsis	<ul style="list-style-type: none"> Intravenous immunoglobulin therapy (treatment) 		<ul style="list-style-type: none"> Symptoms Morbid events Hospitalizations Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> Who are adults with sepsis 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Symptoms Morbid events Hospitalizations Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With severe anemia associated with human parvovirus B19 virus 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With toxic shock syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Corticosteroids 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With idiopathic thrombocytopenic purpura 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Corticosteroids 	Relevant outcomes include: <ul style="list-style-type: none"> Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Guillain-Barré syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Plasma exchange Immunoadsorption Supportive care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Symptoms Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Kawasaki disease 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Disease-specific survival Change in disease status Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With granulomatosis with polyangiitis (Wegener granulomatosis) 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Disease-specific survival Change in disease status Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With chronic inflammatory demyelinating polyneuropathy 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Plasma exchange Corticosteroids Supportive care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With chronic inflammatory demyelinating polyneuropathy 	Interventions of interest are: <ul style="list-style-type: none"> Subcutaneous immunoglobulin 	Comparators of interest are: <ul style="list-style-type: none"> Plasma exchange Corticosteroids Supportive care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events

Populations	Interventions	Comparators	Outcomes
	therapy		<ul style="list-style-type: none"> • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With multifocal motor neuropathy 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With Eaton-Lambert myasthenic syndrome 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With neuromyelitis optica 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With severe refractory myasthenia gravis or myasthenic exacerbation 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Plasma exchange 	Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Symptoms • Change in disease status • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With relapsing-remitting multiple sclerosis 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • With autoimmune mucocutaneous blistering diseases 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With toxic epidermal necrosis or Stevens-Johnson syndrome 	Interventions of interest are: <ul style="list-style-type: none"> • Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With dermatomyositis or 	Interventions of interest are:	Comparators of interest are: <ul style="list-style-type: none"> • Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> • Change in disease status

Populations	Interventions	Comparators	Outcomes
polymyositis	<ul style="list-style-type: none"> Intravenous immunoglobulin therapy 		<ul style="list-style-type: none"> Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With inclusion body myositis 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With systemic lupus erythematosus 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With immune optic neuritis 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Crohn's disease 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With hemophagocytic lymphohistiocytosis 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Supportive care alone Chemotherapy Allogeneic cell transplantation 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With autoimmune hemolytic anemia, refractory to prednisone and splenectomy 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Prednisone Splenectomy Cytotoxic medications 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With antiphospholipid syndrome 	Interventions of interest are: <ul style="list-style-type: none"> Intravenous immunoglobulin therapy 	Comparators of interest are: <ul style="list-style-type: none"> Anticoagulant therapy Antiplatelet therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Quality of life Treatment-related mortality Treatment-related morbidity

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

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

DESCRIPTION

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

OBJECTIVE

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

BACKGROUND

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

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

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

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

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

REGULATORY STATUS

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

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

At least 1 IVIG product is FDA-approved to treat the following conditions¹:

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

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

POLICY

- A. Intramuscular immune globulin is **not medically necessary** for the indications listed in this policy.
- B. Immune Globulin therapy may be **medically necessary** in the following conditions when the associated criteria are met:
1. **Acute Disseminated Encephalomyelitis** when response to intravenous corticosteroid treatment is insufficient.
 2. **Antibody-Mediated Rejection**, following solid organ transplant.
 3. **Antiphospholipid Syndrome**
 4. **Autoimmune Hemolytic Anemia**, refractory to corticosteroids or splenectomy.
 5. **Autoimmune Mucocutaneous Blistering Diseases** (includes pemphigus, pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid [a.k.a. cicatricial pemphigoid], and epidermolysis bullosa acquisita) when corticosteroids, and immuno-suppressive agents have failed.
 6. **B Cell Chronic Lymphocytic Leukemia (CLL)** in patients with:
 - a. Hypogammaglobulinemia (total IgG <400 mg/dL), **AND**
 - b. Recurrent or persistent bacterial infections.
 7. **Birdshot (vitiliginous) Retinochoroidopathy** not responsive to immunosuppressives (eg, corticosteroids, cyclosporine).
 8. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**
 9. **Dermatomyositis, Polymyositis (includes Juvenile)** intolerant or refractory to:
 - a. Corticosteroids; **AND/OR**
 - b. Immuno-suppressants (eg, methotrexate, azathioprine, cyclophosphamide, and cyclosporine).
 10. **Enteroviral Meningoencephalitis**
 11. **Erythrovirus (formerly Parvovirus) B19 Infection, chronic, with severe anemia**
 12. **Fetal Alloimmune Thrombocytopenia (FAIT) or previous pregnancy affected by FAIT**

13. **Guillain-Barré Syndrome (GBS)** (includes GBS variants: Miller Fisher syndrome [MFS], paraneuronal polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy [AMAN], and acute motor and sensory axonal neuropathy [AMSAN]). IVIG should usually be initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms.
14. **Hematopoietic Stem Cell Transplant (HSCT) or Bone Marrow Transplant (BMT)**
 - a. For prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for treatment of recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL) or who have CMV or RSV infection; **OR**
 - b. IVIG is considered medically necessary for steroid-resistant graft-versus-host disease in BMT recipients 20 years of age or older, in the first 100 days post transplant, and who are hypogammaglobulinemic (IgG level less than 400 mg/dL).
15. **Hemolytic Disease of the Newborn**
16. **HIV Associated Polyneuropathy**
17. **HIV Associated Thrombocytopenia**
18. **HIV Infected Children-** who meet the following criteria:
 - a. Serum IgG concentration less than 250 mg/dL; **AND**
 - b. Recurrent serious bacterial infections; **AND**
 - c. Failure to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine; **OR**
 - d. Single dose for HIV-infected children who are exposed to measles; **OR**
 - e. Chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.
19. **Hyperimmunoglobulin E Syndrome** with recurrent staphylococcal abscesses.
20. **Immune Thrombocytopenia (idiopathic thrombocytopenic purpura [ITP])**
 - a. Unresponsive to corticosteroid therapy; **OR**
 - b. To defer or avoid splenectomy; **OR**
 - c. Platelet counts less than 20,000 u/l (risk of intracerebral hemorrhage); **OR**
 - d. Management of acute bleeding with platelet counts less than 30,000 u/l; **OR**
 - e. To increase platelet counts, prior to major surgical procedures.

21. **Immunosuppressed Patients** associated immunosuppression (IgG < 400 mg/dL) with one of the following:
 - a. Solid organ transplants or extensive surgery with immunosuppression; **OR**
 - b. Hematological malignancy; **OR**
 - c. Extensive burns; **OR**
 - d. Collagen-vascular disease.
22. **Kawasaki disease**
23. **Lambert-Eaton Myasthenic Syndrome (LEMS)** and inadequate response to anticholinesterases and diaminopyridine).
24. **Moersch-Woltmann (Stiff-man) Syndrome** (positive anti-GAD antibody) when benzodiazepines (eg, Valium) and/or baclofen, phenytoin, clonidine, tizanidine have failed.
25. **Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) Variant**
26. **Multifocal Motor Neuropathy with Conduction Block**-diagnosed on the basis of electrophysiologic findings.
27. **Multiple Myeloma (MM)**
 - a. IgG level < 600 mg/dL; **AND**
 - b. Recurrent or persistent bacterial infections.
28. **Myasthenia gravis** when other treatments have been unsuccessful or are contraindicated (eg, azathioprine, cyclosporine, cyclophosphamide, and myasthenic crisis).
29. **Neonatal Hemochromatosis**
30. **Neuroblastoma Associated Paraneoplastic Opsoclonus-Myoclonus-Ataxia Syndrome**
31. **Post-Transfusion Purpura (PTP)**
32. **Primary Humoral Immunodeficiencies** (to include X-linked agammaglobulinemia [Bruton] X-linked hyper-IgM syndrome, severe combined immunodeficiency [SCID], common variable immunodeficiency [CVID], Wiskott-Aldrich syndrome, and ataxia telangiectasia) with a history of significant recurrent infections and one of the following:
 - a. A very low level of IgG (eg, 200 mg/dL or less). Assessing vaccine response is not necessary; **OR**

- b. Nonprotective levels of antibodies to pneumococcal vaccine serotypes documented with a 14-serotype panel. If antibodies are at nonprotective levels, a pneumococcal vaccine challenge is required.

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

The interpretation of response to polyvalent pneumococcal polysaccharide vaccine is as follows:

- In children 2 to 5 years of age, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 50% of the serotypes tested.
- In children > 5 years of age and in adults, a normal response consists of a post immunization titer > 1.3 micrograms/mL to at least 70% of the serotypes tested.

Immunoglobulin replacement should be reserved for patients who have failed the following treatments:

- Immunization with conjugate vaccines.
- Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (eg, asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures).
- Prophylactic antibiotics such as amoxicillin-clavulanate or cefdinir.
- Increased vigilance and appropriate antibiotic therapy for infections.

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

33. **Prior to solid organ transplant**, treatment of patients at high risk of antibody-mediated rejection, including highly sensitized patients, and those receiving an ABO incompatible organ.
34. **Rasmussen Encephalitis** refractory to antiepileptic drugs and corticosteroids.
35. **Refractory Opsoclonus-Myoclonus**
36. **Staphylococcal Toxic Shock Syndrome**
37. **Systemic Lupus Erythematosus such as** severe active SLE for whom first- and second-line therapies have been unsuccessful (non-steroidal anti-inflammatory drugs, corticosteroids, antimalarial compounds, methotrexate, azathioprine, or cyclophosphamide).
38. **Toxic Epidermal Necrolysis (Lyell's syndrome) or Stevens-Johnson Syndrome**

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

- C. IVIG is considered **not medically necessary** as a treatment of relapsing / remitting multiple sclerosis.
- D. Other application of IVIG therapy are considered **experimental / investigational**, including, but not limited to, the following conditions:
1. acquired factor VIII inhibitors
 2. acute lymphoblastic leukemia
 3. adrenoleukodystrophy
 4. Alzheimer's disease
 5. aplastic anemia
 6. asthma
 7. autism
 8. Behcet's syndrome
 9. chronic fatigue syndrome
 10. chronic progressive multiple sclerosis
 11. chronic sinusitis
 12. complex regional pain syndrome
 13. Crohn's disease
 14. cystic fibrosis
 15. demyelinating optic neuritis
 16. demyelinating polyneuropathy associated with IgM paraproteinemia
 17. diabetes mellitus
 18. Diamond-Blackfan anemia
 19. epilepsy
 20. hemolytic uremic syndrome
 21. hemophagocytic syndrome
 22. IgG sub-class deficiency
 23. immune-mediated neutropenia
 24. inclusion-body myositis
 25. myasthenia gravis in patients responsive to immunosuppressive treatment
 26. nonimmune thrombocytopenia
 27. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; eg, Wegener's granulomatosis, polyarteritis nodosa), Goodpasture's syndrome, and vasculitis associated with other connective tissue diseases
 28. paraneoplastic syndromes, other than Lambert-Eaton myasthenic syndrome
 29. pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
 30. recent-onset dilated cardiomyopathy
 31. recurrent otitis media
 32. recurrent spontaneous abortion (see below for related laboratory tests)

33. red cell aplasia
34. refractory rheumatoid arthritis and other connective tissue diseases
35. sepsis, including neonatal sepsis
36. thrombotic thrombocytopenic purpura
37. uveitis

Policy Guidelines

Dosing

Rituximab should be administered by a health care professional with appropriate medical support to manage severe and potentially fatal infusion reactions (Biogen & Genentech, 2014).

Black Box Warnings and Precautions

For the intravenous immunoglobulin (IVIG):

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

Additional warnings and precautions include:

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

- IVIG is made from human plasma and may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease agent).
- Passive transfer of antibodies may confound serologic testing.

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

Primary Immunodeficiency Syndromes

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

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

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

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

RATIONALE

Updated literature reviews were conducted most recently through August 24, 2017. The key published literature is summarized below.

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health

outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

Immunodeficiency States

Primary Humoral Immune Deficiencies

Primary humoral immunodeficiency deficiencies refers 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.

In 2010, the National Advisory Committee on Blood and Blood Products (NAC) and Canadian Blood Services (CBS) published a guideline on use of immunoglobulin therapy for patients with primary immune deficiency; recommendations were based on a systematic review of evidence by a panel of experts.² The search identified 3 RCTs, several cohort studies, and numerous case series.

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

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

Section Summary: Primary Humoral Immune Deficiencies

The evidence for 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 guidelines (102 studies) initiated by the CBS and NAC.

Hematopoietic Cell Transplantation (Prophylaxis)

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

The initial use of immunoglobulin for prophylaxis in HCT was based on the randomized controlled trial (RCT) by Sullivan et al in 369 patients undergoing HCT.⁶ The trial showed that neither survival nor risk of relapse was altered by IVIG. However, IVIG treatment was associated with a reduction in the incidence of acute graft-versus-host disease (GVHD) compared to controls (51% vs 34%) and deaths due to transplant-related causes after transplantation of human leukocyte antigen (HLA)-identical marrow (46% vs 30%). There were many methodologic flaws in the trial, including lack of control for type 1 error for multiple comparisons, inclusion of a heterogeneous group of patients, and lack of a placebo control. Subsequent to this pivotal trial, multiple trials have been

conducted and systematic reviews have assessed the efficacy of immunoglobulin prophylaxis in HCT to prevent infection and prolong survival. The most recent systematic review and meta-analysis (2009) included 30 trials with 4223 patients undergoing HCT.⁷ There was no difference in all-cause mortality between IVIG and cytomegalovirus-IVIG compared to 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 to 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 is not recommended.

Section Summary: Hematopoietic Cell Transplantation (Prophylaxis)

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

Acute Antibody-Mediated Rejection After Solid Organ Transplant

Acute rejection after transplant can be broadly divided into 2 categories: the more common acute cellular rejection related to activation of T cells, and the less common acute antibody-mediated rejection (ABMR) related to the presence of antidonor antibodies. Acute ABMR is an entity now better defined and often detected earlier in the clinical course, based on the recognition of characteristic histologic findings, positive C4d staining, and the detection of donor-specific antibodies.

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.

In the National Institutes of Health–sponsored IG02 study, 101 adults with a PRA screen of 50% or higher were randomized to IVIG 2 g/kg monthly for 4 months or placebo.⁸ If transplanted, additional infusions were given at 12 and 24 months. Treatment with IVIG therapy resulted in significant reduction in PRA levels compared to placebo (35% vs 17%). Seven graft failures occurred (4 IVIG, 3 placebo) among adherent patients with similar 2-year graft survival rates (80% IVIG, 75% placebo). The investigators concluded that IVIG therapy was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients with end-stage renal disease. In a follow-up study, the combination of high-dose IVIG and B-cell depletion therapy reduced PRA from 77% to 44% at the time of transplantation.⁹ However, more recent studies have failed to show reduction in PRA levels, specifically in patients with PRA greater than 80%.¹⁰⁻¹² Nonrandomized clinical observations have suggested that a combination of plasmapheresis and low-dose IVIG combined with interleukin-2 blockade or rATG for induction was associated with improved patient survival compared with chronic dialysis for the treatment of sensitized patients.¹³⁻¹⁵

Subsection Summary: Acute Antibody-Mediated Rejection (Prophylaxis)

The evidence for use of IVIG for prophylaxis in patients with high PRA levels prior to solid organ transplant consists of multiple RCTs and noncomparative observational studies. RCTs have shown

conflicting results that prophylaxis with IVIG in patients with high PRA levels prior to solid organ transplant leads to significant reduction in PRA levels.

Treatment

Most studies of IVIG treatment for ABMR are retrospective case series from single institutions. A 2012 systematic review by Roberts et al of treatments for acute ABMR in renal allografts found 10,388 citations but only 5 small RCTs, none of which addressed use of IVIG in the treatment of ABMR.¹⁶ An RCT¹⁷ has demonstrated that IVIG therapy is effective for the treatment of steroid-resistant rejection, however, it was ineligible for inclusion in the systematic review by Roberts et al because 83% of the patients had Banff 1 (pure cellular) rejection on biopsy.¹⁶ According to Roberts et al, 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 use of IVIG in ABMR consists of retrospective case series. According to a 2012 systematic review, the evidence for IVIG treatment of ABMR is very low (GRADE criteria).

Infections

Chronic Lymphocytic Leukemia

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

Multiple trials and a meta-analysis comparing IVIG to placebo have shown decreased bacterial infections but not decreased mortality.¹⁸⁻²³ IVIG has not been directly compared with the use of prophylactic antimicrobials. The randomized trials of prophylactic IVIG found that patients who receive IVIG have a decreased incidence of minor and moderate, but not major, bacterial infections. Treatment with IVIG has not been shown to increase quality of life or survival. The largest study was a multicenter randomized trial in 84 patients with CLL who were at increased risk of bacterial infection due to hypogammaglobulinemia, a history of infection, or both.¹⁸ Although minor or moderate bacterial infections were significantly less common in patients receiving IVIG, there was no impact on the incidence of major infections, mortality, or nonbacterial infections.

Section Summary: Chronic Lymphocytic Leukemia

The evidence for use of IVIG therapy for prophylaxis of infection in CLL preterm consists of multiple RCTs that have generally shown reductions in rates of minor and moderate, but not major, bacterial infections. No benefit in quality of life and mortality has been shown.

HIV-Infected Children

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

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

(RR=0.65 ; $p < 0.05$). The effect was less marked in children with CD4+ counts of less than $0.2 \times 10^9/L$. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children have recommended IVIG to prevent serious bacterial infections in HIV-infected children who have IgG levels less than 400 mg/dL.²⁵ The guidelines for the prevention and treatment of serious opportunistic infections in HIV-infected adults and adolescents do not give such recommendations.²⁶

Subsection Summary: Infections in HIV-Infected Children

The evidence for use of IVIG for prophylaxis of opportunistic infections in HIV-infected children consists of 1 RCT that showed reduction in serious and minor bacterial infections and hospitalization. A reduction in mortality has not been demonstrated so far.

Neonatal Sepsis

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

Prophylaxis of Neonatal Sepsis

A 2013 Cochrane review addressed IVIG for the prevention of infection in preterm and/or low birth weight infants.²⁷ Investigators identified 19 RCTs that compared IVIG to 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 remaining studies had potential biases (eg, lack of caregiver blinding in 10 studies). In 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, meta-analysis of 16 studies showed a significant reduction in serious infection (≥ 1 episodes) with IVIG (RR=0.82; 95% CI, 0.74 to 0.92). However, IVIG was not associated with a significant reduction in mortality. Meta-analysis of 15 studies that reported all-cause mortality found a relative risk of 0.89 (95% CI, 0.75 to 1.05), and meta-analysis of 10 studies that reported mortality due to infection found a relative risk 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 reduction in other clinically important outcomes, including mortality, were of marginal clinical importance. No major adverse effects related to IVIG administration were reported.

Subsection Summary: Prophylaxis of Neonatal Sepsis

The evidence for use of IVIG therapy for prophylaxis of infection in preterm and/or low birth weight infants consists of multiple RCTs that have generally shown reduction in rate of sepsis but no benefit in mortality. A meta-analysis of 10 studies addressing the use of IVIG for prophylaxis of infection in preterm and/or low birth weight infants concluded that a 3% reduction in sepsis and a 4% reduction in 1 or more episodes of any serious infection without reduction in other clinically important outcomes, including mortality, was of marginal clinical importance.

Treatment of Neonatal Sepsis

A 2015 Cochrane review identified 9 trials that compared IVIG with placebo or standard care in neonates (<28 days old) with suspected or proven infection.²⁸ Studies included a total of 3973 infants; the largest trial had a sample size of 3493 and contributed 90% of the data. Meta-analysis of all 9 trials found no statistically significant difference in mortality rate with IVIG versus control (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.

The trial with the large sample size was published by the International Neonatal Immunotherapy Study group in 2011; it was conducted in 9 countries.²⁹ Infants receiving antibiotics for suspected or confirmed serious infection were randomly assigned to receive 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 had major disability compared with 677 (39%) of 1734 children in the placebo group (RR=1.00; 95% CI, 0.92 to 1.08). There were also no statistically significant differences in the primary outcome when prespecified subgroups (eg, birthweight, gestational age at birth, sex) were examined. Moreover, there were no statistically significant differences between groups in secondary outcomes, including rates of subsequent sepsis episodes. The number of reported adverse events was 12 in the IVIG group (including 2 deaths) versus 10 in the placebo group (including 4 deaths).

Section Summary: Treatment of Neonatal Sepsis

The evidence for use of IVIG treatment for suspected or proven infection in neonates consists of multiple RCTs. The largest RCTs in 3493 neonates showed that there was no difference in the rates of death or major disability between IVIG-treated neonates versus placebo-treated neonates. Meta-analysis (9 studies) also found was no difference in mortality rates or major disability with IVIG versus control.

Sepsis in Adults

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

Section Summary: Treatment of Sepsis in Adults

The evidence for use of IVIG treatment for sepsis in adults consists of a meta-analysis of 18 RCTs. Though the meta-analysis demonstrated reductions in mortality risk, most studies included were small, were of low quality, and employed heterogeneous dosing regimens and types of IVIG preparations.

Severe Anemia Associated With Human Parvovirus B19

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

No controlled trials have evaluated IVIG for severe anemia associated with parvovirus B19. Only case reports and small case series are available.³¹⁻³³ One of the larger case series, published in 2013 by Crabol et al, 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 effects associated with IVIG (2 cases of acute reversible renal failure, 2 cases of pulmonary edema). In the same article, Crabol et al 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 use of IVIG treatment for severe anemia associated with human parvovirus B19 consists of case series and case reports. The largest case series (10 patients) showed that there IVIG treatment was associated with correction of anemia in most patients. Controlled trials are lacking.

Toxic Shock Syndrome

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

The evidence for use of IVIG treatment for toxic shock syndrome is limited and includes 1 small RCT³⁵ and multiple observational studies.³⁶⁻³⁹ IVIG is used for treatment of septic shock syndrome to boost antibody levels via passive immunity. The 2003 RCT allocated 21 adults with toxic shock syndrome to IVIG or to placebo.³⁵ Mortality rates were 10% and 36%, respectively, but the difference in mortality rates was not statistically significant. However, the study was originally planned to enroll 120 patients, so was likely underpowered to detect any significant differences. In a 2014 prospective observational study, 23 patients receiving IVIG therapy were compared 44 patients who received placebo.³⁶ The odds ratio for survival was 5.6 for IVIG versus placebo ($p=0.03$). The proportion of patients alive at 28 days by treatment was 87% and 50%, respectively. In 2 retrospective studies, 27 patients with toxic shock syndrome treated with IVIG were compared with historical controls.^{37,38} While the mortality rate was lower with IVIG than with historical controls, lack of randomization or statistical adjustment of the 2 groups pose difficulties when interpreting the results. A 2009 retrospective study including 192 children with toxic shock syndrome failed to show improvement in outcomes with IVIG.³⁹

Section Summary: Toxic Shock Syndrome

The evidence for the use of IVIG treatment for toxic shock syndrome consists of a small RCT and multiple observational studies. Most of these studies showed beneficial effect of treatment on mortality.

Autoimmune and Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

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

In 2007, NAC and CBS 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 that compared IVIG with corticosteroids included 122 patients with severe acute ITP.⁴¹ The primary outcome, mean number of days with platelet count greater than $50 \times 10^9/L$ at day 21, was significantly greater in the IVIG group than in the high-dose methylprednisolone group. Two other trials, 1 nonrandomized (IVIG vs corticosteroids)⁴² and 1 randomized (IVIG alone vs oral prednisone alone vs IVIG plus oral prednisone)⁴³ found no

difference in platelet counts greater than $50 \times 10^9/L$ at 48 hours or in response rates between groups, respectively.

Section Summary: Idiopathic Thrombocytopenic Purpura

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

Guillain-Barré Syndrome

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

A Cochrane review by Hughes et al, updated in 2014, reviewed the results of 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 compared IVIG with immunoabsorption (1 compared of IVIG plus immunoabsorption to 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 (eg, number of patients who improved by ≥ 1 grades). There were insufficient data to pool results for comparisons of IVIG with other types of alternative interventions or for a subgroup analysis by age. However, patients assigned to IVIG were significantly less likely to discontinue treatment than patients assigned to plasma exchange (RR=0.14; 95% CI, 0.05 to 0.36).

Most trials 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 The objectives of the trial were to establish that IVIG is equivalent or superior to plasma exchange and to establish that plasma exchange followed by IVIG is superior to a single treatment. Noninferiority was defined as no more than a 0.5-grade difference in change in disability grade at 4 weeks. At 4 weeks, the difference in improvement between the IVIG group and plasma exchange group was 0.09 grade (95% CI, -0.23 to 0.42); this met the predefined criterion for equivalence of these treatments. Differences were 0.29 grade (95% CI, -0.04 to 0.63) between the IVIG plus plasma exchange group and the IVIG only group, and 0.20 grade (95% CI, -0.14 to 0.54) between the IVIG plus plasma exchange group and the plasma exchange only group. Thus, neither combined treatment groups was 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 2007 Cochrane systematic review evaluated acute immunomodulatory therapies in Fisher syndrome or its variants.⁴⁶ No RCTs were identified.

Section Summary: Guillain-Barré Syndrome

The evidence for IVIG treatment for GBS patients consists of multiple RCTs that compared IVIG therapy with other modalities such as plasma exchange and immunoabsorption but not placebo. The Cochrane meta-analysis of 7 trials comparing IVIG therapy with plasma exchange did not find a significant difference in disability scores. The largest RCT (383 GBS patients) did not show the superiority of combination IVIG plus plasma exchange to either treatment alone.

Kawasaki Disease

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

Multiple RCTs and meta-analysis have demonstrated efficacy of IVIG in preventing cardiac consequences of Kawasaki disease in children. A 2003 systematic review of RCTs identified 59 trials in the initial search and included 16 trials for meta-analysis using relative risk for dichotomous data or weighted mean difference for continuous data.⁴⁷ Results showed a significant decrease in new coronary artery abnormalities in favor of IVIG compared to 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 gm/kg single dose) within 10 days of onset of symptoms.

Section Summary: Kawasaki Syndrome

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

Granulomatosis with Polyangiitis (Wegener Granulomatosis)

The success of IVIG therapy for Kawasaki disease led to investigation of IVIG therapy in other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis.⁴⁸ This trial, published by Jayne et al, 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

A single crossover trial in Wegener granulomatosis demonstrated that IVIG treatment increased in response rates compared to placebo.

Section Summary: Granulomatosis With Polyangiitis (Wegener Granulomatosis)

A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial found significantly more responders in the IVIG treatment group at three months—but no significant differences after three months, or in the frequency of relapse or use of other medications.

Chronic Inflammatory Demyelinating Polyneuropathy

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

Intravenous Immunoglobulin Therapy

In 2013, Eftimov et al published a Cochrane review of RCTs on IVIG for treating CIDP.⁵⁰ Reviewers identified 8 RCTs that enrolled 332 patients with definite or probable CIDP and that compared IVIG with placebo, corticosteroid, or plasma exchange. Three trials compared IVIG with another active treatment,⁵¹⁻⁵³ and the other 5 were placebo-controlled (n=235).⁵⁴⁻⁵⁸ The primary trial outcome was the proportion of participants with a significant improvement in disability within 6 weeks of starting treatment. Studies used a variety of disability measures. When possible, Cochrane reviewers transformed the data on disability to a modified 6-point Rankin Scale for disability. Data from the 5 placebo-controlled RCTs were pooled. The pooled relative risk for improvement in the IVIG group compared with the placebo group was 2.40 (95% CI, 1.72 to 3.36; p<0.001). When data were pooled from 3 studies on IVIG versus placebo in which the disability measures could be converted to the Rankin Scale, the relative risk was similar (2.40) but not statistically significant (95% CI, 0.98 to 5.83; p=0.054). Pooled analyses of data from these 3 placebo-controlled studies found a statistically higher rate of any adverse event with IVIG, but not serious adverse events. Data from studies comparing IVIG with an active treatment were not pooled due to differences in comparators. Limitations of the meta-analysis included the use of different disability scales and varying definitions of clinical response.

ICE, the largest trial included in the meta-analysis, was a double-blind multicenter trial that randomized 117 patients to IVIG or placebo.⁵⁸ The primary outcome measure was proportion of patients showing clinically meaningful improvement in disability at week 24. Results showed that the proportion of patients meeting the primary end point was significantly greater with IVIG treatment (54%) than with placebo (21%), with an absolute difference of 33.5% (95% CI, 15.4% to 51.7%). In the 24-week extension phase, 57 patients who received IVIG in the randomized phase were rerandomized to IVIG or placebo. Relapse rates were significantly lower for patients treated with IVIG (13% vs 45%; hazard ratio [HR], 0.19; 95% CI, 0.05 to 0.70). Benefits of IVIG treatment extended to as long as 48 weeks with maintenance treatments of 1 g/kg every 3 weeks.

A 2012 evidence-based guideline on IVIG for treating neuromuscular disorders, prepared by a subcommittee of American Academy of Neurology, stated that IVIG should be offered for the long-term treatment of CIDP.⁵⁹

Subsection Summary: Intravenous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy

The evidence for use of IVIG treatment for CIDP consists of multiple RCTs. The largest trial (117 patients) demonstrated that IVIG treatment led to clinically meaningful improvements in disability compared to placebo. A Cochrane meta-analysis of 5 RCTs comparing IVIG with placebo demonstrated that IVIG treatment led to improvement in disability.

Subcutaneous Immunoglobulin Therapy

One crossover RCT comparing IVIG and SCIG for CIDP was identified; the trial was published in 2017 by Markvardsen et al and 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 study. Change in isokinetic muscle strength increased by 7.4% during SCIG and 14% during IVIG; the difference between groups was not statistically significant. Conclusions about the relative efficacy of SCIG and IVIG cannot be drawn from this study due to the small sample size, high dropout rate, short-term follow-up, and the crossover design without a washout period.

Subsection Summary: Subcutaneous Immunoglobulin Therapy for Chronic Inflammatory Demyelinating Polyneuropathy

The relative benefit of SCIG therapy over IVIG therapy in CIDP remains unclear because of lack of direct comparison between therapies.

Multifocal Motor Neuropathy

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities, a presentation similar to that of motor neuron disease. The benefit of IVIG for MMN has been evaluated in 4 RCTs (total N=53 patients).⁶¹⁻⁶⁴ The largest of the 4 RCTs randomized 19 patients with MMN with persistent conduction block to IVIG or placebo. Response to treatment was assessed by measuring Medical Research Council (MRC) score in 28 muscles; a responder was defined as at least 1 more MRC point in 2 affected muscles plus 1 point less in 2 activities of daily life compared with baseline. At 4 months, 7 of 9 patients who received IVIG responded compared with 2 of 9 patients treated with placebo. Van Schaik et al (2005) included 4 RCTs (total N=34 patients) in a meta-analysis to assess the efficacy and safety of IVIG in MMN.⁶⁵ Strength improved in 78% of patients treated with IVIG vs 4% in placebo-treated patients. Disability was reduced in 39% and 11%, respectively ($p=NS$). Mild, transient side effects were reported in 71% of IVIG-treated patients. Serious side effects were not encountered.

Section Summary: Multifocal Motor Neuropathy

The evidence for use IVIG therapy for MMN consists of multiple RCTs. A Cochrane meta-analysis of 4 RCTs comparing IVIG with placebo found that IVIG treatment led to significant improvements in muscle strength but not reduction in disability level. The largest trial of 19 patients found that IVIG treatment with IVIG led to improvements in muscle strength compared with placebo.

Eaton-Lambert Myasthenic Syndrome

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

One crossover RCT (1996) of 9 patients treated with IVIG therapy (1 g/kg/d for 2 days) or placebo showed statistically significant improvements in serial measurements of limb, respiratory, and bulbar muscle strength associated with IVIG treatment, and a nonsignificant improvement in the resting compound muscle action potential amplitude.⁶⁶ A number of noncomparative studies have substantiated clinical benefits.⁶⁷⁻⁷⁰

Section Summary: Eaton-Lambert Myasthenic Syndrome

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

Neuromyelitis Optica

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

There are no published comparative trials evaluating the efficacy of IVIG treatment in NMO. Published literature consists of case reports and case series.⁷¹⁻⁷⁴ A 2014 retrospective review 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 2013 case series of 9 Spanish NMO patients yielded positive results using bimonthly IVIG treatment (0.7 g/kg body weight per day for 3 days) for up to 2 years.⁷⁴

Section Summary: Neuromyelitis Optica

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

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

Myasthenia gravis is a relatively rare autoimmune disorder in which antibodies form against acetylcholine nicotinic postsynaptic receptors at the neuromuscular junction of skeletal muscles resulting in characteristic patterns of progressively reduced muscle strength with repeated use and recovery of muscle strength after a period of rest.

In 2012, a Cochrane systematic review assessed IVIG therapy for acute exacerbations or for chronic long-term myasthenia gravis.⁷⁵ Reviewers identified 7 RCTs including one unpublished trial, all of which investigated short-term benefit. The trials varied in inclusion criteria, comparator interventions, and outcome measures and, thus, study findings were not pooled. Five trials evaluated IVIG for treating myasthenia gravis worsening or exacerbation, and two evaluated IVIG for treatment of moderate or severe myasthenia gravis. Several trials were small, with insufficient statistical power. Reviewers concluded that there was some evidence for efficacy in exacerbations of myasthenia gravis, and that evidence for treating chronic myasthenia gravis was insufficient to form conclusions about efficacy.

Zinman et al (2007) is the only RCT that compared IVIG against placebo in 51 patients who had myasthenia gravis with progressive weakness.⁷⁶ 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. Remaining RCTs either compared IVIG with plasma exchange or compared 2 doses of IVIG. Gajdos et al (1997) compared IVIG with plasma exchange in 87 patients with myasthenia gravis exacerbations.⁷⁷ The study did not find a statistically significant difference in the efficacy between the 2 treatments; however, the study did determine that IVIG was better tolerated. Nine patients experienced adverse events (eight in the plasma exchange group, one in the IVIG group). Barth et al (2011) compared IVIG with plasma exchange in 84 patients with moderate-to-severe myasthenia gravis.⁷⁸ The study also did not find a statistically significant difference in the efficacy between treatments. Gajdos et al (2005) compared 2 doses of IVIG (1 g and 2 g/kg) in 170 patients with acute exacerbation of myasthenia

gravis.⁷⁹ Mean improvement in the myasthenic muscular scores did not differ significantly between doses after 2 weeks.

Section Summary: Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

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

Relapsing-Remitting Multiple Sclerosis

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

A 1998 TEC Assessment concluded that IVIG therapy for RRMS met TEC criteria.⁸⁰ However, by 2002, AAN was recommending the use of interferon beta (type B recommendation) and glatiramer acetate (type A recommendation). AAN suggested that IVIG was no longer considered a drug of choice for RRMS.⁸¹

Section Summary: Relapsing-Remitting Multiple Sclerosis

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

Autoimmune Mucocutaneous Blistering Diseases

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

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

The RCT, published in 2009 by Amagai et al, was multicenter, placebo-controlled and double-blind; it included adults with glucocorticoid-resistant pemphigus (defined as a failure to respond to the equivalent of prednisolone ≥ 20 mg/d).⁸³ Patients were randomized to a single cycle of IVIG 400 mg/kg/d for 5 days, IVIG 200 mg/kg/d for 5 days, or a placebo infusion for 5 days. The primary end point was the duration of time that patients could be maintained on the treatment protocol before symptoms required additional treatment (ie, time to escape protocol). Time to escape protocol was significantly longer for patients in the IVIG 400-mg group than for patients in the placebo group but not between the IVIG 200-mg group and the placebo group. Furthermore, a significant decrease in a pemphigus activity score was detected at all study observation points for patients in the IVIG 400-mg group and at all study observation points after day 15 in the IVIG

200-mg group. The pemphigus activity score did not decrease significantly at any time point in the placebo group.

Another RCT by the same research group was published in 2017 and evaluated IVIG for bullous pemphigoid.⁸⁴ The trial was multicenter, double-blind and placebo-controlled randomized trial and included 56 patients. The IVIG group received an intravenous drip infusion of human IgG, 400 mg/kg/d for 5 days and the placebo group received an intravenous drip infusion of saline for 5 days. The primary end point was the Disease Activity Score (DAS) on day 15 (lower score is a better outcome). Mean scores were 19.8 in the IVIG group and 32.3 in the placebo group, but the difference between groups was not statistically significant ($p=0.089$). In a post hoc analysis using the DAS on day 1 as a covariate, the DAS was significantly lower in the IVIG group (19.7) than in the placebo group (32.4) at day 15 ($p=0.041$). In patients with severe disease, there were significantly lower DAS scores in the IVIG than in the placebo group on days 8, 15, and 22; between-group scores did not differ in patients with mild or moderate disease.

Section Summary: Autoimmune Mucocutaneous Blistering Diseases

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

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

Several systematic reviews have evaluated the literature on toxic epidermal necrosis (TEN) and Stevens-Johnson syndrome (SJS). Most recently, in 2016, Huang et al identified 11 studies evaluating IVIG for TEN or SJS and TEN, none of which were RCTs.⁸⁵ Three of the studies had control groups and two of these included historical controls. IVIG was not found to reduce mortality in TEN or SJS and TEN. The pooled standardized mortality ratio in the 10 studies was 1.00 (95% CI, 0.76 to 1.32, $p=0.67$). A 2015 meta-analysis also did not demonstrate a survival advantage of IVIG for TEN and/or SJS.⁸⁶

Section Summary: Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

No RCTs have been published evaluating IVIG for TEN or SJS. There are several systematic reviews of observational studies, controlled and uncontrolled. A 2016 pooled analysis of data from 11 studies did not find a statistically significant benefit of IVIG therapy for mortality.

Idiopathic Inflammatory Myopathies

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

Dermatomyositis and Polymyositis

In 2012, Wang et al published a systematic review on IVIG treatment for adults with refractory dermatomyositis or polymyositis.⁸⁷ Reviewers identified 14 studies including 2 RCTs, 9 prospective case series, and 3 retrospective case series. Eleven of 14 studies included patients with refractory

disease. For example, a 1993 trial by Dalakas et al compared prednisone plus IVIG with prednisone plus placebo in 15 patients with refractory dermatomyositis.⁸⁸ At 3 months, there were significant increases in muscle strength in the IVIG group, as measured by mean scores on the modified MRC scale and the Neuromuscular Symptom Scale (mean modified MRC scale score, 84.6 IVIG vs 78.6 placebo; mean Neuromuscular Symptom Scale score, 51.4 IVIG vs 45.7 placebo). Repeated transfusions every 6 to 8 weeks can be required to maintain a benefit.

Miyasaka et al (2012) in Japan conducted an RCT of 26 patients with corticosteroid-resistant polymyositis or dermatomyositis who had received high-dose corticosteroid therapy for at least 1 month.⁸⁹ Patients were randomized to treatment with IVIG (n=12) or placebo (n=14) once daily for 6 consecutive days. The primary end point was change from baseline mean manual muscle test scores at 8 weeks. Change in mean manual muscle test was 11.8 points in the IVIG group vs 9.9 points in the placebo group. This difference was not statistically significant (1.9 points; 95% CI, -4.8 to 8.5). Other outcomes also did not differ significantly between groups.

A 2002 case series of 35 patients with polymyositis, all of whom had disease that required ongoing glucocorticoid therapy and none could be weaned from glucocorticoids despite trials of 1 or more additional therapies, showed some clinical benefit; 33 patients with initially elevated serum creatine kinase levels showed biochemical improvement; 25 of 35 showed improvement in muscle strength, which returned to near-normal in 10 of the 25 responders; 8 of 11 patients with esophageal dysfunction showed resolution of dysphagia; 12 of the 25 responders had complete clinical responses (absence of myositis activity) while receiving not more than prednisone 6 mg/d.⁹⁰ Mean follow-up for these patients was 39 months. Five patients discontinued all other medical treatments for myositis.

Subsection Summary: Dermatomyositis and Polymyositis

Idiopathic inflammatory myopathies comprise of dermatomyositis, polymyositis, and inclusion body myositis. The evidence for IVIG treatment of dermatomyositis and polymyositis consists of multiple RCTs and noncomparative studies. A systematic review of 12 studies concluded that IVIG therapy is effective for adults with refractory polymyositis or dermatomyositis. However, a recent RCT failed to show significant differences in muscle test scores between IVIG and placebo.

Inclusion Body Myositis

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

Subsection Summary: Inclusion Body Myositis

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

Systemic Lupus Erythematosus

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

IVIG therapy is proposed for SLE because of its immunomodulatory properties and also because it prevents infection in patients taking immunosuppressive drugs. A 2014 systematic review by Sakthiswary et al identified 13 studies on IVIG for treatment of SLE.⁹⁴ Three studies had control groups, and only one was an RCT.⁹⁵ Most studies had small sample sizes; only 3 had more than 50 patients, and the single RCT included only 14 patients. In a meta-analysis of 6 studies (n=216 patients), there was a statistically significant difference in SLE disease activity in IVIG-treated groups (SMD=0.58; 95% CI, 0.22 to 0.95). This analysis was limited because there were few data in non-IVIG-treated patients. A meta-analysis of data from 8 studies on the effect of IVIG on complement levels found a pooled response rate of 30.9% (95% CI, 22.1% to 41.3%). Findings on other outcomes were not pooled. However, there has been limited anecdotal experience and concerns about potential prothromboembolic effects and possible IVIG-associated azotemia in SLE.⁹⁶

Section Summary: Systemic Lupus Erythematosus

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

Immune Optic Neuritis

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

Two RCTs have studied the potential benefit of IVIG in this disease. Noseworthy et al (2001) planned to randomize 60 patients with persistent acuity loss after optic neuritis to IVIG or placebo.⁹⁷ The trial was terminated early after 55 patients were enrolled because investigators did not find a difference in the logMAR visual scores at 6 months (p=0.766). Roed et al (2005) randomized 68 in the acute phase of optic neuritis to IVIG (n=34) or placebo (n=34).⁹⁸ They found no differences in the visual outcome measure and disease activity as measured by magnetic resonance imaging after 6 months.

Section Summary: Immune Optic Neuritis

The evidence for IVIG treatment of immune optic neuritis consists of 2 RCTs that failed to demonstrate any benefit in visual outcomes measures with IVIG.

Crohn Disease

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

A 2012 systematic review of IVIG therapy for Crohn disease did not identify any randomized or nonrandomized controlled trials.⁹⁹ Reviewers found 5 case reports of IVIG used for single patients with Crohn disease, and the remaining literature identified included conference papers, abstracts only, or a nonsystematic review.

Section Summary: Crohn Disease

The evidence for IVIG treatment of Crohn disease consists of multiple case reports.

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. Published literature on the use of IVIG in hemophagocytic syndrome is limited to small case series.¹⁰⁰⁻¹⁰²

A 2012 systematic review on diagnosing and treating hemophagocytic lymphohistiocytosis in the tropics identified 156 cases; a portion of these patients were treated with IVIG.¹⁰³ Steroids were the most common treatment. IVIG was used in 30% of children and in 4% of adults.

Hemophagocytic syndrome–related mortality occurred in 32% of children and in 28% of adults.

Section Summary: Hemophagocytic Lymphohistiocytosis

The evidence for IVIG treatment of hemophagocytic lymphohistiocytosis consists of multiple case series and reports.

Warm Antibody Autoimmune Hemolytic Anemia

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

Published literature on the use of IVIG in warm antibody autoimmune hemolytic anemia is limited to observational data for 37 patients pooled from 3 institutions¹⁰⁴ and a case report.¹⁰⁵ Overall, 29 (39.7%) of 73 patients responded to IVIG therapy. Because of limited therapeutic value, it is used in patients refractory to conventional therapy with prednisone and splenectomy or as a conjunctive therapy in patients with very severe disease. Further, the effect is usually transient, unless repeated courses are given every 3 weeks.

Section Summary: Warm Antibody Autoimmune Hemolytic Anemia

The evidence for IVIG treatment of warm antibody autoimmune hemolytic anemia consists of pooled case series and a single case report.

Antiphospholipid Syndrome

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

Published literature on the use of IVIG in antiphospholipid syndrome includes a pooled analysis of 250 single case reports from a registry.¹⁰⁶ Results showed that a higher proportion of patients survived after the episode of antiphospholipid syndrome if they received triple therapy of anticoagulants, corticosteroids, plasma exchange, and/or IVIGs compared with combinations that did not use plasma exchange, IVIG, or both.

Section Summary: Antiphospholipid Syndrome

The evidence for IVIG treatment of antiphospholipid syndrome consists of pooled case series from a registry.

Alloimmune Processes

Neonatal Alloimmune Thrombocytopenia

Fetal and neonatal thrombocytopenia occurs when a maternal antibody directed against a paternal platelet-antigen crosses the placenta and causes thrombocytopenia in the fetus. Intracranial hemorrhage (ICH) is identified in 10% to 30% of affected neonates. Currently, screening for this condition is unavailable and, thus, thrombocytopenia is only identified at birth. However, subsequent fetuses that are platelet-antigen positive also will be at risk for thrombocytopenia, and the severity of thrombocytopenia may be increased. Treatment has focused on neonatal platelet transfusions, corticosteroids, and IVIG.

There are no RCTs evaluating the efficacy of IVIG or steroids alone vs placebo in alloimmune thrombocytopenia. Trials of this nature would be unethical because of the known risk of ICH with this condition. Rayment et al (2011), in a Cochrane systematic review, summarized the results of 4 RCTs on the maternal administration of corticosteroids and IVIG in pregnancies with neonatal alloimmune thrombocytopenia in 206 patients.¹⁰⁷ 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. Bussel et al (1996) did not find any differences in the fetal platelet counts between IVIG and IVIG with steroids.¹⁰⁸ Although there was no placebo-controlled arm, results can be compared with the course in a prior affected sibling, because the natural history of the disease suggests that subsequent births should be similarly, if not more severely, affected with thrombocytopenia. The study reported a mean increase in platelet count of 69,000/mL. There were no instances of ICHs, although hemorrhage had occurred previously in 10 untreated siblings. 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.¹⁰⁹ In a 2007 trial, Berkowitz et al showed good outcomes and comparable results between the IVIG group and the IVIG plus prednisone group in standard-risk pregnancies.¹¹⁰ Paridaans et al (2015) evaluated the effectiveness of a lower dose of IVIG (0.5 g/kg/wk vs 1 g/kg/wk) in an RCT of 23 women.¹¹¹ The primary outcome was fetal or neonatal ICH. The median newborn platelet count was $81 \times 10^9/L$ in the 0.5-g/kg group vs $110 \times 10^9/L$ in the 1-g/kg group ($p=0.644$).

Section Summary: Neonatal Alloimmune Thrombocytopenia

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

Recurrent Spontaneous Abortion

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

A 2006 Cochrane review of various immunotherapies for treating recurrent miscarriage concluded that IVIG therapy provides no significant beneficial effect over placebo in preventing further miscarriages.¹¹² Meta-analyses published in 2015 and 2016 that included 11 RCTs also found no significant difference in the frequency of the number of live birth with IVIG vs placebo or treatment as usual.^{113,114} A 1999 blinded RCT of 41 women treated with IVIG or saline placebo also found no differences in live birth rates.¹¹⁵ Likewise, a 2000 multicenter RCT comparing heparin plus low-dose aspirin with or without IVIG in women with lupus anticoagulant, anticardiolipin antibody,

or both, found no significant differences.¹¹⁶ In addition, a 2002 RCT of 58 women with at least 4 unexplained miscarriages compared IVIG with placebo and analyzed results by intention to treat.¹¹⁷ The live birth rate was similar for both groups; also, there were no differences in neonatal data (eg, birth weight, gestational age at delivery). Other nonrandomized but controlled trials have also reported no benefit for IVIG treatment.

Section Summary: Recurrent Spontaneous Abortion

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

Miscellaneous Indications

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

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

Two RCTs were identified. In 2016, Williams et al 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.¹¹⁸ After a 6-week double-blind treatment phase, there was the option of continuing treatment on an open-label basis for nonresponders. The primary outcome at 6 weeks, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score, did not differ significantly between groups. There was a mean decrease in the CY-BOCS of 23.9% in the IVIG group and 11.7% in the placebo group (effect size, 0.28; 95% CI, -0.39 to 0.95). Improvement in other outcomes (eg, mean Clinical Global Impressions improvement scores) also did not differ significantly between groups. A total of 24 participants met criteria for nonresponse at 6 weeks and received open-label IVIG. At week 12, scores on the CY-BOCS improved significantly compared with 6 weeks; however, the 12-week analysis did not include a placebo comparison.

A 1999 RCT by Perlmutter et al included 30 children who had new or severe exacerbations of obsessive-compulsive disorder or tic disorder after streptococcal infections.¹¹⁹ Patients were randomized to IVIG, plasma exchange, or placebo (10 per group). At the 1-month follow-up, IVIG and plasma exchange showed statistically significant improvements in obsessive-compulsive symptoms, anxiety, and overall functioning. The study included only 10 children who were treated with IVIG.

Section Summary: Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

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

Autism Spectrum Disorder

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

The evidence base supporting the use of IVIG in autism includes 3 case series. The first included 10 patients with abnormal immune parameters who received IVIG therapy monthly.¹²⁰ After 6 months, 5 of 10 patients showed marked improvement in several autistic characteristics. Remaining 2 case series failed to replicate these findings. In the second, 1 of 10 patients showed improvements in autistic symptoms after receiving IVIG.¹²¹ No improvements were observed in the third series.¹²² There are no randomized comparative trials evaluating IVIG therapy in autism.

Section Summary: Autism Spectrum Disorder

The evidence for IVIG treatment of autism spectrum disorder consists of multiple case series with conflicted findings; one case series reported benefit while two others failed to replicate those findings.

Complex Regional Pain Syndrome

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 lesion.

The evidence base supporting the use of IVIG treatment for complex regional pain syndrome consists of a crossover double-blinded RCT published by Goebel et al in 2010; it was conducted at an academic pain management center in the U.K.¹²³ 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. Authors reported that the mean pain intensity was 1.55 points lower after IVIG than after saline (95% CI, 1.29 to 1.82; $p < 0.001$). This is a short-term RCT with a small number of patients, and findings need to be confirmed in larger trials with longer follow-up. The optimal dose and treatment regimen are unknown.

Section Summary: Complex Regional Pain Syndrome

The evidence for IVIG treatment of complex regional pain syndrome consists of a small crossover RCT that showed improvements in pain scores compared with placebo. However, the evidence is insufficient to draw conclusions about the impact of IVIG on health outcomes in those who suffer with complex regional pain syndrome.

Alzheimer Disease

Three placebo-controlled double-blind, randomized trials in patients with Alzheimer disease were identified. Two RCTs included patients with mild-to-moderate Alzheimer disease. In a 2013 trial by Dodel et al with 56 patients, the primary outcome (area under the curve of plasma amyloid β (A β)_{1–40}) did not differ between the IVIG and the placebo groups.¹²⁴ Secondary outcomes, including cognitive and functional scales, also did not differ between groups. In 2017, Relkin et al 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.¹²⁵ The primary outcomes were change from baseline to 18 months on the cognitive subscale of the Alzheimer Disease Assessment scale and on the Alzheimer Disease Cooperative Study-Activities of Daily Living Inventory. Neither outcome was significantly improved in either IVIG groups compared with the placebo group.

The third RCT, published by Kile et al in 2017, included 50 patients with mild cognitive impairment (MCI) related to Alzheimer disease.¹²⁶ Patients were stratified into early and late MCI stages based on scores on the Clinical Dementia Rating, Sum of Boxes test (1 or less for the early MCI group and more than 1 for the late MCI group). Patients received a total IVIG dose of 2g/kg over 5 sessions, or placebo. The primary outcome was brain atrophy, defined as annualized percent change in the ventricular volume (APCV) measured by magnetic resonance imaging. In unadjusted analyses, APCV did not differ significantly between groups at 12 months or 24 months. In a subgroup analysis, the APCV was significantly lower in the IVIG compared with placebo group in patients with early MCI but not late MCI at 12 months, and there was not a significant difference at 12 months in either the early or late MCI groups. Secondary outcomes, cognition scores, and conversion to Alzheimer disease dementia did not differ between the IVIG and placebo groups at 12 or 24 months. As with the primary outcome, for several secondary outcomes, IVIG showed a significant benefit in the early MCI group at 12 months but not 24 months.

Section Summary: Alzheimer Disease

Three double-blind placebo-controlled randomized trials have been published evaluating IVIG in patients with Alzheimer disease. With the exception of a few subgroup analyses by MCI status, IVIG did not show significantly better outcomes than placebo for brain atrophy, level of plasma amyloid β (A β)1–40, and cognition and function. Studies differed in factors such as treatment protocols, outcomes assessed, and 2 of the 3 had relatively small sample sizes. Additional RCTs could be conducted to confirm whether IVIG benefits patients with early MCI.

Paraproteinemic Neuropathy

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

Results of a 1996 double-blind, placebo-controlled, randomized crossover trial of IVIG vs placebo in 11 patients with paraproteinemic IgM demyelinating polyneuropathy showed only a mild and transitory effect in 3 patients.¹²⁷ A 2002 RCT of 22 patients focused on short-term outcomes at 2 weeks.¹²⁸ No significant differences were found between the treatment and placebo groups.

Section Summary: Paraproteinemic Neuropathy

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

Chronic Fatigue Syndrome

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

Numerous noncomparative studies have shown subjective benefits of IVIG therapy on chronic fatigue syndrome, but a 1997 double-blind, randomized, placebo-controlled trial in 99 patients with chronic fatigue syndrome reported no therapeutic benefit of IVIG.¹²⁹

Section Summary: Chronic Fatigue Syndrome

The evidence for IVIG treatment of chronic fatigue syndrome consists of multiple noncomparative studies and an RCT that failed to show a benefit of IVIG.

Acute Myocarditis

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

Multiple case reports have suggested that patients with acute myocarditis may benefit from high-dose IVIG.⁹⁶ Spontaneous rapid or gradual improvement is common with acute myocarditis, and improvement noted in these case series may have been part of the natural history of the disease. The literature has been summarized in a 2015 Cochrane systematic review¹³⁰ that included a 2001 placebo-controlled randomized trial of 62 adult patients with recent-onset dilated cardiomyopathy¹³¹ and a 2012 quasi-randomized study of 83 children with suspected viral encephalitis and associated myocarditis with a left ventricular ejection fraction less than 0.40.¹³² Both trials were rated as very low quality and had high risk of bias. In the RCT of adults, event-free survival did not differ significantly but favored the control group (OR=0.52; 95% CI, 0.12 to 2.30). The major limitation was that some patients did not have viral myocarditis because only 10 of 62 patients showed inflammation on cardiac biopsy. In the quasi-randomized trial in children, the incidence of event-free survival was 25 (96%) of 26 in the treated group and 44 (77%) of 57 in the control group (OR=7.39; 95% CI, 0.91 to 59.86).

Section Summary: Acute Myocarditis

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

Refractory Recurrent Pericarditis

Refractory recurrent pericarditis is defined as recurrent pericarditis not responding to conventional anti-inflammatories such as aspirin, nonsteroidal inflammatory drugs, corticosteroids, and colchicine.

Imazio et al (2016) conducted a systematic review and summarized data of 30 patients (4 case series, 13 case reports).¹³³ Approximately 47% of patients had idiopathic recurrent pericarditis, 10% had an infective cause, and the remainder had systemic inflammatory disease. IVIG was generally administered at a dose of 400 to 500 mg/kg/d for 5 consecutive days, with repeated cycles according to the clinical response. Overall, recurrences occurred in 26.6% of cases after the first IVIG cycle, and 22 (73.3%) of the 30 patients were recurrence-free after a mean follow-up of approximately 33 months.

Section Summary: Refractory Recurrent Pericarditis

The evidence for IVIG treatment of refractory recurrent pericarditis consists of multiple case reports and case series that reported benefit. Controlled trials are lacking.

Stiff Person Syndrome

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

Multiple case reports have suggested that patients with stiff person syndrome may benefit from IVIG. The benefit was confirmed in a small 2001 crossover randomized comparing IVIG with placebo in 16 patients with stiff person syndrome and anti-GAD65 autoantibodies who were all maintained on current doses of benzodiazepines throughout the study.¹³⁴ After a 1-month washout period, patients were crossed over to 3 months of the alternative treatment. Stiffness scores decreased significantly on IVIG, but not on placebo, regardless of order. Eleven (69%) patients were able to walk more easily or without assistance; the frequency of falls decreased, and patients were able to perform work-related or household tasks. The duration of benefit lasted 6 weeks to 1 year without additional treatment.

Section Summary: Stiff Person Syndrome

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

Noninfectious Uveitis

Noninfectious uveitis is the inflammation of the eye that results from noninfectious causes such as eye trauma, anomalous immune processes, or unknown etiology.

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

Section Summary: Noninfectious Uveitis

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

Postpolio Syndrome

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

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

Section Summary: Postpolio Syndrome

The evidence for IVIG treatment of postpolio syndrome consists of multiple RCTS and noncomparative studies that were summarized in a systematic review; it concluded that IVIG

treatment was not associated with reduction in pain and fatigue or an improvement in muscle strength.

Necrotizing Fasciitis

In 2017, Madsen et al published a placebo-controlled randomized trial evaluating IVIG for patients with necrotizing soft issue infection (eg, necrotizing fasciitis).¹³⁸ The trial included 100 patients with confirmed necrotizing soft tissue infection who were admitted or had planned admissions to the intensive care unit. The primary outcome was patient-reported physical function at 6 months, assessed using the Physical Component Summary score of the 36-Item Short-Form Health Survey. The mean Physical Component Summary score adjusted for site of infection was 36 in the IVIG group and 21 in the placebo group. The difference between groups was not statistically significant ($p=0.81$). Other outcomes (ie, mortality, use of life support in the intensive care unit, bleeding, amputation) did not differ significantly between groups.

Section Summary: Necrotizing Fasciitis

The evidence for IVIG treatment of necrotizing fasciitis consists of an RCT that did not find a significant difference in outcomes between IVIG and placebo. The evidence is insufficient to draw conclusions on the impact of IVIG on health outcomes in patients with necrotizing fasciitis.

SUMMARY OF EVIDENCE

Immunodeficiency States

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

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

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

For individuals who have acute ABMR after solid organ transplant who receive IVIG therapy, the evidence includes retrospective case series and a systematic review. Relevant outcomes are

disease-specific survival, symptoms, change in disease status, morbid events, quality of life, hospitalizations, and treatment-related mortality and morbidity. Compared with standard of care, IVIG treatment for ABMR has shown potential benefit in retrospective or small prospective studies. Larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Infections

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

For individuals who are HIV-infected children with recurrent bacterial infection and intravenous immunoglobulin G levels below 400 mg/dL who receive IVIG therapy, the evidence includes a single RCT. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy for prevention of opportunistic infections in HIV-infected children has shown reductions in serious and minor infections without reduction in other clinically important outcomes, including mortality. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who are preterm and low birth weight infants with sepsis who receive IVIG therapy (treatment), the evidence includes multiple RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, morbid events, hospitalizations, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for neonatal sepsis has shown no differences in the rates of death or major disability. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

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

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

For individuals who have toxic shock syndrome who receive IVIG therapy, the evidence includes 1 small RCT and multiple observational studies. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with placebo, IVIG treatment for toxic shock syndrome in adults has shown reductions in mortality in the small RCT and in multiple observational studies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Autoimmune and Inflammatory Conditions

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

For individuals who have Guillain-Barré syndrome who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, and treatment-related mortality and morbidity. Compared with plasma exchange or combination with plasma exchange, IVIG therapy did not show any difference in outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. For individuals who have Kawasaki disease who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are disease-specific mortality, change in disease status, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown significant decreases in new coronary artery abnormalities. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have granulomatosis with polyangiitis (Wegener granulomatosis) who receive IVIG therapy, the evidence includes systematic reviews and a least 1 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 in other vasculitides such as Wegener granulomatosis. A 2013 Cochrane review identified 1 RCT on IVIG for Wegener granulomatosis. This small trial, found significantly more responders in the IVIG treatment group at 3 months but no significant differences after 3 months or in the frequency of relapse or use of other medications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic inflammatory demyelinating polyneuropathy (CIDP) who receive IVIG therapy, the evidence includes multiple RCTs, a systematic review, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG

therapy has shown clinically meaningful improvements in disability. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CIDP who receive SCIG therapy, the evidence includes single RCT. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, SCIG therapy has shown clinically meaningful improvements in disability. However, the relative benefits of SCIG therapy over IVIG remain unclear because of lack of direct comparison with IVIG. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

For individuals who have Eaton-Lambert myasthenic syndrome who receive IVIG therapy, the evidence includes 1 RCT and multiple observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in outcomes that measured muscle strength and activity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have severe refractory myasthenia gravis or myasthenic exacerbation who receive IVIG therapy, the evidence includes multiple RCTs and 1 meta-analysis. Relevant outcomes are overall survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in disability and muscle strength. Compared with plasma exchange, IVIG therapy did not show significant improvement but was better tolerated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsing-remitting multiple sclerosis (RRMS) who receive IVIG therapy, the evidence includes multiple RCTs and technology assessments. Relevant outcomes are overall survival, symptoms, disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. According to

technology assessments, IVIG therapy is no longer considered a treatment of choice for RRMS. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

For individuals who have autoimmune mucocutaneous blistering diseases who receive IVIG therapy, the evidence includes multiple uncontrolled studies, 1 RCT, and a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown clinically meaningful improvements in disease activity. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have toxic epidermal necrosis or Stevens-Johnson syndrome who receive IVIG therapy, the evidence includes multiple systematic reviews and meta-analysis. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has not shown statistically significant benefits for mortality. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have dermatomyositis or polymyositis who receive IVIG therapy, the evidence includes 2 RCTs, multiple noncomparative observational studies, and a systematic review. Relevant outcomes are change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. In 1 RCT, compared with placebo, IVIG therapy has shown improvements in muscle strength. A large case series also noted improvements in most patients. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have systemic lupus erythematosus who receive IVIG therapy, the evidence includes 1 RCT, multiple observational studies, and a meta-analysis. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Although observed improvements in outcomes have suggested potential benefit with IVIG therapy for surrogate outcomes, data are retrospective. RCTs are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have Crohn's disease who receive IVIG therapy, the evidence includes 5 case reports of single patients summarized in a systematic review. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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

Alloimmune Processes

For individuals who have neonatal alloimmune thrombocytopenia who receive IVIG therapy, the evidence includes multiple 2 RCTs and a systematic review. Relevant outcomes are disease-specific survival, change in disease status, and treatment-related mortality and morbidity. Compared with combination use with corticosteroids, IVIG alone did not show any additional improvements in platelet counts. Multiple trials have demonstrated increased platelet counts with IVIG therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Miscellaneous Indications

For individuals who have pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections who receive IVIG therapy, the evidence includes 1 small RCT. Relevant outcomes are symptoms, change in disease status, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown improvements in obsessive-compulsive symptoms, anxiety, and overall functioning. The optimal dose and duration of treatment are

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

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

For individuals who have complex regional pain syndrome who receive IVIG therapy, the evidence includes 1 RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown improvements in pain scores. However, methodologic limitations restrict the conclusions drawn from these data of 12 patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Alzheimer disease who receive IVIG therapy, the evidence includes multiple RCTs. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show improvements in biomarkers. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have chronic fatigue syndrome who receive IVIG therapy, the evidence includes anecdotal reports and 1 RCT. Relevant outcomes are symptoms, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown no therapeutic benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute myocarditis who receive IVIG therapy, the evidence includes multiple case reports, 1 quasi-randomized, and 1 RCT. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has failed to show improvements in event-free survival in the RCT while a quasi-randomized study showed favorable effects on incidences of event-free survival. However, both studies were rated as very low quality and had high risk of bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have refractory recurrent pericarditis who receive IVIG therapy, the evidence includes multiple case reports and case series. Relevant outcomes are overall survival, change in disease status, quality of life, and treatment-related mortality and morbidity. Although improvements were observed in some patients, controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have stiff person syndrome who receive IVIG therapy, the evidence includes multiple case reports and 1 RCT. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Compared with placebo, IVIG therapy has shown decreases in stiffness score and improvements in functional outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

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

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

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

Additional clinical input was obtained in June 2013, focusing on severe anemia due to parvovirus B19. Input was received from 3 reviewers, all hematologists, and there was consensus that IVIG

is not investigational for this indication. There was a lack of consensus among the 3 reviewers on any specific clinical or patient characteristics that can be used to select patients with severe anemia due to parvovirus B19 for treatment with IVIG and on any treatments that should be used by these patients before IVIG.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Immunodeficiency States

Primary Humoral Immune Deficiencies

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

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

American Academy of Allergy, Asthma, and Immunology

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

Hematopoietic Cell Transplantation (Prophylaxis)

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

Acute Antibody-Mediated Rejection After Solid Organ Transplant

In 2010, the CBS and NAC developed guidelines addressing the use of IVIG for sensitized individuals undergoing solid organ transplantation.¹⁴⁰ The following conclusions were issued on nonkidney solid organ transplantation:

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

Chronic Lymphocytic Leukemia

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

Infections

Infections in HIV-Infected Children

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

Neonatal Sepsis

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

Autoimmune/Inflammatory Conditions

Idiopathic Thrombocytopenic Purpura

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

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

Guillain-Barré Syndrome

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

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

Kawasaki Syndrome and Other Vasculitides

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

Chronic Inflammatory Demyelinating Polyneuropathy

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

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

Multifocal Motor Neuropathy

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

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

Eaton-Lambert Myasthenic Syndrome

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

Neuromyelitis Optica

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

Severe Refractory Myasthenia Gravis or Myasthenic Exacerbation

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

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

Relapsing-Remitting Multiple Sclerosis

In 2002, AAN published a technology assessment on therapies for multiple sclerosis.⁸¹ The assessment was reviewed and reaffirmed in 2008. AAN's rating system was A (established as effective), B (probably effective, ineffective, or harmful), C (possibly effective, ineffective, or harmful), or U (data inadequate). The assessment offered the following recommendations on IVIG:

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

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

Autoimmune Mucocutaneous Blistering Diseases

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

Toxic Epidermal Necrosis and Stevens-Johnson Syndrome

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

Idiopathic Inflammatory Myopathies

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

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

Immune Optic Neuritis

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

Alloimmune Processes

Neonatal Alloimmune Thrombocytopenia

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

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

Recurrent Spontaneous Abortion

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

Miscellaneous

Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

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

Autism Spectrum Disorder

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

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

Chronic Fatigue Syndrome

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

Viral Myocarditis

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

Stiff Person Syndrome

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

Postpolio Syndrome

EFNS updated its guidelines on the definition and management of postpolio syndrome in 2011.¹⁵³ The guidelines indicated that IVIG could have a modest therapeutic effect on postpolio syndrome, though there were limitations to the study evidence (small sample size, inadequate comparators, appropriate dosage). Due to these limitations, EFNS concluded that IVIG cannot be recommended as a standard treatment.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00892112 ^a	Intravenous Immunoglobulin (IVIg) for Parvovirus B19(PVB19) Mediated Cardiomyopathy	50	Mar 2018
NCT02176863 ^a	Study of the Efficacy and Safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in Patients With Post-polio Syndrome (FORCE)	210	Sep 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03065244	KIDCARE (Kawasaki Disease Comparative Effectiveness Trial) (KIDCARE)	250	Sep 2020
NCT02899702	Effectiveness of Intravenous Immunoglobulins (IVIg) in Toxic Shock Syndromes in Children (IGHN2)	156	Jan 2021
NCT03194815	IVIg and Rituximab in Antibody-associated Psychosis - SINAPPS2 (SINAPPS2)	80	Dec 2021

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

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

CPT/HCPCS

- 90283 Immune globulin (IgIV), human, for intravenous use
- 90284 Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
- 96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- 96366 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
- 96369 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to one hour, including pump set-up and establishment of subcutaneous infusion site(s)
- 96370 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
- 96371 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure)
- J1459 Injection, immune globulin (Privigen), intravenous, nonlyophilized (eg, liquid), 500 mg
- J1555 Injection, immune globulin, 100mg
- J1556 Injection, immune globulin (bivigam), 500 mg
- J1557 Injection, immune globulin (Gammaplex), intravenous, nonlyophilized (eg, liquid), 500 mg
- J1559 Injection, immune globulin (Hizentra), 100 mg
- J1561 Injection, immune globulin (Gamunex/Gamunex-C/Gammaked), nonlyophilized (eg, liquid), 500 mg
- J1566 Injection, immune globulin, intravenous, lyophilized (eg, powder), not otherwise specified, 500 mg
- J1568 Injection, immune globulin (Octagam) intravenous, nonlyophilized (eg, liquid), 500 mg
- J1569 Injection, immune globulin (Gammagard liquid) intravenous, nonlyophilized (eg, liquid), 500 mg
- J1572 Injection, immune globulin (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (eg, liquid), 500 mg
- J1575 Injection, immune globulin/hyaluronidase (Hyqvia), 100 mg
- J1599 Injection, immune globulin, intravenous, nonlyophilized (eg, liquid), not otherwise specified, 500 mg

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

ICD-10 Diagnoses

A48.3	Toxic shock syndrome
B20	Human immunodeficiency virus [HIV] disease
B95.0	Streptococcus, group A, as the cause of diseases classified elsewhere
B95.1	Streptococcus, group B, as the cause of diseases classified elsewhere
B95.2	Enterococcus as the cause of diseases classified elsewhere
B95.3	Streptococcus pneumoniae as the cause of diseases classified elsewhere
B95.4	Other streptococcus as the cause of diseases classified elsewhere
B95.5	Unspecified streptococcus as the cause of diseases classified elsewhere
B95.61	Methicillin susceptible Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.62	Methicillin resistant Staphylococcus aureus infection as the cause of diseases classified elsewhere
B95.7	Other staphylococcus as the cause of diseases classified elsewhere
B95.8	Unspecified staphylococcus as the cause of diseases classified elsewhere
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D59.1	Other autoimmune hemolytic anemias
D68.61	Antiphospholipid syndrome
D69.3	Immune thrombocytopenic purpura
D69.6	Thrombocytopenia, unspecified
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.2	Selective deficiency of immunoglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D80.7	Transient hypogammaglobulinemia of infancy
D80.8	Other immunodeficiencies with predominantly antibody defects
D80.9	Immunodeficiency with predominantly antibody defects, unspecified
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.8	Other common variable immunodeficiencies
D83.9	Common variable immunodeficiency, unspecified
G11.3	Telangiectasia (cerebellar) (Louis-Bar)
G35	Multiple sclerosis
G60.0	Hereditary motor and sensory neuropathy
G60.1	Refsum's disease

- G60.2 Neuropathy in association with hereditary ataxia
- G60.3 Idiopathic progressive neuropathy
- G60.8 Other hereditary and idiopathic neuropathies
- G60.9 Hereditary and idiopathic neuropathy, unspecified
- G61.0 Guillain-Barré syndrome
- G70.01 Myasthenia gravis with (acute) exacerbation
- G73.3 Myasthenic syndromes in other diseases classified elsewhere
- I44.0 Atrioventricular block, first degree
- I44.1 Atrioventricular block, second degree
- I44.2 Atrioventricular block, complete
- I44.30 Unspecified atrioventricular block
- I44.39 Other atrioventricular block
- I44.4 Left anterior fascicular block
- I44.5 Left posterior fascicular block
- I44.60 Unspecified fascicular block
- I44.69 Other fascicular block
- I44.7 Left bundle-branch block, unspecified
- I45.0 Right fascicular block
- I45.10 Unspecified right bundle-branch block
- I45.19 Other right bundle-branch block
- I45.2 Bifascicular block
- I45.3 Trifascicular block
- I45.4 Nonspecific intraventricular block
- I45.5 Other specified heart block
- I45.6 Pre-excitation syndrome
- I45.81 Long QT syndrome
- I45.89 Other specified conduction disorders
- I45.9 Conduction disorder, unspecified
- L10.0 Pemphigus vulgaris
- L10.1 Pemphigus vegetans
- L10.2 Pemphigus foliaceus
- L10.3 Brazilian pemphigus [fogo selvagem]
- L10.4 Pemphigus erythematosus
- L10.5 Drug-induced pemphigus
- L10.81 Paraneoplastic pemphigus
- L10.89 Other pemphigus
- L10.9 Pemphigus, unspecified
- L12.0 Bullous pemphigoid
- L12.1 Cicatricial pemphigoid
- L12.2 Chronic bullous disease of childhood
- L12.30 Acquired epidermolysis bullosa, unspecified
- L12.31 Epidermolysis bullosa due to drug
- L12.35 Other acquired epidermolysis bullosa
- L12.8 Other pemphigoid
- L12.9 Pemphigoid, unspecified
- L51.3 Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
- M30.3 Mucocutaneous lymph node syndrome [Kawasaki]
- M33.90 Dermatopolymyositis, unspecified, organ involvement unspecified
- M33.91 Dermatopolymyositis, unspecified with respiratory involvement

- M33.92 Dermatopolymyositis, unspecified with myopathy
- M33.93 Dermatopolymyositis, unspecified without myopathy
- M33.99 Dermatopolymyositis, unspecified with other organ involvement
- P61.0 Transient neonatal thrombocytopenia
- Z94.81 Bone marrow transplant status

REVISIONS

<p>01-12-2007 effective 04-01-2007</p>	<p>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.</p> <p>In "Policy" section, added #23 "Prior to renal transplantation with high levels of panel reactive antibodies (PBA)" as recommended by the Medical Director.</p> <p>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."</p> <p>In "Coding" CPT/HCPCS section, added HCPCS codes J1562 due to the 2007 CPT changes.</p> <p>In "Reference" Government Agency; Medical Society; and Other Authoritative Publications section added #2.</p>
<p>09-12-2007</p>	<p>Revised wording of Policy #1 – Primary humoral immunodeficiencies:</p> <ol style="list-style-type: none"> 1. Primary humoral immunodeficiencies <ol style="list-style-type: none"> a. Normal or subnormal gamma globulin and/or subclasses with recurrent significant infections. A functional 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. <p>Moved to Policy #24 - Chronic B Cell Lymphocytic Leukemia, multiple myeloma, or B cell lymphoma with low immunoglobulin levels</p> <p>Moved to Policy #25 - Profound neutropenia in neonatal sepsis (WBC 5,000 or below) –Allow for a single dose.</p>
<p>02-28-2011</p>	<p>Significant updates to Policy Language section. The following policy language has been updated:</p> <p>All immune globulin therapy will be reviewed for medical necessity prior to payment. See Utilization Section for details. Indications for immune globulin include:</p> <ol style="list-style-type: none"> 1. Immunodeficiency states: <p>One of the following six is required:</p> <ol style="list-style-type: none"> a. A functional immune deficiency manifested by recurrent serious infections. Needs to be demonstrated by the lack of antibody response to pneumococcal vaccine with pre and post antibody titers (patients with selective antibody deficiencies may have normal IgG levels but suboptimal response to pneumococcal vaccine. At least a two fold increase in antibody levels to at least half of 12 serotypes constitutes a normal response to pneumococcal immunization) and recurrent significant infections or b. A total IgG level of less than 200 mg/dl with a history of life threatening infection such as bacterial meningitis or sepsis. Testing for pneumococcal antibody response is not needed.

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| | <ul style="list-style-type: none"> c. B Cell Lymphocytic Leukemia (CLL) (eg multiple myeloma, chronic lymphocytic leukemia with low immunoglobulin levels or B cell lymphoma). d. Transient hypogammaglobulinemia of childhood <ul style="list-style-type: none"> • 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) <ul style="list-style-type: none"> • 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. <ol style="list-style-type: none"> 2. Idiopathic thrombocytopenia (ITP) <ol style="list-style-type: none"> a. Acute Idiopathic thrombocytopenia (ITP) <ol style="list-style-type: none"> 1) Management of acute bleeding, due to severe thrombocytopenia (platelet counts usually less than 30,000/ul; 2) To increase platelet counts prior to invasive surgical procedures, eg, splenectomy; 3) In patients with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage b. Chronic Refractory ITP <ol style="list-style-type: none"> 1) Prior to treatment with corticosteroids and splenectomy and; 2) Duration of illness of greater than six months and; 3) Age of 10 years or older and; 4) No concurrent illness/disease explaining thrombocytopenia and; 5) Platelet counts persistently at or below 20,000/ul. 3. HIV associated thrombocytopenia – Allow treatment (same as ITP) 4. Immune thrombocytopenic purpura of pregnancy – Allow for 5 days. 5. Neonatal alloimmune thrombocytopenia – Allow for 5 days. 6. Kawasaki Syndrome 7. Organ transplant – graft versus host disease. Allow treatment, but treatment should be short-term unless it is "chronic" graft versus host. 8. Guillain Barré Syndrome – Allow for no longer than 1 month. 9. Bone Marrow transplant 10. Landau-Kleffner Syndrome – Allow for six weeks with documented speech improvement, only if patient has completed a course of prednisone. Additional treatment requires prior approval. 11. Polymyositis – Allow for six months if no response to steroids and observe for relapse. 12. Dermatomyositis – Allow for six months if no response to steroids and observe for relapse. 13. HIV associated polyneuropathy. 14. Multifocal motor neuropathy. 15. Chronic inflammatory demyelinating polyneuropathy (CIDP) 16. Myasthenia gravis – Only when all other treatments fail. 17. Intractable seizure – Not recommended unless all other measures fail. 18. Rasmussen encephalitis |
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	<p>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)</p> <p>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.</p> <p>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.</p> <p>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</p> <p>Reference section updated.</p>
07-15-2011	<p>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”</p> <p>In the Coding Section Added HCPCS code J1559</p>
08-19-2011	<p>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.”</p> <p>In the Policy section: ▪ Item 16, b, added “; or “at the end. ▪ Item 16, added the following: ○ “c. Platelet counts less than 20,000/ul (risk of intracerebral hemorrhage; or” ○ “d. Management of acute bleeding with platelet counts less than 30,000/ ul; or” ○ “e. Increase platelet counts, prior to major surgical procedures.”</p> <p>Updated the Rationale section. Updated the Reference section.</p>
01-01-2012	<p>In the Coding section: ▪ Removed HCPCS code C9270 ▪ Added HCPCS code J1561. ▪ Revised HCPCS code J1561: to include Gammaked</p>
04-13-2012	<p>Updated Description section.</p>

	<p>In the Policy section:</p> <ul style="list-style-type: none"> • In Item B, #1, b, fourth paragraph, removed “with clearly impaired responses to both protein and / or polysaccharide antigens and” and inserted “who” to read “Immunoglobulin replacements should be reserved for patients who have failed the following treatments:” ▪ In Item B, #1, b, fourth paragraph, second bullet, removed “A high percentage of patients have concurrent allergic disease.” and inserted “anatomic abnormalities conducive to ENT procedures” to read “(eg asthma, allergic rhinitis, anatomic abnormalities conducive to ENT procedures).” ▪ In Item B, #5, removed “or the member has experienced significant complications” to read “...when corticosteroids, and immune-suppressive agents have failed.” ▪ In Item B, #8, removed “with IgG level less than 600 mg/dL; and:” to read “Chronic Lymphocytic Leukemia (CLL) in Patients with Hypogammaglobulinemia” ▪ In Item B, #8, a, removed “1 server bacterial infection within preceding 6 months or 2 or more bacterial infections in one year; or” and inserted “recurrent or persistent bacterial infections” ▪ In Item B, #11, inserted “or previous pregnancy affected by FAIT” ▪ In Item B, #14, removed “Bacterial Infection” and “infected children” to read “HIV Infected Children who meet the following criteria:” ▪ In Item B, #14, b, removed “ie, defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1 year period” to read “Recurrent serious bacterial infections;” ▪ In Item B, #14, c, removed “Living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live” to read “Failure to form antibodies to common antigens, such as measles, pneumococcal, and / or Haemophilus influenza type b vaccine;” ▪ In Item B, #14, e, removed “HIV infected children with” to read “Chronic bronchiectasis that is...” ▪ In Item B, #26, inserted “diagnosed on the basis of electrophysiologic findings.” ▪ In Item B, #27, b, removed “Two or more and “or a single life threatening infection” to read “Recurrent significant infections in last year;” ▪ In Item B, #33, removed “for children whose symptoms do not improve with” and inserted “refractory to” to read “Rasmussen Encephalitis refractory to antiepileptic drugs and corticosteroids.” • In Item B, #34, removed “Sever cases of toxic shock syndrome that have not responded to fluids and vasopressors” ▪ In Item D, inserted the following conditions: <ol style="list-style-type: none"> 1. chronic progressive multiple sclerosis; 2. refractory rheumatoid arthritis and other connective tissue diseases, including systemic lupus erythematosus; 3. recurrent spontaneous abortion (see below for related laboratory tests); 4. inclusion-body myositis; 5. polymyositis, including refractory polymyositis; 6. myasthenia gravis in patients responsive to immunosuppressive treatment; 7. other vasculitides besides Kawasaki disease, including vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA; eg, 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;
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	<ul style="list-style-type: none"> 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	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ 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.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added HCPCS codes: C9130 and J1599 ▪ Removed HCPCS code J1562 ▪ Added ICD-10 diagnosis codes (<i>Effective October 1, 2014</i>)
	Updated Reference section.
01-21-2014	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added new code: J1556 (<i>Effective January 1, 2014</i>) ▪ Removed code: C9130 (<i>Deleted code, effective December 31, 2013</i>)
09-12-2014	<p>In Policy section:</p> <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Added ICD-9 code 334.8 ▪ Added ICD-10 code G11.3
	Updated Reference section.
11-12-2014	In Description section: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ In Item B, diseases were alphabetized for research ease. ▪ In Item B, #5, added "B Cell", and "(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: <ul style="list-style-type: none"> ▪ In Item B, corrected numbering of items 33-40.
07-10-2015	In Policy section: <ul style="list-style-type: none"> ▪ In Item B 28 b, removed "significant: and "in last year", to read, "Recurrent or persistent infections;" ▪ Removed Item B 28 c, "Evidence of specific antibody deficiency such as those to pneumococcal vaccine serotypes." ▪ In Item B 32, added "common variable immunodeficiency [CVID]" to read "Primary Humoral Immunodeficiencies (to include X-linked agammaglobulinemia [Burton] X-linked hyper-IgM syndrome, severe combined immunodeficiency [SCID], common variable immunodeficiency [CVID], Wiskott-Aldrich syndrome, and ataxis telangiectasia) with a history of significant recurrent infections and one of the following:" ▪ In Item B 32 b, added "polyvalent" and polysaccharide" to read, "The interpretation of response to polyvalent pneumococcal polysaccharide vaccine is as follows:" ▪ Removed Item D, 28, "organ transplant rejection;"
	Updated References section.
08-20-2015	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> ▪ 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

	<p>organ transplant."</p> <ul style="list-style-type: none"> ▪ Alphabetized Item B criteria. ▪ Alphabetized Item D criteria. <p>In Policy Guidelines section:</p> <ul style="list-style-type: none"> ▪ 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	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ 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.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added coding bullets.
	Updated References section.
10-01-2017	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 code: M33.93.
11-08-2017	Updated Description section.
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Removed ICD-9 codes.
01-01-2018	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added HCPCS code: J1555. ▪ Updated coding bullets.

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