



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Immune Globulin Intravenous (Human) (IVIG): Carimune™ NF, Flebogamma®, Gammagard™, Gammar®, P.I.V., Gamunex®, Gamunex-C®, Iveegam® EN, Octagam®, Panglobulin® NF, Polygam® S/D, Privigen®**

Effective Date ..... 4/15/2011  
Next Review Date ..... 4/15/2012  
Coverage Policy Number ..... 5026

## Table of Contents

Coverage Policy ..... 1  
General Background ..... 8  
Coding/Billing Information ..... 24  
References ..... 26  
Policy History ..... 31

## Hyperlink to Related Coverage Policies

Immune Globulin Subcutaneous [Human] (Gamunex-C®, Hizentra™, Vivaglobin®)

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supersedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

CIGNA covers intravenous immune globulin (human) (IVIG) as medically necessary for any of the conditions listed below when ALL of the following are present:

- The medical condition-specific criteria as listed below are fully met.
- The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to IVIG therapy for the condition being addressed.

Initial authorizations are restricted to 3 months unless otherwise specified within the individual criteria listed below by indication.

A reauthorization for up to 6 months is covered as medically necessary when ALL of the following criteria are met:

- the medical condition or disease under treatment has not fully resolved and the treatment has not exceeded any applicable duration listed below
- there continues to be a sustained beneficial response to IVIG as evidenced by treatment notes or a clinical narrative detailing progress to date and the expected frequency and duration of any proposed IVIG use going forward
- the requested frequency and dosage of IVIG is supported by evidence-based literature
- where clinically appropriate, titration has occurred to the minimum dose and frequency to achieve sustained clinical effect

### Primary Immunodeficiency

Condition	Criteria for Use
Primary Immunodeficiency	Either (1) or (2)

#### 1) Hypo or Normogammaglobulinemia (including Common Variable Immunodeficiency [CVID]) when ALL of the following criteria are met (A, B, and C):

##### A) Immunologic evaluation – (Any ONE of the following):

- Serum IgG below the lower limits of normal on at least 2 occasions
- IgG sub-class deficiency of 1 or more serum IgG subclasses below the lower limits of normal on at least 2 occasions
- For Specific Antibody Deficiency (SAD), normal immunoglobulin levels

##### B) Impaired Antibody Response (ONE of the following)

- Lack of protective antibody titers (Tetanus and diphtheria or HiB) measured 3-4 weeks after immunization
- Inadequate response to polysaccharide vaccine (pneumococcal vaccine) in at least 30% of the serotypes tested as evidenced by either a post immunization antibody concentration of less than 1.3 mcg/mL OR less than a 4-fold increase over baseline

##### C) Recurrent Infection (ALL of the following)

- history of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy
- evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable
- supporting diagnostic imaging and/or laboratory results where applicable

#### 2) Selected Specific Primary Immunodeficiency Disorders when ONE of the following criteria is met:

- Agammaglobulinemia defined as serum IgG < 200 mg/dl
- Extremely low (<2%) or absent B cell count (CD19<sup>+</sup>)
- documentation of a recognized genetic defect supporting diagnosis\*
- transient hypogammaglobulinemia of infancy with serum immunoglobulins below the age-specific normal range and evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIG is only used for up to 6 months before re-evaluating the need for continued treatment)
- Hyperimmunoglobulinemia E syndrome as evidenced by an elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and skin infections (abscess)
- Selective IgA deficiency documented by serum IgA less than 0.07 g/L with normal IgG, IgM in an individual older than 4 years with history of recurrent gastrointestinal infections

### Secondary Immunodeficiency

Condition	Criteria for Use
High-risk, preterm, low-birth-weight neonates	Prevention or adjunct treatment for infection
HIV-infected children	Prevention of bacterial infections for CD4+ counts > 200/μl,

Condition	Criteria for Use
	when used in conjunction with antiretroviral treatment
Acquired hypogammaglobulin conditions, including: <ul style="list-style-type: none"> <li>Multiple Myeloma</li> <li>B-cell chronic lymphocytic leukemia (CLL)</li> </ul>	Treatment when the following criteria are met: <ul style="list-style-type: none"> <li>serum IgG below the lower limits of normal on at least 2 occasions</li> <li>recurrent sinopulmonary or serious bacterial infections</li> </ul>
Allogeneic hematopoietic stem cell transplant (HSCT) or bone marrow transplantation (BMT)	Prevention of infection in allogeneic HSCT recipients with serum IgG below the lower limits of normal on at least 2 occasions: <ul style="list-style-type: none"> <li>within the first 100 days after transplant</li> <li>after 100 days and evidence of recurrent sinopulmonary infections</li> </ul>
Solid organ transplants	Treatment for either of the following: <ul style="list-style-type: none"> <li>desensitization for highly-allosensitized transplant candidates</li> <li>antibody-mediated rejection (AMR)</li> </ul>

### Hematology

Condition	Criteria for Use
Acute idiopathic thrombocytopenic purpura (ITP)	Treatment for either of the following: <ul style="list-style-type: none"> <li>Active bleeding <b>AND</b> a platelet count &lt; 30,000/mm<sup>3</sup></li> <li>preoperative treatment prior to a major surgical procedure (e.g. splenectomy)</li> </ul>
Chronic idiopathic thrombocytopenic purpura (ITP)	Treatment when <b>ALL</b> of the following are met: <ul style="list-style-type: none"> <li>Duration greater than 6 months</li> <li>No other concurrent illness/disease explaining thrombocytopenia</li> <li>Prior treatment with a reasonable course of corticosteroids or splenectomy</li> <li>Platelet count &lt; 30,000/mm<sup>3</sup> in children, or &lt; 20,000/mm<sup>3</sup> in adults</li> </ul>
HIV-associated thrombocytopenia	Treatment for <b>ANY</b> of the following: <ul style="list-style-type: none"> <li>Active bleeding <b>AND</b> a platelet count &lt; 30,000/mm<sup>3</sup></li> <li>Platelet count &lt;20,000/ mm<sup>3</sup></li> <li>Preoperative treatment prior to a major surgical procedure (e.g., splenectomy)</li> </ul>
Fetal alloimmune thrombocytopenia (FAIT)	Treatment for <b>ALL</b> of the following: <ul style="list-style-type: none"> <li>Documentation of maternal antibodies to paternal platelet antigen</li> <li>Previous pregnancy complicated by FAIT</li> <li>Fetal blood sampling documents thrombocytopenia</li> </ul>
Idiopathic thrombocytopenic purpura (ITP) in pregnancy	Treatment for <b>ANY</b> of the following: <ul style="list-style-type: none"> <li>Previously delivered infant(s) with autoimmune thrombocytopenia</li> <li>Platelet count &lt; 75,000/mm<sup>3</sup> during the current pregnancy</li> <li>Platelet count &lt; 30,000/mL associated with bleeding before vaginal delivery or C-section</li> <li>Refractory to corticosteroids - platelet counts &lt; 10,000/mL in the third trimester</li> <li>History of splenectomy</li> </ul>
Post-transfusion purpura	Acute treatment only
Neonatal isoimmune	Acute treatment only

Condition	Criteria for Use
hemolytic disease in conjunction with phototherapy	
Warm type autoimmune hemolytic anemia (characterized by predominance of IgG antibodies as opposed to cold type that is predominated by IgM antibodies)	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e. azathioprine, cyclophosphamide, cyclosporine, prednisone, plasmapheresis, or splenectomy)
Anemia related to chronic parvovirus B19 infection	Treatment when there is a severe refractory anemia and evidence of viremia
Evan's syndrome	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e. azathioprine, cyclophosphamide, cyclosporine or prednisone)

### Neurology

Condition	Criteria for Use
Acute inflammatory demyelinating polyneuropathy (AIDP)	Acute treatment only
Myasthenia gravis	Treatment when <b>ANY</b> of the following is present: <ul style="list-style-type: none"> <li>• before planned thymectomy or during the postoperative period following thymectomy</li> <li>• during an acute crisis (e.g. significant dysphagia, respiratory failure, inability to perform physical activity) duration of treatment should not exceed 5 days</li> <li>• during initiation of immunosuppressive treatment</li> </ul>
Chronic inflammatory demyelinating polyneuropathy (CIDP)	<p><b>Treatment when ALL of the following are present:</b></p> <ul style="list-style-type: none"> <li>• <b>Progressive symptoms present for at least 2 months</b></li> <li>• <b>Physical findings</b> - symptomatic polyradiculoneuropathy as indicated by <b>BOTH</b> of the following: <ul style="list-style-type: none"> <li>○ progressive or relapsing motor or sensory impairment of more than one limb</li> <li>○ widespread hyporeflexia or areflexia</li> </ul> </li> <li>• <b>Electrophysiologic Findings*</b> (see American Academy of Neurology (AAN) conduction criteria note below): when Any 3 of the following 4 criteria are present: <ul style="list-style-type: none"> <li>○ Partial conduction block of <math>\geq 1</math> motor nerve,</li> <li>○ reduced conduction velocity of <math>\geq 2</math> motor nerves,</li> <li>○ prolonged distal latency of <math>\geq 2</math> motor nerves, or</li> <li>○ prolonged F-wave latencies of <math>\geq 2</math> motor nerves or the absence of F waves</li> </ul> </li> <li>• <b>CSF – both of the following findings following lumbar puncture:</b> <ul style="list-style-type: none"> <li>○ White blood cell count <math>&lt; 10/mm^3</math>,</li> <li>○ negative VDRL</li> </ul> </li> <li>• For reauthorizations, <b>significant improvement</b> in clinical condition has been documented by an objective measurement such as Rankin, Modified Rankin, or MRC scales <b>AND</b>, when applicable, a reduction in the level of sensory loss should be noted</li> </ul>

Condition	Criteria for Use
	<ul style="list-style-type: none"> <li>For long-term treatment, evidence that the dose has been periodically reduced or the treatment withdrawn, and the effects measured</li> </ul>
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) (Lewis Sumner Syndrome)	<p><b>Treatment when ALL of the following are present:</b></p> <ul style="list-style-type: none"> <li><b>Progressive symptoms present for at least 2 months.</b></li> <li><b>Physical findings</b> - asymmetric presentations (multifocal acquired demyelinating sensory and motor [MADSAM] Lewis–Sumner syndrome Focal presentations (e.g. involvement of the brachial plexus or of one or more peripheral nerves in one upper limb)</li> <li><b>Electrophysiologic Findings</b> that show evidence of demyelinating neuropathy (such as partial conduction block, slow conduction velocities, temporal dispersion, prolonged distal and F wave latencies)</li> </ul>
Multifocal Motor Neuropathy (MMN)	<p><b>Treatment when ALL of the following are present:</b></p> <ul style="list-style-type: none"> <li><b>Progressive symptoms present for at least 2 months.</b></li> <li><b>Physical findings</b> - as indicated by <b>BOTH</b> of the following: <ul style="list-style-type: none"> <li>Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves</li> <li>No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs</li> </ul> </li> <li><b>Electrophysiologic Findings**</b> (see Consensus Criteria For The Diagnosis Of Multifocal Motor Neuropathy from the American Association of Electrodiagnostic Medicine below): <ul style="list-style-type: none"> <li>Definite conduction block on 1 nerve or probable conduction block on 2 nerves,</li> <li>Normal sensory nerve conduction in upper limb segments with CB and normal sensory nerve action potential (SNAP) amplitudes</li> </ul> </li> </ul>
Relapsing-Remitting Multiple Sclerosis	Chronic treatment when there is failure, contraindication, or intolerance to standard conventional therapies (e.g. interferon beta, glatiramer)
Guillain-Barré syndrome (GBS)	<p>Acute treatment when <b>ALL</b> of the following criteria have been met:</p> <ul style="list-style-type: none"> <li>initial treatment within 4 weeks of the onset of symptoms</li> <li>no concomitant use of plasmapheresis</li> <li>treatment may be repeated once but should not extend beyond 8 weeks from the onset of symptoms</li> </ul>
Lambert-Eaton myasthenic syndrome (LEMS)	Treatment when there is failure, contraindication, or intolerance to other symptomatic therapies (e.g. acetylcholinesterase inhibitors such as mestinon and immunosuppressants such as prednisone, azathioprine)
Stiff person syndrome (Moersch-Woltmann Syndrome)	Treatment when there is failure, contraindication, or intolerance to available standard medical therapy (e.g. diazepam, baclofen, phenytoin, clonidine, or tizanidine)

**\*American Academy of Neurology (AAN) criteria:**

- A partial conduction block** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of < 15% in duration between proximal and distal site stimulation.

- **A possible conduction block or temporal dispersion** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of at least 15% in duration between proximal and distal site stimulation.
- **A reduced conduction velocity** is a velocity of < 80% of the lower limit of the normal range if the amplitude of the compound muscle action potential (CMAP) is > 80% of the lower limit of the normal range or < 70% of the lower limit if the CMAP amplitude is less than 80% of the lower limit.
- **Prolonged distal latency** is more than 125% of the upper limit of the normal range if the CMAP amplitude is more than 80% of the lower limit of the normal range or more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit.
- **An absent F wave or F-wave latency** is more than 125% of the upper limit if the CMAP amplitude is more than 80% of the lower limit or latency is more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit.

**\*\* Consensus Criteria For The Diagnosis Of Multifocal Motor Neuropathy (American Association of Electrodiagnostic Medicine)**

- **Definite conduction block** is present in two or more nerves outside of common entrapment sites.\* Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block. Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.
- **Probable conduction block** in two or more motor nerve segments that are not common entrapment sites, or Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, neither of which segments are common entrapment sites. Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block, when this segment is technically feasible for study (that is, this is not required for segments proximal to axilla or popliteal fossa).
- Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested.
- The absence of each of the following upper motor neuronsigns: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.

\*Median nerve at wrist; ulnar nerve at elbow or wrist; peroneal nerve at fibular head.

**Rheumatologic Disorders**

Condition	Criteria for Use
Dermatomyositis or Polymyositis	Treatment when <b>ALL</b> of the following are present <ul style="list-style-type: none"> <li>• dermatomyositis or polymyositis established by biopsy</li> <li>• failure of standard medical therapy (at least a 4 month trial of corticosteroids and/or immunosuppressants) unless contraindicated. (IVIG may be covered after less than a four month trial of prednisone or prednisone combination therapies when there is profound, rapidly progressive and/or potentially life threatening muscular weakness refractory or intolerant to previous therapy)</li> <li>• documented lack of response/poor response to prior therapies, as reflected by persistently elevated serum creatine kinase (CK) levels and/or lack of improvement on muscle strength improvement scales</li> </ul>
Kawasaki disease	Acute treatment when given in conjunction with aspirin within ten days of onset of symptoms

**Infectious Disease**

Condition	Criteria for Use
Staphylococcal or streptococcal toxic shock syndrome	Acute treatment for <b>ANY</b> of the following: <ul style="list-style-type: none"> <li>• the infection is refractory to aggressive treatment</li> <li>• presence of an undrainable focus</li> </ul>

Condition	Criteria for Use
	<ul style="list-style-type: none"> <li>• persistent oliguria with pulmonary edema</li> </ul>
HIV-positive children and adolescents who either have been exposed to measles or live in a high-prevalence measles area	Prevention of bacterial infections
Maternal-fetal transmission of HIV in women who are in their third trimester of pregnancy	When used in conjunction with antiretroviral treatment
Hepatitis A	Vaccination when intramuscular gammaglobulin is contraindicated
Tetanus	Vaccination when Tetanus Immune Globulin is unavailable
Varicella	Vaccination when Varicella Immune Globulin is unavailable

### Dermatology

Condition	Criteria for Use
Autoimmune mucocutaneous blistering diseases; such as: <ul style="list-style-type: none"> <li>○ Pemphigus</li> <li>○ Pemphigoid</li> <li>○ Epidermolysis Bullosa Acquisita</li> </ul>	Treatment when <b>EITHER</b> of the following criteria is met: <ul style="list-style-type: none"> <li>• failure, contraindication or intolerance of conventional therapy (corticosteroids, azathioprine, cyclophosphamide, CellCept)</li> <li>• rapidly progressive disease in which a clinical response can not be affected quickly enough using conventional agents. In these situations, IVIG therapy should be given along with conventional treatment(s) and the IVIG used only until conventional therapy takes effect</li> </ul> <p><b>Note:</b> IVIG for the treatment of autoimmune mucocutaneous blistering disease is covered only for short-term therapy (<b>no longer than 6 consecutive months</b>) and not as a maintenance therapy</p>
Stevens–Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)	Acute treatment only

**\*See appendices for the following information:**

**Appendix 1 – Standard Reference Ranges for Serum immunoglobulin Levels**

**Appendix 2 – Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1,2,3,4)**

**Appendix 3 – Selected Genetic Based Primary Immunodeficiency (PID) Disorders**

**CIGNA does not cover the use of intravenous immune globulin (human) (IVIG) for ANY of the following conditions because it is considered experimental, investigational or unproven (this list may not be all-inclusive):**

- amyotrophic lateral sclerosis
- atopic dermatitis
- autoimmune neutropenia
- cellular immunodeficiencies including IFN, IL, CD4, NK
- chronic fatigue syndrome
- chronic mucocutaneous candidiasis (CMCC)
- complement deficiencies
- complex regional pain syndrome (CRPS)
- inclusion body myositis
- intractable pediatric epilepsy

- Lyme disease
- myasthenia gravis – chronic management
- clinically isolated syndrome-multiple sclerosis
- pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- paraproteinemic demyelinating neuropathy (PDN)
- post-polio syndrome
- recurrent spontaneous miscarriage
- rheumatic fever
- systemic lupus erythematosus

## FDA Information

Immune globulin intravenous (human) (IVIG) products are labeled for the treatment of primary immunodeficiency syndromes, idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, chronic lymphocytic leukemia (CLL), bone marrow transplantation (BMT), and pediatric HIV infection. In 2009 the FDA approved use of IVIG for the first neurological disorder – chronic inflammatory demyelinating polyneuropathy (CIDP). Specific labeled uses vary for the individual products (see Table 1). All the available IVIG products are derived from pooled human plasma. All IVIG products are processed to remove as many viruses as possible. Each product undergoes two or more viral reduction methods. In addition, donors are carefully screened, and IVIG products are tested for significant viral pathogens.

**Table 1 – FDA Approved Indications for IVIG Products**

<b>IVIG Brand Name</b>	<b>FDA Approved Indications</b>
Carimune NF	Primary immunodeficiencies, immune thrombocytopenic purpura
Flebogamma	Primary immunodeficiencies
Gammagard	Primary immunodeficiencies
Gammar P.I.V.	Primary immunodeficiencies
Gamunex Gamunex-C	Primary immunodeficiencies, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy
Iveegam EN	Primary immunodeficiencies, Kawasaki syndrome
Octagam	Primary immunodeficiencies
Panglobulin NF	Primary immunodeficiencies, immune thrombocytopenic purpura
Polygam S/D	Primary immunodeficiencies, immune thrombocytopenic purpura, Kawasaki syndrome, B-cell chronic lymphocytic leukemia
Privigen	Primary immunodeficiencies, immune thrombocytopenic purpura

## General Background

### Guidelines

#### **American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)**

IVIG is a therapeutic biologic agent that has been prescribed for over two decades to treat various neuromuscular conditions. Most of the treatments are given off-label, as little evidence from large randomized trials exists to support its use. Recently, IVIG-C has received an indication for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). Because of the lack of evidence, an ad hoc committee of the AANEM was convened to draft a consensus statement on the rational use of IVIG for neuromuscular disorders. Recommendations were categorized as Class I–IV based on the strength of the medical literature. Class I evidence exists to support the prescription of IVIG to treat patients with Guillain–Barre´ syndrome (GBS), CIDP, multifocal motor neuropathy, refractory

exacerbations of myasthenia gravis, Lambert–Eaton syndrome, dermatomyositis, and stiff person syndrome. Treatment of Fisher syndrome, polymyositis, and certain presumed autoimmune neuromuscular disorders is supported only by Class IV studies, whereas there is no convincing data to substantiate the treatment of inclusion body myopathy (IBM), idiopathic neuropathies, brachial plexopathy, or diabetic amyotrophy using IVIG. Treatment with IVIG must be administered in the context of its known adverse effects. There is little evidence to advise the clinician on the proper dosing of IVIG and duration of therapy.

### **American Academy of Allergy, Asthma and Immunology (2009)**

The appropriate use of IVIG for indications supported by rigorous scientific clinical evidence is essential. This is required to ensure that the patients who will benefit most from IVIG will have access to treatment. IVIG must be respected as a scarce resource, and its judicious use must be promoted and practiced within the medical community.

IVIG is indicated as replacement therapy for patients with primary and selected secondary immunodeficiency diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infections. IVIG has also been used in a number of diseases that result in a secondary humoral immunodeficiency. Although there are anecdotal reports of the use of IVIG in conditions that have the potential to impair humoral immunity, recommendations are limited to 3 diseases, B-cell chronic lymphocytic leukemia, pediatric HIV infection, and prematurity, the first 2 of which are FDA-approved indications for IVIG use in the United States.

### **Clinical Efficacy**

#### **Off-Label Uses**

**Unlabeled indications included in criteria:** Based on peer-reviewed literature and the pharmaceutical compendium of drug information from the American Society of Health-System Pharmacists (AHFS), there is sufficient evidence to support the use of IVIG for the following indications.

- **Infection Prophylaxis and Treatment in Neonates**

- **Infection Prophylaxis:** No head-to-head trials have directly compared the individual IVIG products for this use. However, a Cochrane systematic review and a meta-analysis have evaluated the efficacy of IVIG for preventing infection in preterm or low birth weight infants. Based on these analyses, IVIG appears to be effective for reducing sepsis and serious infection. It remains unclear whether IVIG prophylaxis improves survival.

The Cochrane systematic review included 19 trials comparing IVIG with placebo (albumin, dextrose, saline, sucrose) or no treatment. The total IVIG dose ranged from 120 mg/kg to 5 g/kg, given as a single dose or repeated every 7–21 days. A variety of IVIG preparations were used, including Gammagard, Sandoglobulin, Gamimune-N, Intraglobin, Ig-Vena, and Venogamma. Compared to controls, risk of sepsis was lower with IVIG ( $p < 0.05$ ) with an absolute risk reduction of -0.03 (95% CI 0 to -0.05), giving an NNT of 33. Risk of serious infection was lower with IVIG ( $p < 0.05$  between groups) with an absolute risk reduction of -0.04 and an NNT of 25. There was no difference between IVIG and control in risk of necrotizing enterocolitis, intraventricular hemorrhage, all-cause mortality, infection-related mortality, or length of hospital stay. The authors noted significant heterogeneity for the endpoints of sepsis and serious infection, which may have been caused by differences in IVIG dosage regimens. The meta-analysis included 12 trials comparing IVIG with placebo (not specified) or no treatment. The total IVIG dose ranged from 120 mg/kg to 5 g/kg, given as a single dose or repeated every 14–21 days. A variety of IVIG preparations were used, including Gammagard, Sandoglobulin, Gamimune-N, Intraglobin, and Venogamma. IVIG reduced total mortality compared to control ( $p = 0.0193$ ), although study heterogeneity was too great to calculate a pooled odds ratio. Significant heterogeneity remained even when data were reanalyzed by type of IVIG preparation used.

- **Treatment of Infection:** One trial has directly compared IVIG products with each other, although neither product is available in the U.S. Patients were given Intraglobin or

Pentaglobin 250 mg/kg/day IV for four days, starting therapy as soon as infection was suspected. In patients with proven sepsis, all-cause mortality was similar with Intraglobin (14.2%) and Pentaglobin (6.8%, NS vs. Intraglobin). All-cause mortality was numerically higher with Intraglobin (15.8%) than Pentaglobin (6.8%) in patients with proven or suspected sepsis; no statistics were reported for this comparison. Leukopenia resolved slightly faster with Intraglobin (29.6 days) than Pentaglobin (19.1 days), although no statistics were reported for this comparison. The ratio of immature to total neutrophils normalized more quickly with Intraglobin (51 days) than Pentaglobin (35.1 days,  $p < 0.05$  vs. Intraglobin). This study enrolled small numbers of patients and may have lacked statistical power to detect small differences between groups for some endpoints. A Cochrane systematic review and a meta-analysis have also evaluated the efficacy of IVIG for this indication. The Cochrane systematic review included nine trials comparing IVIG to placebo (albumin, dextrose, maltose, saline or no treatment in term or preterm infants). The total IVIG dose ranged from 500 mg/kg to 6 g (not based on weight). A variety of IVIG preparations were used, including Sandoglobulin, Gamimune-N, Intraglobin, and Pentaglobin. Compared to controls, all-cause mortality in suspected infection was lower with IVIG ( $p = 0.05$ ), with an absolute risk reduction of -0.09. Treatment with IVIG also reduced all-cause mortality in proven infection compared to control ( $p = 0.04$ ). There was no difference in hospital length of stay for term or preterm infants. There was significant heterogeneity in length of stay for term infants but not in mortality or length of stay for preterm infants. Heterogeneity may have been caused by differences in IVIG dosage regimens. The meta-analysis included three trials comparing IVIG to placebo (not specified) or no treatment. The total IVIG dose ranged from 500 mg/kg to 6 g (not based on weight). The trials used two IVIG preparations; Sandoglobulin and Pentaglobin. Total mortality was significantly lower with IVIG ( $p = 0.007$ ) compared to control. No significant heterogeneity was noted.

- **Neonatal Isoimmune Hemolytic Disease:** Five controlled clinical trials have evaluated IVIG in neonatal isoimmune hemolytic disease. All found a significant benefit when IVIG was added to phototherapy, compared to phototherapy alone. The IVIG doses given ranged from 500–1,000 mg/kg given as a single dose, to 500–800 mg/kg/day for three days. In a Cochrane systemic review of the three single-dose trials (189 patients), 15% of patients given IVIG needed blood exchange transfusions, compared to 52% of patients given phototherapy alone (relative risk 0.28, 95% CI 0.17–0.47, number needed to treat 2.7). The fourth trial (37 patients) did not report number of blood exchange transfusions but did report a lower rate of total blood transfusions with IVIG (42%) compared to phototherapy alone (67%,  $p < 0.05$ ). In the final trial (61 patients), fewer infants required exchange transfusion with a three-day IVIG course (0%,  $p < 0.05$  vs. both other groups) compared to either a one-day IVIG course (15%,  $p < 0.05$  vs. phototherapy alone) or phototherapy alone (33%). In two of the included trials, the addition of IVIG significantly reduced mean duration of hospitalization ( $p < 0.05$  vs. phototherapy alone). Case reports and case series were not reviewed for this indication.
- **Infection Prophylaxis in Multiple Myeloma:** Two randomized clinical trials have evaluated IVIG for infection prophylaxis in patients with multiple myeloma. In the largest trial ( $n = 83$ ), the incidence of serious infections was significantly lower with IVIG 400 mg/kg every four weeks (0.042 infections/patient-month) than placebo (0.081 infections/patient-month,  $p = 0.02$ ). This reduction corresponds to a number needed to treat of 2.2 patients to prevent one serious infection per patient-year. When analyzed by specific infection type, IVIG significantly reduced the risk of septicemia, pneumonia, and non-pneumonia chest infections compared to placebo ( $p < 0.05$  for all subgroups). The risk of urinary tract infection and other serious infections was similar in both treatment groups. Mortality data were not evaluated due to the study's relatively short duration of 12 months.

The second trial followed 25 patients for 24 months and found similar results. There were fewer serious infections with IVIG 300 mg/kg every four weeks (0.038 infections/patient-month) than no therapy (0.12 infections/patient-month,  $p < 0.002$ ). However, the incidence of minor infections was similar with IVIG (0.088 infections/patient-month) and no therapy (0.108 infections/patient-month).

- **Prevent Complications of Hematopoietic Stem Cell Transplantation (HSCT):** The Centers for Disease Control (CDC) have established guidelines that recommend use of IVIG to prevent bacterial infections (e.g., *Streptococcus pneumoniae* sinopulmonary infections) in allogeneic HSCT recipients who experience severe hypogammaglobulinemia (i.e., Immunoglobulin G [IgG] less than 400 mg/dL) within the first 100 days after transplant. The CDC guidelines also state that in the absence of severe demonstrable hypogammaglobulinemia (i.e., IgG levels < 400 mg/dL, which might be associated with recurrent sinopulmonary infections), routine monthly IVIG administration to HSCT recipients > 90 days after HSCT is not recommended as a means of preventing bacterial infections.
- **Allosensitized Solid Organ Transplants:** Two controlled trials have evaluated IVIG in allosensitized patients undergoing transplantation. These trials suggest IVIG improves outcomes in allosensitized cardiac transplant patients and may improve transplantation rates in highly-sensitized patients awaiting renal transplantation. In the first trial, allosensitized patients received plasmapheresis followed by IVIG 20 g as a single dose immediately prior to cardiac transplantation, while unsensitized patients received no intervention. At baseline, more allosensitized patients had positive cross matches, pulmonary hypertension, and required mechanical circulatory support ( $p < 0.05$  vs. unsensitized patients for each). There was no difference between allosensitized and unsensitized patients in post-transplant length of stay, one-year survival, or risk of rejection.

A second trial evaluated IVIG 2 g/kg monthly for four months in allosensitized patients awaiting renal transplantation. More patients were able to receive transplants after IVIG (35%) than placebo (20%, one-tailed  $p = 0.069$ ), although this trend did not achieve statistical significance. When only cadaveric transplants were considered, more patients were transplanted after IVIG (31%) than placebo (12%, one-tailed  $p = 0.0137$ ). When stratified by prior transplantation status, transplantation was more likely with IVIG than placebo, both in patients with prior transplants (IVIG 22%, placebo 7%, two-tailed  $p = 0.047$ ) and in those without prior transplants (IVIG 50%, placebo 28%, two-tailed  $p = 0.047$ ). Therapy with IVIG reduced projected mean time to transplantation (4.8 years) compared to placebo (10.3 years, one-tailed  $p = 0.049$ ). After transplantation, there was no difference between IVIG and placebo in graft failure, graft survival rate, or serum creatinine concentration of viable grafts. However, acute rejection episodes were more common with IVIG (53%) than placebo (10%,  $p = 0.042$ ).

Several case reports noted beneficial effects in allosensitized patients awaiting solid organ transplant with a variety of IVIG regimens, including 2 g/kg as a single dose prior to transplantation, plasmapheresis followed by 20 g as a single dose prior to transplantation, 500 mg/kg once weekly until transplantation, or 10 g every three weeks until transplantation.

- **Fetal Alloimmune Thrombocytopenia:** Two randomized clinical trials, one Cochrane systematic review, and three observational trials have evaluated IVIG in this disorder. Bussel et al. (1996) conducted an open-label experimental trial, randomizing 54 women to therapy with IVIG 1 g/kg weekly plus oral dexamethasone 1.5 mg/day or monotherapy with IVIG 1 g/kg weekly. Fetal platelet counts were similar with IVIG alone or with the combination, both during pregnancy and at birth. No intracranial hemorrhages occurred in either treatment group.

Berkowitz et al. (2006) conducted a parallel, randomized, multicenter study that stratified 79 patients to two different treatment arms based on the presence of a peripartum intracranial hemorrhage in a previously affected sibling and/or the initial fetal platelet count. Forty women whose children from a previous birth had a peripartum intracranial hemorrhage or whose current fetus had an initial platelet count less than  $20,000/\text{mL}^3$  were randomly assigned to receive IVIG plus prednisone or IVIG alone. The mean increase in fetal platelet counts in the following three to eight weeks was  $67,100/\text{mL}^3$  and  $17,300/\text{mL}^3$ , respectively ( $p < 0.001$ ). Thirty-nine patients whose previously affected child did not have an intracranial hemorrhage and whose current fetus had an initial platelet count of more than  $20,000/\text{mL}^3$  were randomly assigned to receive IVIG alone or prednisone alone. In this group, there were no significant differences, and 33 (85%) had birth platelet counts more than  $50,000/\text{mL}^3$ .

In one observational follow-up trial in 37 women with documented fetal or neonatal alloimmune thrombocytopenia, therapeutic failure occurred in 33% of IVIG-treated pregnancies compared to 70% of corticosteroid-treated pregnancies (no statistics reported). Therapeutic success occurred in 26% of pregnancies with IVIG and 10% with corticosteroids (no statistics reported). In the other two observational follow-up trials (61 patients), pregnant mothers served as their own historical controls, comparing results after IVIG therapy to outcomes of their earlier pregnancy. Intracranial hemorrhage occurred in 0/28 (0%) pregnancies treated with IVIG compared to 13/33 (39%) of the earlier pregnancies.

A Cochrane systematic review has been published, evaluating one clinical trial comparing the efficacy of IVIG plus dexamethasone versus IVIG alone. No significant differences were reported between the treatment and control groups in any outcome measured: mean platelet count at birth (weighted mean difference (WMD)  $14.10 \times 10^9/L$ , 95% confidence interval (CI) -30.26 to 58.46), mean gestational age at birth (WMD -0.50 weeks, 95% CI -2.69 to 1.69), mean rise in platelet count from first to second fetal blood screen (WMD  $-3.50 \times 10^9/L$ , 95% CI -24.62 to 17.62) and mean rise in platelet count from birth to first fetal blood screen (WMD  $24.40 \times 10^9/L$  (95% CI -14.17 to 62.97)). However, the authors noted that, although this trial had adequate methodological quality, the method used to calculate sample size was inappropriate; therefore, the power calculation was not sufficient to determine any significance in differences between the treatment groups. The authors concluded that, although no randomized controlled trials have been conducted to investigate the role of intravenous immunoglobulin, data from observational studies have suggested an improvement in clinical outcome and probable reduction in risk for intracranial hemorrhage when intravenous immunoglobulin is administered to the mother throughout pregnancy. Furthermore, the authors noted that practice has evolved such that intravenous immunoglobulin is currently first-line treatment in the antenatal management of fetal alloimmune thrombocytopenia.

American College of Obstetricians and Gynecologists (ACOG) guidelines also recommend that neonatal alloimmune thrombocytopenia should be treated with IVIG as the initial approach when fetal thrombocytopenia is documented.

- **Chronic Parvovirus B19 Infection:** There are no published clinical trials evaluating the efficacy of IVIG for this indication. Six case series describe the use of IVIG for chronic parvovirus B19 infection in a total of 27 patients. Therapy with IVIG 1-2 g/kg (divided and given over 1–10 days) consistently induced symptom resolution and improved anemia. Remissions lasted from one month to four years, although many patients relapsed without additional IVIG. Many of the included patients had experienced parvovirus symptoms for a prolonged duration (12–24 months) but these resolved within 2–4 weeks of IVIG therapy. Four of these case series included AIDS patients, as symptomatic parvovirus B19 infection is rare in patients with healthy immune systems. The results of these case series are consistent with multiple single case reports which are not included in the evidence tables.
- **Guillain-Barré Syndrome**
  - **Acute Inflammatory Demyelinating Polyneuropathy (AIDP):** The American Academy of Neurology has published treatment guidelines (2003). There is no cure for AIDP. Treatment consists of supportive care, physical therapy, and immune modulating therapy (i.e., plasmapheresis or IVIG). Both plasmapheresis and high-dose IVIG significantly speed recovery when performed within two weeks of symptom onset. Although the treatments are equal in efficacy, IVIG is easier to administer and may be preferred. The usual IVIG regimen is 400 mg/kg/day IV for five days. Relapse may occur 1–2 weeks after initial therapy and may be treated with a repeat course of the initial therapy. Sequential treatment with plasmapheresis and IVIG does not improve outcomes and is not recommended. Corticosteroids are not recommended. Cochrane systematic review has evaluated the efficacy of IVIG in patients with AIDP of less than two weeks' duration. The Cochrane systematic review included nine trials comparing IVIG to plasma exchange, plasma exchange followed by IVIG, immunoadsorption, immunoadsorption followed by IVIG, or supportive care. The total IVIG dose ranged from 1.2–2.4 g/kg. The authors did

not report which specific IVIG preparations were used. There was no difference between IVIG and plasma exchange in disability improvement at four weeks, time until patient could walk unaided, time until patient could breathe without ventilator, mortality, or the combined endpoint of death or disability at 12 months. In children, the time to bulbar/respiratory recovery or two-grade improvement in muscle strength was shorter with IVIG (17 days) than plasma exchange (30 days,  $p < 0.0001$ ). Risk of adverse effects was similar with IVIG and plasma exchange, but IVIG patients were less likely to discontinue therapy ( $p = 0.0001$  vs. plasma exchange). There was no difference between IVIG and immunoadsorption in disability improvement at four weeks or mortality. Studies comparing IVIG with supportive care could not be pooled and did not evaluate specified outcomes. Compared to lower IVIG doses (1.2 g/kg), higher IVIG doses (2.4 g/kg total) did not significantly improve disability at four weeks, mortality, or chance of full recovery at 12 months. There was a trend towards shorter time until patients could walk unaided with high-dose IVIG (84 days) than low-dose IVIG (131 days,  $p = 0.08$ ). Combining IVIG with other immunomodulatory treatments does not significantly improve efficacy. Compared to plasma exchange alone, the addition of IVIG to plasma exchange did not significantly affect disability improvement at four weeks, time until patient could walk unaided, time until patient could breathe without ventilator, mortality, or the combined endpoint of death or disability at 12 months. Similarly, the addition of IVIG to immunoadsorption was no more effective than immunoadsorption alone for improving disability at 12 months or mortality, although disability improved more at four weeks with combination therapy ( $p = 0.004$  vs. immunoadsorption alone).

- **Treatment of Acute Myasthenic Crisis with Decompensation:** Few well-designed clinical trials have been published on this disorder. A 2006 Cochrane systematic review of five trials has evaluated short-term efficacy of IVIG (up to 16 weeks). The reviewers stated that the methodologic quality of the included trials was debatable. Results could not be pooled and no meta-analysis was performed. However, in two trials evaluating IVIG efficacy for disease exacerbation, there was no difference between IVIG and methylprednisolone or plasma exchange in effects on muscle strength/fatigue. Another trial evaluating IVIG efficacy for disease exacerbation showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIG. The other two trials evaluated efficacy for chronic stable disease and found no difference between IVIG and plasma exchange or placebo in effects on activities of daily living or muscle strength/fatigue. The IVIG regimens given included 400 mg/kg/day for 3–5 days, 1 g/kg/day for one day, 1 g/kg/day for two days, and 30 g/day for five days.

The American Hospital Formulary Service (AHFS) Drug Information<sup>®</sup> states that IVIG may be beneficial in myasthenia gravis patients with acute severe decompensation when other treatments have been unsuccessful or are contraindicated.

- **Lambert-Eaton Myasthenic Syndrome (LEMS):** Cochrane systematic review and a placebo-controlled trial have evaluated the efficacy of IVIG in patients with LEMS. The Cochrane systematic review included three trials evaluating the efficacy of IVIG, 3, 4-diaminopyridine, or placebo in patients with LEMS with or without small-cell lung cancer. One included trial evaluated the efficacy of IVIG 2 g/kg (total dose), although the specific preparation was not reported. No meta-analysis could be performed, since only one trial was included. Muscle strength and mean resting CMAP improved slightly more with IVIG than placebo, but this difference did not reach statistical significance. Compared to placebo, 3, 4-diaminopyridine caused greater improvement in mean resting CMAP ( $p < 0.05$  vs. placebo).

One crossover trial compared IVIG with placebo in patients with LEMS without small-cell lung cancer. Patients were given a single course of placebo or IVIG 1 g/kg/day IV for two days, followed by an eight-week washout before crossover. In the IVIG arm, patients could receive either Flebogamma (as Alphaglobin) or Gammagard although no comparisons were made between these two products. Eighty percent of patients given IVIG reported increased strength at two weeks (no statistical comparison reported). Compared with placebo (no values reported), IVIG caused greater improvements in limb strength (improved 20%,  $p = 0.038$  vs. placebo), vital capacity (improved 8%,  $p = 0.028$  vs. placebo), drinking time (improved 15%,  $p = 0.017$  vs.

placebo), and antibody titer ( $p=0.028$  vs. placebo). There was a trend towards greater improvement in mean resting CMAP with IVIG ( $p=0.066$  vs. placebo). Calcium-channel antibodies decreased more with IVIG at weeks 4–6 ( $p<0.05$  vs. placebo), then slowly began increasing. There was no evidence that IVIG directly neutralizes calcium-channel antibodies.

- **Multifocal Motor Neuropathy:** The comparative efficacy of the available IVIG products for this use has not been assessed in published individual trials, Cochrane systematic reviews, or meta-analyses. Instead, four placebo-controlled trials were included evaluating the short-term efficacy of various IVIG preparations including Endobulin, Gamimune-N, Dutch Central Laboratory Blood Transfusion IVIG, and French National Center for Blood Transfusion IVIG. Based on these trials, IVIG is more effective than placebo at improving functional ability and may also improve muscle strength and nerve function. Seventy-eight to 100% of patients responded to IVIG therapy. Treatment with IVIG is effective in both newly-diagnosed patients and those who have relapsed after prior response to IVIG therapy. Response to IVIG therapy correlates inversely with age, with responders being much younger (mean 33.1 years) than nonresponders (mean 51.8 years,  $p=0.0014$ ). Two trials found IVIG had no effect on conduction block, while a third trial reported decreased conduction block after IVIG. Antibody titers to ganglioside GM1 are not routinely affected by IVIG.
- **Relapsing-Remitting Multiple Sclerosis (RRMS):** The meta-analysis included four trials evaluating the efficacy of IVIG or placebo in patients with RRMS ( $n=260$ ) or secondary progressive multiple sclerosis (SPMS) ( $n=5$ ). The IVIG dose varied from 150–2,000 mg/kg IV every month to 400 mg/kg IV every two months. The specific preparation used was not reported. Disability improved more with IVIG than placebo ( $p=0.042$ ). Patients were 11% less likely to report worsening of disability after IVIG than placebo ( $p=0.03$ ), although there was significant heterogeneity between studies. Patients were 16% more likely to report improvement of disability after IVIG than placebo ( $p=0.006$ ); there was significant heterogeneity between studies. The annual relapse rate was lower with IVIG than placebo ( $p=0.00003$ ). Compared to placebo, 29% more IVIG-treated patients were relapse-free at the study's end ( $p<0.05$ ).

The Cochrane systematic review included two trials evaluating the efficacy of IVIG or placebo in patients with RRMS. Although the authors planned to include trials of both RRMS and SPMS, no published trials were available for SPMS. The IVIG dose varied from 150–200 mg/kg IV every month to 400 mg/kg IV every two months. The specific IVIG preparation used was not reported. No meta-analysis could be performed, since only two trials were included. Disability improved more with IVIG than placebo ( $p=0.008$ ). Fewer patients reported worsening of disability after IVIG (13%) than placebo (17%,  $p=0.03$ ). The reported relapse rates were lower with IVIG (range: 0.52–0.59 relapses/year) than placebo (range: 1.26–1.61 relapses/year,  $p<0.05$  in both included trials). At the study's end, more patients were relapse-free with IVIG (range: 30–53%) than placebo (range: 0–36%,  $p<0.05$  in both included trials). Time to first relapse was longer with IVIG (range: 233–237 days) than placebo (range: 82–151 days) in one trial but was similar in the other study.

A study compared IVIG 400 mg/kg/day IV for five days each month to placebo in 24 patients with RRMS. The specific IVIG preparation used was not reported, and the authors did not report any statistical comparisons between treatment groups. Disability score improved with IVIG but worsened with placebo. Fewer numbers of patients reported disease worsening with IVIG (8.3%) than placebo (25%). Greater numbers of patients reported disease improvement with IVIG (25%) than placebo (8.3%). The change in disability score correlated with the size and number of brain lesions. There was a significant negative correlation with IVIG ( $p=0.022$ ) and a significant positive correlation with placebo ( $p=0.014$ ), suggesting that magnetic resonance imaging (MRI) may be more useful than disability score for detecting early beneficial effects of IVIG. After treatment, both the number and volume of brain lesions decreased significantly from baseline with IVIG but increased significantly with placebo.

- **Stiff Person Syndrome:** Randomized clinical trials have evaluated IVIG for stiff person syndrome. One placebo-controlled trial ( $n=16$ ) has been published evaluating IVIG for this indication. Overall stiffness improved significantly with IVIG 1 g/kg/day IV for two days each

month ( $p=0.01$  vs. placebo). A subgroup analysis found that IVIG significantly reduced stiffness in the abdomen, trunk, and face ( $p<0.01$  vs. placebo for each site). Frequency of spasms was also reduced significantly with IVIG ( $p=0.03$  vs. placebo). Eleven of 14 patients improved with IVIG, while none improved and four patients worsened with placebo. Thirteen of 14 patients requested additional IVIG treatments after the study ended. The investigators noted a significant carryover effect when IVIG was given first. Anti-GAD65 antibodies decreased from baseline with IVIG, although antibody titers did not correlate with either disease severity or magnitude of response to IVIG.

A descriptive case series evaluated the effect of IVIG on quality of life in six adults with stiff person syndrome. Before and two weeks after a course of IVIG (400 mg/kg/day for five days), investigators assessed quality of life using the Short Form-36 (SF-36) and general health status by visual analog scale. Both general health status and total SF-36 score improved significantly with IVIG ( $p<0.05$  vs. baseline for both outcomes). Subgroup analysis showed improvements in specific SF-36 subscales for pain, social functioning, mental health, and energy-vitality ( $p<0.05$  vs. baseline for each subgroup). Five of six patients reported moderate-to-marked symptom improvement with IVIG.

- **Steroid-Resistant Dermatomyositis/Polymyositis:** Based on several clinical trials, IVIG improves functional ability, muscle strength, and nerve function. About 71–75% of patients reported improvement with IVIG therapy. Treatment with IVIG may be more effective in patients with shorter disease duration compared to those with longer disease duration. Dalakas et al. (1994) compared IVIG 2 g/kg IV monthly with placebo in patients with dermatomyositis refractory to prednisone or immunosuppressants. Patients were given three courses of therapy and then given the option of crossing over to the alternate therapy. Out of all patients treated, major functional improvement was reported more often with IVIG (75%) than placebo (0%, no statistics reported). Patients were less likely to report worsening function with IVIG (0%) than placebo (42%, no statistics reported). Mean number of muscle fibers decreased with IVIG, although mean fiber diameter increased significantly ( $p<0.04$  vs. baseline). Mean number of muscle capillaries increased with IVIG, but mean capillary diameter decreased ( $p<0.01$  vs. baseline). The muscle fiber to capillary ratio was 1.5 after IVIG treatment, approaching normal. Results were analyzed both by original treatment allocation and separately in patients who chose to cross over. Four patients from each group chose to cross over to the alternate therapy. Results from the original treatment allocation showed that muscle strength improved with IVIG and was unchanged with placebo ( $p<0.018$  between groups). Similarly, mean neuromuscular symptom score improved from baseline with IVIG and was unchanged with placebo ( $p<0.035$  between groups). The greatest benefit of IVIG was seen in patients with the most severe weakness at baseline. After crossover, both muscle strength and neuromuscular symptoms improved in patients switching to IVIG but worsened in those switching to placebo (no statistics reported). A subgroup analysis of this trial evaluated the effects of IVIG on complement activation. Activated complement (C3) uptake was significantly inhibited with IVIG ( $p<0.001$  vs. baseline) but was unchanged with placebo (NS vs. baseline, not compared with IVIG). In patients given IVIG, complement membrane attack complexes were found in muscle capillaries prior to therapy, but completely disappeared after therapy. Results were not reported for the placebo group.

Few published trials have evaluated the efficacy of IVIG in patients with polymyositis. In a case series of 35 adults treated with polymyositis refractory to prednisone, immunosuppressants, pheresis, or radiotherapy, patients were treated for at least three months with IVIG 1 g/kg/day IV for two days each month. After IVIG treatment, muscle strength improved in 71% of patients, was unchanged in 26%, and worsened in 3%. Muscle disability score improved from baseline with IVIG ( $p<0.01$  vs. baseline). In patients with esophageal disorders at baseline, 73% reported resolution with IVIG. Mean disease duration was significantly shorter in patients responding to therapy (26 months) than in non-responders (43 months,  $p<0.05$  vs. responders). Creatine kinase decreased significantly with IVIG in responders ( $p<0.05$  vs. baseline) but was unchanged in non-responders. Daily steroid requirements were reduced significantly with IVIG (21.9 mg/day) compared to baseline (32.7 mg/day,  $p<0.05$  vs. baseline). Long-term efficacy was evaluated in 25 responders who were followed for a mean of 51.4 months. Forty-eight percent (12/25) of responders required no further therapy, while 24% (6/25) needed to continue IVIG, and 28%

(7/25) relapsed. The mean time to relapse was 17.1 months after discontinuing IVIG therapy.

- **Toxic Shock Syndrome:** One placebo-controlled trial has evaluated IVIG (1 g/kg IV on day 1, then 500 mg/kg/day on days 2 and 3) in 21 patients with streptococcal toxic shock syndrome. Enrollment was terminated early due to slow patient recruitment, which may have reduced the study's power to detect treatment differences. Fewer patients had died at day 28 with IVIG (10%) than placebo (36%), although this did not reach statistical significance. Similar results were seen at day 120. Symptoms of shock resolved somewhat more quickly with IVIG (88 hours) than placebo (122 hours), although no statistics were reported for this comparison. However, it took longer for necrotizing fasciitis and cellulitis to stop progressing with IVIG (68 hours) than placebo (36 hours, no statistics reported). The sepsis-related organ failure score (or SOFA score) improved significantly more with IVIG at both days 2 and 3 than with placebo ( $p < 0.05$  at both time points), and IVIG patients were more likely to have plasma neutralizing activity against superantigens ( $p = 0.04$  vs. placebo).

The AHFS Drug Information states that use of IVIG may be considered as an adjunct in the treatment of staphylococcal or streptococcal toxic shock syndrome. The American Academy of Pediatrics (AAP) states that IVIG may be considered in the management of staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the patient has persistent oliguria with pulmonary edema.

- **Hepatitis A Virus (HAV):** The Advisory Committee on Immunization Practices (ACIP) states that IVIG may be used as an alternative to IGIM for prophylaxis against HAV in patients with thrombocytopenia or disorders that cause IM hemorrhage and contraindicate use of IGIM. However, no data are available concerning the efficacy of IVIG in preventing HAV, and IGIM is the preferred preparation when immune globulin is indicated for prophylaxis of this infection. Because immune globulin modified for IV use is made from relatively small pools of donors, it may not contain antibodies to HAV.
- **Varicella:** IVIG has been used and is recommended as an alternative to VZIG for post-exposure prophylaxis of varicella infection in susceptible individuals when VZIG is unavailable. The ACIP states that VZIG is the preferred immune globulin for post-exposure prophylaxis of varicella in patients who do not have evidence of immunity (i.e., without a history of varicella or varicella vaccination) and are at high risk for severe disease and complications. When post-exposure prophylaxis of varicella is indicated, healthcare providers should make every effort to obtain and administer VZIG. However, when it does not appear possible to obtain VZIG within 96 hours of exposure, IVIG can be used as an alternative. The ACIP states that IVIG may be used in the following patients when VZIG is unavailable: immunocompromised patients, neonates whose mothers develop signs and symptoms of varicella around the time of delivery (i.e., five days before to two days after delivery), premature infants exposed during the neonatal period whose mothers do not have evidence of varicella immunity, or premature infants exposed during the neonatal period who were born at less than 28 weeks of gestation or with a birth weight of 1 kg or less (regardless of maternal history of varicella). In addition, the ACIP states that clinicians may choose to use IVIG for post-exposure prophylaxis of varicella in pregnant women. Post-exposure prophylaxis with IVIG may not be necessary in patients receiving IVIG replacement therapy (dosage of 400 mg/kg or greater given at regular intervals) if the last dose was administered within three weeks prior to exposure. Because post-exposure prophylaxis with IVIG may prolong the incubation period, patients who receive the immune globulin should be observed closely for signs or symptoms of varicella for 28 days following exposure. If the exposed patient does not develop varicella, varicella virus vaccine live should be administered at a later date, unless contraindicated.
- **Tetanus:** Although tetanus immune globulin (TIG) is the immune globulin of choice, IVIG can be used as an alternative for the treatment of tetanus when TIG is unavailable.

- **Immune Mediated Blistering Diseases:** Therapy with IVIG has been evaluated in many variants of immune mediated blistering diseases, primarily in case reports and case series. Clinical trials were included when available. The available evidence for each specific disorder is discussed in more detail below:
  - **Pemphigus Vulgaris:** Seven case series (n=62 total) discuss the effects of IVIG in resistant cases of pemphigus vulgaris. In two case series with similar methodology, patients received initial therapy with IVIG 1–2 g/kg IV divided and given over three days each cycle. This regimen was repeated every 3–4 weeks until all lesions were healed, then the cycle interval was gradually extended to 16 weeks before being discontinued. All 36 patients in these two reports experienced complete disease remission with this regimen. In three of the five remaining case series, IVIG 400 mg/kg/day IV for five days produced wound healing and disease remission in 18/19 patients. However, in the two remaining case series, clinical benefit was seen in only 1/10 patients, when given doses ranging from 400 mg/kg/day IV for five days to IVIG 2 g/kg IV every 3–4 weeks. Patients were able to reduce their corticosteroid requirements in two of the case series. The results of these seven case series are consistent with multiple single-case reports.
  - **Pemphigus Foliaceus:** Three case series (n=26 total) report the effects of IVIG in patients with pemphigus foliaceus. All three case series administered initial therapy with IVIG 1–2 g/kg IV divided and given over three days each cycle. This regimen was repeated every 3–4 weeks until all lesions were healed, then the cycle interval was gradually extended to 16 weeks before being discontinued. All 26 patients in the study responded to therapy, with 20/26 achieving complete remission and the others (6/26) experiencing clinical improvement. Corticosteroid requirements were significantly lower after IVIG therapy in two of the case series. These results are consistent with two additional case reports of single patients treated with 40–400 mg/kg/day for five days.
  - **Bullous Pemphigoid:** Six case series (n=35 total) report the effects of IVIG in bullous pemphigoid. Treatment with IVIG 2 g/kg (divided and given over 3–5 days) caused marked improvement in 28/33 patients, reducing appearance of new blisters, improving healing of old lesions, and reducing corticosteroid needs. Treatment was ineffective in 5/33 patients given this regimen after up to seven courses of therapy. In two patients given lower IVIG doses (100 or 300 mg/kg/day), no response occurred after the initial course, but both responded briefly to a second course of therapy. In many cases, relapse occurred within two weeks of the final IVIG dose, although some patients had more prolonged remissions.
  - **Cicatricial Pemphigoid (or Mucus Membrane Pemphigoid):** There are no randomized clinical trials evaluating IVIG in patients with either the oral or ocular variants of this disorder. One observational follow-up study (n=20) and two case series (n=9) discuss the effects of IVIG in patients with oral-cicatricial pemphigoid. In the observational follow-up study, eight patients received initial therapy of IVIG 1–2 g/kg/cycle IV divided over three days. The cycle was repeated every four weeks until complete lesion healing, then the interval between cycles was gradually extended to 16 weeks before discontinuing therapy. Patients in the control group received conventional therapy with corticosteroids or immunosuppressants. Clinical remission was more common with IVIG (8/8, 100%) than conventional therapy (5/12, 42%, p<0.005). Clinical relapse was less common with IVIG (1/8, 13%) than conventional therapy (10/12, 83%, p<0.001). Two subsequent case series using similar IVIG regimens confirmed these results in nine patients with severe oral-cicatricial pemphigoid resistant to conventional therapy. One case report (n=1) found no benefit with IVIG, although no additional details are available.

In ocular-cicatricial pemphigoid, one observational follow-up study (n=16) and one case series (n=10) discuss the effects of IVIG in these patients. In the observational follow-up study, eight patients received initial therapy with IVIG 2 g/kg IV divided over three days. This cycle was repeated every two weeks until conjunctival inflammation resolved, then the interval between cycles was gradually extended to 16 weeks before discontinuing

therapy. Patients in the control group received conventional therapy with immunosuppressives and as-needed corticosteroids. Clinical remission occurred in all 16 patients, although time to remission was significantly shorter with IVIG (four months) than conventional therapy (8.5 months,  $p < 0.01$ ). Ocular inflammation recurred more often with conventional therapy (5/8) than IVIG (0/8,  $p < 0.05$ ). Disease progression was more common with conventional therapy (4/8) than IVIG (0/8,  $p$  value not reported). These results were confirmed in a case series using a similar IVIG regimen in 10 patients with ocular-cicatricial pemphigoid resistant to conventional therapy. Similar results were also reported in two single-case reports.

- **Epidermolysis Bullosa Acquisita:** Eight case reports discuss the use of IVIG for this indication. These reports describe a total of eight patients (age 16–63 years) with a long duration (0.5–15 years) of refractory blistering and ulceration. In six out of eight reports, patients received IVIG 1.2–2 g/kg divided over 3–5 days, with cycles repeated every 2–6 weeks. This IVIG regimen produced dramatic resolution of blistering symptoms in all six patients. Similar results were noted with IVIG 40 mg/kg/day for five days in another case report, suggesting that lower doses may be effective in some patients. In one of the remaining reports, a patient received IVIG 2 g/kg/day every two weeks, but had no objective reduction in blistering after eight courses of therapy and three months of follow-up.
- **Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)**  
Toxic epidermal necrolysis (TEN) is a rare, life-threatening condition caused by certain medications. Keratinocytes affected by TEN have been found to undergo apoptosis mediated by Fas-FasL interactions. Treatment with intravenous immunoglobulin (IVIG) has been proposed to inhibit this interaction. A retrospective analysis of 16 consecutive patients with TEN who were treated with IVIG were studied. The SCORTEN system, a validated predictor of TEN mortality, was used to analyze the data of these patients. Using SCORTEN, we compared the predicted mortality of our patient population with observed mortality. All 16 patients received IVIG treatment daily for 4 days. Fifteen patients received 1 g/kg per day and 1 patient received 0.4 g/kg per day. For each patient, causes of TEN and other medical problems were documented prior to IVIG therapy, as were the 7 independent SCORTEN risk factors. One patient died. Based on the SCORTEN system, 5.81 patients were expected to die. These mortality rates were compared using the standardized mortality ratio (SMR) analysis to determine the efficacy of this treatment, which showed that patients with TEN treated with IVIG were 83% less likely to die than those not treated with IVIG (SMR=0.17; 95% confidence interval, 0.0-0.96). Based on comparison of our observed mortality rate with the SCORTEN-predicted mortality rate, treatment with IVIG significantly decreased mortality in patients with TEN.

### Ongoing Studies

**Unlabeled indications NOT included in criteria** – Due to limited or insufficient clinical evidence, the use of IVIG for the following indications is not included in the criteria for the coverage policy.

- **Amyotrophic Lateral Sclerosis:** There are no published controlled trials evaluating IVIG in patients with amyotrophic lateral sclerosis (ALS). Two case series found that IVIG did not alter disease progression in patients treated for up to 13 months. In fact, disease symptoms continued to worsen during IVIG treatment, including muscle strength, disability, and bulbar function. In one case series, five of nine patients reported transient subjective improvements in muscle strength after the second IVIG dose. One study evaluated IVIG 1 g/kg/day for two days each month, while the other evaluated IVIG 400 mg/kg/day IV for five days the first month followed by 400 mg/kg/day for two days each month thereafter.
- **Intractable Pediatric Epilepsy:** Immune globulin intravenous has been studied in many rare subtypes of pediatric epilepsy, including Landau-Kleffner syndrome, West syndrome, Rasmussen's syndrome, and Lennox-Gastaut syndrome. However, only two controlled trials have been published evaluating efficacy in refractory cases of these disorders. Based on these studies, IVIG may reduce seizure frequency more than placebo, although more study is needed.

Van Rijckevorsel-Harmant et al. (1994) found a trend toward more responders (patients with at least 50% decrease in seizure frequency) with IVIG (52%) than placebo (28%,  $p=0.095$ ) for the entire study group. In the subgroup of patients with only partial seizures, response rate was higher with IVIG (56%) than placebo (17%,  $p=0.041$ ). There was no relationship between IVIG dose and efficacy, although the study gave IVIG doses ranging from 100–400 mg/kg/dose given four times during the first week, then once weekly during weeks two, three and six. In the second study, IVIG 400 mg/kg IV given every 14 days reduced seizure frequency by 19–100% in 7/10 patients compared to placebo, although seizure frequency was unchanged in one patient and increased by 50–100% in the last two patients. There was marked variability between patients in type and frequency of seizures at baseline, and no comparative statistics were reported.

- **Autoimmune Neutropenia:** There are no published clinical trials of IVIG in patients with autoimmune neutropenia. Four case reports and four case series evaluated the effects of IVIG in this disorder. These reports describe a total of 21 patients (age range: one week to 67 years) with absolute neutrophil counts (ANC) less than 500 cells/mm<sup>3</sup>. Patients received regimens of IVIG 300–500 mg/kg/day for 2–6 days, IVIG 1 g/kg/day for two days, IVIG 1 g/kg/day until ANC is above 1,000 cells/mm<sup>3</sup>. In 19/21 patients, the initial course of IVIG increased ANC by 1,000–3,000 cells/mm<sup>3</sup> from baseline. All 19 cases were reported as positive clinical responses to therapy. In two case series (13 patients), ANC returned to baseline an average of 14 days after IVIG therapy. In three reports (four patients), patients were given a second course of IVIG therapy after their ANC returned to baseline values. Only one of these patients experienced a meaningful increase in ANC after the second course of IVIG.
- **Immune Mediated Blistering Diseases:** Therapy with IVIG has been evaluated in many variants of immune mediated blistering diseases, primarily in case reports and case series. Clinical trials were included when available. The available evidence for each specific disorder is discussed in more detail below.
  - **Paraneoplastic Pemphigus:** Four case reports discuss the use of IVIG in paraneoplastic pemphigus. Therapy with IVIG was limited to a single dose in two reports and a single course of therapy in one report. The final report did not specify the IVIG dose or duration of therapy. Two patients improved slightly after IVIG, and one patient had no response. Therapy outcome was not reported for the final patient. There were many confounding factors in these reports, including use of multiple immunosuppressive agents and poor reporting. The clinical effects of IVIG remain unknown in this disorder.
  - **Pemphigoid Gestationis:** This related disorder has been evaluated only in single case reports (total of two patients), which are not included in the evidence tables. Patients were treated with 1–2 g/kg/day each month with good results. Both patients were able to reduce their corticosteroid requirements after IVIG therapy.
  - **Linear Immunoglobulin A (IgA) Bullous Disease.** Four case reports have evaluated IVIG in linear IgA bullous disease. Symptoms decreased in all patients after IVIG doses of 1–2 g/kg (given over 1–5 days), with courses repeated every 2–4 weeks. Response is maintained with continued therapy, although symptoms may recur within four weeks of the final dose.
- **Primary Recurrent Spontaneous Miscarriage:** Seven randomized clinical trials and two meta-analyses have evaluated IVIG in women with recurrent spontaneous miscarriage. A variety of IVIG regimens were used including: 500 mg/kg monthly; 800 mg/kg weekly until 20 weeks gestation, then 1 g/kg every 14 days from 20–26 weeks gestation; 20 g every three weeks for five doses; 25 g/day for two days, then 25 g every three weeks; 30 g as a single dose, followed by 20 g every three weeks; or 30–40 g weekly in gestational weeks 5–6, followed by 20–30 g every 14 days in weeks 7–26, then 25–35 g every 14 days in weeks 28–34. It remains controversial whether IVIG improves live birth rates in these patients. The earliest randomized trial reported significantly higher live birth rates with IVIG (62%) than placebo (34%,  $p=0.04$ ). However, the next six published trials found no benefit with IVIG, with live birth rates of 45–77% for IVIG and

29–79% for placebo. A 1998 meta-analysis of the first four trials found similar results. Live birth rate was 58% with IVIG and 48% with placebo ( $p=0.17$ ). When patients with any other cause for miscarriage were excluded, live birth rate was higher with IVIG (63%) than placebo (49%,  $p=0.041$ ). However, a 2003 Cochrane systematic review of all seven randomized trials found no difference in live birth rate between IVIG (58%) or placebo (59%). A 2006 Cochrane systematic review found similar results and concluded that IVIG provides no significant beneficial effect over placebo in improving the live birth rate. Case series and nonrandomized trials have been published but were not reviewed.

- **Secondary Recurrent Spontaneous Miscarriage:** A systematic search strategy was applied to Medline (1966 to June 2005) and the Cochrane Register of Controlled Trials (June 2005). Selection criteria included all randomized controlled trials comparing all dosages of IVIG to placebo or an active control. Two investigators independently extracted data using a standardized data collection form. Measures of effect were derived for each trial independently, and studies were pooled based on clinical and methodologic appropriateness. Eight trials were identified involving 442 women that evaluated IVIG therapy used to treat recurrent miscarriage. Overall, IVIG did not significantly increase the odds ratio (OR) of live birth when compared to placebo for treatment of recurrent miscarriage (OR 1.28, 95% CI 0.78-2.10). There was, however, a significant increase in live births following IVIG use in women with secondary recurrent miscarriage (OR 2.71, 95% CI 1.09–6.73), while those with primary miscarriage did not experience the same benefit (OR 0.66, 95% CI 0.35–1.26).
- **Complex Regional Pain Syndrome (CRPS):** Treatment of long-standing complex regional pain syndrome (CRPS) is empirical and often of limited efficacy. Preliminary data suggest that the immune system is involved in sustaining this condition and that treatment with low-dose intravenous immunoglobulin (IVIG) may substantially reduce pain in some patients. A randomized, double-blind, placebo-controlled crossover trial was performed. Persons who had pain intensity greater than 4 on an 11-point (0 to 10) numerical rating scale and had CRPS for 6 to 30 months that was refractory to standard treatment. IVIG, 0.5 g/kg, and normal saline in separate treatments, divided by a washout period of at least 28 days was given as treatment. 13 eligible participants were randomly assigned between November 2005 and May 2008; 12 completed the trial. The average pain intensity was 1.55 units lower after IVIG treatment than after saline (95% CI, 1.29 to 1.82;  $P < 0.001$ ). In 3 patients, pain intensity after IVIG was less than after saline by 50% or more. No serious adverse reactions were reported. The trial was small, and recruitment bias and chance variation could have influenced results and their interpretation. IVIG, 0.5 g/kg, can reduce pain in refractory CRPS. Studies are required to determine the best immunoglobulin dose, the duration of effect, and when repeated treatments are needed.
- **Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS):** PANDAS is a condition defined by five clinical characteristics – the presence of obsessive compulsive disorder (OCD) and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing-remitting symptom course, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and a temporal association between symptom exacerbations and a Group-A beta-hemolytic streptococcal (GAS) infection. These five criteria have been used for the purpose of conducting research on PANDAS as well as studies of the pathophysiology of post-streptococcal OCD and tic disorders (Swedo et. al., 2004).

The diagnosis and treatment of PANDAS remains a controversial issue. Several studies are either recruiting or ongoing at this time to address the proper diagnosis and treatment of PANDAS. Preliminary results of certain studies even suggest enlarging the spectrum of PANDAS to include attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) (Martino, et. al., 2009). To date, there is limited data for randomized, well controlled studies on the use of IVIG in PANDAS. Several case reports and literature reviews are available but provide no conclusive evidence.

There are limited data available on the effectiveness of IVIG in tic disorders. In a study conducted by Hoekstra, et. al. (2004), thirty patients with a DSM-IV tic disorder were randomly assigned to

receive IVIG or placebo. A five month study showed no statistically significant differences between IVIG and placebo for tic severity as measured by the Yale Global Tic Severity Scale. IVIG treatment was associated with significantly more side effects than placebo, most notably headache. Based upon the study results IVIG cannot be recommended in tic disorders. A secondary measure - severity of obsessions and compulsions – as measured by the Yale-Brown Obsessive Compulsive Scale, decreased significantly in the IVIG group compared to placebo at week 6 (p=.02). This finding requires further investigation as both IVIG and placebo groups had a subclinical score at the start of the study. Since the primary objective of this study was tic severity, the improvement of obsessions and compulsions are limited and considered preliminary results and therefore, require further studies.

Currently, available research lacks conclusive, evidence-based results regarding the usefulness of IVIG in PANDAS. (Martino, et. al., 2009). PANDAS remains ill-defined due to the lack of immunologic biomarkers for conclusive evidence of the disease. Until further research can elucidate a clear diagnosis of PANDAS, its spectrum of characteristics, and demonstrate IVIG support for a positive outcome of the treatment of PANDAS, IVIG use in PANDAS remains controversial and inconclusive

### **Adverse Reactions/Contraindications**

Immune globulin intravenous (human) is contraindicated in patients with selective IgA deficiency or prior anaphylactic reaction to IVIG. Patients with selective IgA deficiency have an increased risk of anaphylaxis to IVIG products containing IgA, even when only small concentrations are present. Select a product with lower IgA content (e.g., Gammagard, Polygam S/D) if IVIG treatment is necessary for such patients.

Immune globulin intravenous (human) has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. IVIG should be administered at the minimum concentration available and the minimum rate of infusion possible in patients who are predisposed to acute renal failure (e.g., patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs). While renal dysfunction and acute renal failure have been reported with the use of many of the licensed IVIG products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number.

Patients with diabetes may be at risk for hyperglycemia when given IVIG products stabilized with glucose (e.g., Gammagard, Iveegam, Polygam S/D). Use of products without glucose may be warranted (Carimune NF, Flebogamma, Gamunex, Octagam).

Antibodies present in IVIG may interfere with the immune response to live viral vaccines, including measles, mumps, rubella, and varicella. These vaccines should not be administered simultaneously with or for specified intervals before or after administration of IVIG.

Adverse effects occur in 1–23% of patients given IVIG, but are usually mild. The most common reactions include fever, chills, rigors, tremor, flushing, renal dysfunction, headache, nausea, vomiting, diarrhea, back pain, chest pain, chest tightness, malaise, or myalgia. Many adverse effects are related to infusion rate and resolve when the infusion is slowed or temporarily stopped. Premedication with antihistamines, acetaminophen, or corticosteroids may prevent or alleviate these reactions.

*In Oct 2010, Gamunex-C was introduced by its manufacturer as a product that will phase out the use of Gamunex once Gamunex supplies have run out. It is approved for IV use for ITP and CIDP and subcutaneous use for PID.*

**Note: The standard threshold for lower limit of normal is two standard deviations below the mean. This number may vary among different laboratories.**

**Appendix 1**  
**Standard Reference Ranges for Serum Immunoglobulin Levels**

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

<b>Normal Serum Immunoglobulin Levels (mg/dL)</b>			
<b>Age</b>	<b>IgA</b>	<b>IgG</b>	<b>IgM</b>
0 – 30 days	1 – 7	<b>611 – 1542</b>	0 – 24
1 mo	1 – 53	<b>241 – 870</b>	19 – 83
2 mo	3 – 47	<b>198 – 577</b>	16 – 100
3 mo	5 – 46	<b>169 – 558</b>	23 – 85
4 mo	4 – 72	<b>188 – 536</b>	26 – 96
5 mo	8 – 83	<b>165 – 781</b>	31 – 103
6 mo	8 – 67	<b>206 – 676</b>	33 – 97
7 – 8 mo	11 – 89	<b>208 – 868</b>	32 – 120
9 – 11 mo	16 – 83	<b>282 – 1026</b>	39 – 142
1 yr	14 – 105	<b>331 – 1164</b>	41 – 164
2 yr	14 – 122	<b>407 – 1009</b>	46 – 160
3 yr	22 – 157	<b>423 – 1090</b>	45 – 190
4 yr	25 – 152	<b>444 – 1187</b>	41 – 186
5 – 7 yr	33 – 200	<b>608 – 1229</b>	46 – 197
8 – 9 yr	45 – 234	<b>584 – 1509</b>	49 – 230
10 yr & older	68 – 378	<b>768 – 1632</b>	60 – 263

Immunoglobulins, Serum Quantitative. Accessed April 6, 2009.  
 Available at: <http://www.aruplab.com/guides/ug/tests/0050630.jsp>

**Appendix 2**  
**Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1,2,3)**

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

<b>Age</b>	<b>IgG 1</b>	<b>IgG 2</b>	<b>IgG 3</b>	<b>IgG 4</b>
Cord Blood	435-1084	143-453	27-146	1-47
0-2 months	218-498	40-167	4-23	1-33
3-5 months	143-394	23-147	4-70	1-14
6-8 months	190-388	37-60	12-62	1-16
9-23 months	288-880	30-327	13-82	1-65

2 years	170-950	22-440	4-69	0-120
3-4 years	290-1065	28-315	4-71	0-90
5-6 years	330-1065	57-345	8-126	2-116
7-8 years	225-1100	42-375	9-107	0-138
9-10 years	390-1235	61-430	10-98	1-95
11-12 years	380-1420	73-455	16-194	1-153
13-14 years	165-1440	71-460	12-178	2-143
15 years & older	240-1118	124-549	21-134	7-89

Immunoglobulin G Subclass Levels (1,2,3,4). Accessed April 6, 2009.  
Available at: <http://www.aruplab.com/guides/ug/tests/0050577.jsp>

### Appendix 3

#### Selected Genetic Based Primary Immunodeficiency Syndrome (PID)

Condition	Features
<b>Congenital / X-linked agammaglobulinemia-XLA</b>	Bruton's Disease- BTK gene impaired
<b>Autosomal recessive agammaglobulinemia -ARA</b>	IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired
<b>Autosomal recessive hyperimmuno-globulin M syndrome (HIM)</b>	AICDA or UNG gene impaired
<b>Congenital Hypogammaglobulinemia</b>	late onset, ICOS impaired
<b>ICF Syndrome</b>	<ul style="list-style-type: none"> <li>• Abnormal Facies</li> <li>• Respiratory Tract Infections</li> <li>• Hypogammaglobulinemia</li> <li>• Characteristic Chromosomal Abnormalities</li> </ul>
<b>Specific Antibody Deficiency (SAD)</b>	<ul style="list-style-type: none"> <li>• generally does not require IVIG replacement for control of recurrent bacterial infections</li> <li>• Rare patients will have infection susceptibility with normal vaccine responses</li> </ul>
<b>Hypogammaglobulinemia, unspecified</b>	N/A
<b>Transient hypogammaglobulinemia of infancy</b>	only requires short-term IVIG replacement for recurrent severe bacterial infections
<b>Selective IgG subclass deficiencies (IGGSD)</b>	<ul style="list-style-type: none"> <li>• persistent absence of IgG1, IgG2, and/or IgG3</li> <li>• generally does not require IVIG replacement for control of recurrent bacterial infections</li> <li>• Rare patients will have infection susceptibility with normal vaccine responses</li> </ul>
<b>Combined immunodeficiency disorders (not all-inclusive)</b>	<ul style="list-style-type: none"> <li>• ataxia-telangiectasia (<b>A-T</b>)</li> <li>• Wiskott Aldrich syndrome (<b>WAS</b>),</li> </ul>

	<ul style="list-style-type: none"> <li>• DiGeorge syndrome (<b>DGS</b>)</li> <li>• Nijmegen breakage syndrome (<b>NBS</b>)</li> <li>• (<b>WHIM</b>) warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis</li> </ul>
<b>Severe combined immunodeficiency disorder (SCID)</b>	N/A
<b>Hyperimmuno-globulinemia E syndrome (HIES)</b>	N/A

## Coding/Billing Information

Covered when medically necessary subject to the criteria indicated in the Coverage Policy:

<b>CPT<sup>®</sup>* Codes</b>	<b>Description</b>
90283	Immune globulin (IVIG), human, for intravenous use
90399 <sup>†</sup>	Unlisted immune globulin
90779 <sup>†</sup>	Unlisted therapeutic, prophylactic or diagnostic intravenous or intra-arterial injection or infusion

<b>HCPCS Codes</b>	<b>Description</b>
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1561	Injection, immune globulin, (Gamunex), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, nonlyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1599 <sup>†</sup>	Injection, immune globulin, intravenous, non-lyophilized (e.g. liquid), not otherwise specified, 500 mg
J7799 <sup>†</sup>	NOC drugs, other than inhalation solution, administered through DME
J3490 <sup>†</sup>	Unclassified drugs
J3590 <sup>†</sup>	Unclassified biologics
Q4082 <sup>†</sup>	Drug or biological, not otherwise classified, Part B drug competitive acquisition program (CAP)

<sup>†</sup>**Note:** Covered when medically necessary when used to represent Immune Globulin Intravenous not reported by another code (e.g.: Human, IVIG).

The following ICD-9-CM Diagnosis Codes are covered when medically necessary subject to the criteria indicated in the Coverage Policy.

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
037	Tetanus
040.82	Toxic shock syndrome

042	Human immunodeficiency virus [HIV]
052.9	Varicella without mention of complication
070.1	Viral hepatitis A without mention of hepatic coma
079.83	Parvovirus B19
203.00	Multiple myeloma, without mention of having achieved remission
203.01	Multiple myeloma in remission
203.02	Multiple myeloma, in relapse
204.10	Chronic lymphoid leukemia, without mention of having achieved remission
204.11	Chronic lymphoid leukemia in remission
204.12	Chronic lymphoid leukemia, in relapse
279.00	Unspecified hypogammaglobulinemia
279.03	Other selective immunoglobulin deficiencies
279.04	Congenital hypogammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.11	DiGeorge's syndrome
279.12	Wiskott-Aldrich syndrome
279.2	Combined immunity deficiency
283.0	Autoimmune hemolytic anemias
287.31	Immune thrombocytopenic purpura
287.32	Evans' syndrome
287.41	Post-transfusion purpura
287.49	Other secondary thrombocytopenia
288.1	Functional disorders of polymorphonuclear neutrophils
333.91	Stiff-man syndrome
334.8	Other spinocerebellar diseases
340	Multiple sclerosis
357.0	Acute infective polyneuritis
357.81	Chronic inflammatory demyelinating polyneuritis
357.89	Other inflammatory and toxic neuropathy
358.01	Myasthenia gravis with (acute) exacerbation
358.1	Myasthenic syndromes in diseases classified elsewhere
359.89	Other myopathies
446.1	Acute febrile mucocutaneous lymph node syndrome (MCLS)
694.4	Pemphigus
694.5	Pemphigoid
694.60	Benign mucous membrane pemphigoid without mention of ocular involvement
694.61	Benign mucous membrane pemphigoid with ocular involvement
694.8	Other specified bullous dermatosis
695.13	Stevens-Johnson syndrome
695.14	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
695.15	Toxic epidermal necrolysis
710.3	Dermatomyositis
710.4	Polymyositis
773.0	Hemolytic disease due to Rh isoimmunization of fetus or newborn
773.1	Hemolytic disease due to ABO isoimmunization of fetus or newborn
773.2	Hemolytic disease due to other and unspecified isoimmunization of fetus or newborn
776.1	Transient neonatal thrombocytopenia
V42.81	Bone marrow replaced by transplant

**Experimental/Investigational/Unproven/Not Covered:**

ICD-9-CM Diagnosis	Description
-----------------------	-------------

Codes	
138	Late effects of acute poliomyelitis
273.1	Monoclonal paraproteinemia
288.09	Other neutropenia
335.20	Amyotrophic lateral sclerosis
345.81	Other forms of epilepsy and recurrent seizures, with intractable epilepsy
356.4	Idiopathic progressive polyneuropathy
356.8	Other specified idiopathic peripheral neuropathy
356.9	Unspecified hereditary and idiopathic peripheral neuropathy
390	Rheumatic fever without mention of heart involvement
691.8	Other atopic dermatitis and related conditions
710.0	Systemic lupus erythematosus
728.89	Other disorder of muscle, ligament, and fascia
780.71	Chronic fatigue syndrome

**\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

## References

1. Ahmed AR, Colon JE. Comparison between intravenous immunoglobulin and conventional immunosuppressive therapy regimens in patients with severe oral pemphigoid: effects on disease progression in patients nonresponsive to dapsone therapy. *Arch Dermatol*. Sep 2001;137(9):1181-1189.
2. Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. *J Am Acad Dermatol*. Jan 2002;46(1):42-49.
3. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol*. Dec 2001;45(6):825-835.
4. Ahmed AR. Intravenous immunoglobulin therapy in the treatment of patients with pemphigus vulgaris unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol*. Nov 2001;45(5):679-690.
5. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. *Cochrane Database Syst Rev*. 2002(3):CD003313.
6. American College of Obstetricians and Gynecologists. Thrombocytopenia in pregnancy. Available at: <http://www.guideline.gov>. Accessed August 22, 2006.
7. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol*. Jan 2003;139(1):33-36.
8. Baxter Brasil. Endobulin. Available online at: [www.baxter.com.br/hyland\\_endobulin.htm](http://www.baxter.com.br/hyland_endobulin.htm). Accessed on December 21, 2004. Sao Paulo, Brazil: Baxter Brazil; 2004.
9. Baxter. Gammagard liquid [Immune Globulin Intravenous (Human)] 10% package insert. Westlake Village, CA: Baxter Healthcare Corporation; April 2005.
10. Baxter. Immune globulin intravenous (Human) Iivegam EN package insert. Westlake Village, CA: Baxter Healthcare Corporation; April, 2005.
11. Bayer. Press Release: Bayer Biological Products submits new immune globulin intravenous treatment for approval in key global markets (August 27, 2002). Research Triangle Park, NC: Bayer Biological Products; 2002.

12. Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. *Obstet Gynecol.* Jan 2006;107(1):91-6.
13. Bhattacharyya J, Kumar R, Tyagi S, Kishore J, Mahapatra M, Choudhry VP. Human parvovirus B19-induced acquired pure amegakaryocytic thrombocytopenia. *Br J Haematol.* Jan 2005;128(1):128-129.
14. Bingel U, Pinter JD, Sotero de Menezes M, Rho JM. Intravenous immunoglobulin as adjunctive therapy for juvenile spasms. *J Child Neurol.* Jun 2003;18(6):379-382.
15. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol.* May 2005;94(5 Suppl 1):S1-63.
16. Bystryn JC, Jiao D, Natow S. Treatment of pemphigus with intravenous immunoglobulin. *J Am Acad Dermatol.* Sep 2002;47(3):358-363.
17. Carp HJ, Toder V, Gazit E, et al. Further experience with intravenous immunoglobulin in women with recurrent miscarriage and a poor prognosis. *Am J Reprod Immunol.* Oct 2001;46(4):268-273.
18. Cavazzuti GB. Infantile encephalopathies. *Neurol Sci.* Oct 2003;24 Suppl 4:S244-245.
19. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. *MMWR* 2000;49(No. RR-10):1-147. Available online at: <http://www.cdc.gov/mmwr/PDF/rr/rr4910.pdf>
20. Chen C, Danekas LH, Ratko TA, Vlasses PH, Matuszewski KA. A multicenter drug use surveillance of intravenous immunoglobulin utilization in US academic health centers. *Ann Pharmacother.* Vol 34; 2000:295-299.
21. Chorzelski T, Hashimoto T, Maciejewska B, Amagai M, Anhalt GJ, Jablonska S. Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis and bronchiolitis obliterans. *J Am Acad Dermatol.* Sep 1999;41(3 Pt 1):393-400.
22. Christiansen OB, Pedersen B, Rosgaard A, Husth M. A randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin in the prevention of recurrent miscarriage: evidence for a therapeutic effect in women with secondary recurrent miscarriage. *Hum Reprod.* Mar 2002;17(3):809-816.
23. Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulins (IVIg) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). *J Assist Reprod Genet.* 2006 Jan;23(1):1-13.
24. Cranberry. In: "Immune Globulin Intravenous (IVIg)". St. Louis (MO): Facts and Comparisons; 2006 [updated 2006 Jul; cited 2006 Aug 11] Available from: <http://online.factsandcomparisons.com/>
25. CSL Behring LLC. Privigen<sup>®</sup>, Immune Globulin Intravenous (Human), 10% Liquid Prescribing Information. Kankakee, IL: CSL Behring LLC. June 2009.
26. Customer Service. Availability of Sandoglobulin {personal communication, October 22}. Glendale, CA: ZLB Behring; 2004.
27. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med.* Dec 27 2001;345(26):1870-1876.
28. Darenberg J, Ihendyane N, Sjolín J, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis.* Aug 1 2003;37(3):333-340.

29. Deda G, Caksen H. Atypical benign partial epilepsy of childhood (pseudo-Lennox syndrome): report of two brothers. *Neurol India*. Sep 2002;50(3):337-339.
30. D'Eufemia P, Nigro G, Celli M, Finocchiaro R, Iannetti P, Giardini O. Low-dosage immunoglobulins for an infant with hypogammaglobulinemia, maple syrup urine disease, and parvovirus B19-associated aplastic crisis. *J Pediatr Hematol Oncol*. Sep-Oct 2000;22(5):485-487.
31. Engineer L, Ahmed AR. Role of intravenous immunoglobulin in the treatment of bullous pemphigoid: analysis of current data. *J Am Acad Dermatol*. Jan 2001;44(1):83-88.
32. Engineer L, Dow EC, Braverman IM, Ahmed AR. Epidermolysis bullosa acquisita and multiple myeloma. *J Am Acad Dermatol*. Dec 2002;47(6):943-946.
33. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev*. Apr 19 2006;(2):CD002277.
34. Gergely L, Varoczy L, Vadasz G, Remenyik E, Illes A. Successful treatment of B cell chronic lymphocytic leukemia-associated severe paraneoplastic pemphigus with cyclosporin A. *Acta Haematol*. 2003;109(4):202-205.
35. Gerschlager W, Brown P. Effect of treatment with intravenous immunoglobulin on quality of life in patients with stiff-person syndrome. *Mov Disord*. May 2002;17(3):590-593.
36. Gourgiotou K, Exadaktylou D, Aroni K, et al. Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins. *J Eur Acad Dermatol Venereol*. Jan 2002;16(1):77-80.
37. Granata T, Fusco L, Gobbi G, et al. Experience with immunomodulatory treatments in Rasmussen's encephalitis. *Neurology*. Dec 23 2003;61(12):1807-1810.
38. Grifols. Flebogamma® 5% {immune globulin intravenous (Human)} package insert. Los Angeles, CA: Grifols Biologicals, Inc.; November, 2006.
39. Hebert AA, Bogle MA. Intravenous immunoglobulin prophylaxis for recurrent Stevens-Johnson syndrome. *J Am Acad Dermatol*. Feb 2004;50(2):286-288.
40. Hoekstra PJ, Minderaa RB, Kallenberg CG. Lack of effect of intravenous immunoglobulins on tics: a double-blind placebo-controlled study. *J Clin Psychiatry*. 2004 Apr;65(4):537-42.
41. Hutton B, Sharma R, Fergusson D, Tinmouth A, Hebert P, Jamieson J, Walker M. Use of intravenous immunoglobulin for treatment of recurrent miscarriage: a systematic review. *BJOG*. Feb 2007; 114 (2): 134-42.
42. Iaccheri B, Roque M, Fiore T, et al. Ocular cicatricial pemphigoid, keratomycosis, and intravenous immunoglobulin therapy. *Cornea*. Nov 2004;23(8):819-822.
43. Isobe Y, Sugimoto K, Shiraki Y, Nishitani M, Koike K, Oshimi K. Successful high-titer immunoglobulin therapy for persistent parvovirus B19 infection in a lymphoma patient treated with rituximab-combined chemotherapy. *Am J Hematol*. Dec 2004;77(4):370-373.
44. Jablonowska B, Selbing A, Palfi M, Ernerudh J, Kjellberg S, Lindton B. Prevention of recurrent spontaneous abortion by intravenous immunoglobulin: a double-blind placebo-controlled study. *Hum Reprod*. Mar 1999;14(3):838-841.
45. Jordan SC, Tyan D, Stablein D, et al. Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with endstage renal disease: report of the NIH IG02 trial. *J Am Soc Nephrol*. Dec 2004;15(12):3256- 3262.
46. Jordan SC, Vo A, Bunnapradist S, et al. Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation*. Aug 27 2003;76(4):631-636.

47. Kerr JR, Cunniffe VS, Kelleher P, Bernstein RM, Bruce IN. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis*. May 1 2003;36(9):e100-106.
48. Kreuter A, Harati A, Breuckmann F, Appelhans C, Altmeyer P. Intravenous immune globulin in the treatment of persistent pemphigoid gestationis. *J Am Acad Dermatol*. Dec 2004;51(6):1027-1028.
49. Letko E, Bhol K, Foster CS, Ahmed AR. Linear IgA bullous disease limited to the eye: a diagnostic dilemma: response to intravenous immunoglobulin therapy. *Ophthalmology*. Aug 2000;107(8):1524-1528.
50. Letko E, Bhol K, Foster SC, Ahmed RA. Influence of intravenous immunoglobulin therapy on serum levels of anti-beta 4 antibodies in ocular cicatricial pemphigoid. A correlation with disease activity. A preliminary study. *Curr Eye Res*. Aug 2000;21(2):646-654.
51. Letko E, Miserocchi E, Daoud YJ, Christen W, Foster CS, Ahmed AR. A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. *Clin Immunol*. Jun 2004;111(3):303-310.
52. Leverkus M, Georgi M, Nie Z, Hashimoto T, Brocker EB, Zillikens D. Cicatricial pemphigoid with circulating IgA and IgG autoantibodies to the central portion of the BP180 ectodomain: beneficial effect of adjuvant therapy with high-dose intravenous immunoglobulin. *J Am Acad Dermatol*. Jan 2002;46(1):116-122.
53. Mareschal-Desandes R, Andre JL, Lesesve JF, Krier MJ, Bordigoni P, Humbert JC. Successful treatment of chronic parvovirus B19 infection by high-dose immunoglobulin. *Clin Nephrol*. Apr 2003;59(4):311-312.
54. Martino D, Defazio G, Giovannoni G. The PANDAS subgroup of tic disorders and childhood-onset obsessive-compulsive disorder. *J Psychosom Res*. 2009 Dec;67(6):547-57.
55. McEvoy GK, ed. AHFS 2011 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2011.
56. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics*. Dec 2003;112(6 Pt 1):1430-1436.
57. Mikati MA, Saab R, Fayad MN, Choueiri RN. Efficacy of intravenous immunoglobulin in Landau-Kleffner syndrome. *Pediatr Neurol*. Apr 2002;26(4):298-300.
58. Nicolson et al: An Open Trial of Plasma Exchange in Childhood Onset Obsessive-compulsive Disorder Without Poststreptococcal Exacerbations. "J Am Acad Child Adolesc Psychiatry 2000," 39[10]: 1313-1315.
59. Octapharma. Immune globulin intravenous (Human) 5%, Solvent/Detergent Treated (Octagam®) package insert. Centreville, VA: Octapharma USA, Inc.; April 2006.
60. Olson JA, Olson DM, Sandborg C, Alexander S, Buckingham B. Type 1 diabetes mellitus and epilepsy partialis continua in a 6-year-old boy with elevated anti-GAD65 antibodies. *Pediatrics*. Mar 2002;109(3):E50.
61. Orange, Jordan S., et. al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immun*. April 2006.
62. Pickering LK, Baker CJ, Long SS, McMillan JA, eds. Toxic shock syndrome. In: *Red Book: 2006 Report of the Committee on Infectious Diseases*. 27th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2006:660-5.

63. Porter TF, LaCoursiere Y, Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev*. Apr 19 2006;(2):CD000112.
64. Prins C, Kerdel FA, Padilla RS, et al. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol*. Jan 2003;139(1):26-32.
65. Prins C, Vittorio C, Padilla RS, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology*. 2003;207(1):96- 99.
66. Rayment R, Brunskill SJ, Stanworth S, Soothill PW, Roberts DJ, Murphy MF. Antenatal Interventions for fetomaternal alloimmune thrombocytopenia. *Cochrane Database Syst Rev*. Jan 25 2005;(1):CD004226.
67. Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin. *Clin Exp Immunol*. Sep 2002;129(3):533-540.
68. Sami N, Letko E, Androudi S, Daoud Y, Foster CS, Ahmed AR. Intravenous immunoglobulin therapy in patients with ocular-cicatricial pemphigoid: a long-term follow-up. *Ophthalmology*. Jul 2004;111(7):1380-1382.
69. Sami N, Qureshi A, Ahmed AR. Steroid sparing effect of intravenous immunoglobulin therapy in patients with pemphigus foliaceus. *Eur J Dermatol*. Mar-Apr 2002;12(2):174-178.
70. Sami N, Qureshi A, Ruocco E, Ahmed AR. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. *Arch Dermatol*. Sep 2002;138(9):1158-1162.
71. Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev*. 2003(1):CD000112.
72. Siegel J. Intravenous immune globulins: Therapeutic, pharmaceutical, and cost considerations. *Pharmacy Practice News*. Vol January; 2004:39-43.
73. Snider LA, Swedo SE. Childhood-onset obsessive-compulsive disorder and tic disorders: case report and literature review. *J Child Adolesc Psychopharmacol*. 2003;13 Suppl 1:S81-8.
74. Snider LA, Swedo SE. PANDAS: current status and directions for research. *Mol Psychiatry*. 2004 Oct;9(10):900-7.
75. Stahl HD, Pfeiffer R, Emmrich F. Intravenous treatment with immunoglobulins may improve chronic undifferentiated mono- and oligoarthritis. *Clin Exp Rheumatol*. Jul-Aug 2000;18(4):515-517.
76. Stella M, Cassano P, Bollero D, Clemente A, Giorio G. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology*. 2001;203(1):45-49.
77. Stiehm ER. Shortage of IV immunoglobulin. *Ann Allergy Asthma Immunol*. Vol 85; 2000:424.
78. Stricker RB, Steinleitner A, Bookoff CN, Weckstein LN, Winger EE. Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin. *Fertil Steril*. Mar 2000;73(3):536-540.
79. Swedo SE, Garvey M, Snider L, Hamilton C, Leonard HL. The PANDAS subgroup: recognition and treatment. *CNS Spectr*. 2001 May;6(5):419-22, 425-6.
80. Talecris Biotherapeutics, Inc. Immune globulin intravenous (Human), 10%, caprylate/chromatography purified (Gamunex<sup>®</sup>) package insert. Research Triangle Park, NC: Talecris Biotherapeutics; November 2005.

81. Talecris Biotherapeutics, Inc. Immune globulin intravenous (Human), 10%, caprylate/chromatography purified (Gamunex-C<sup>®</sup>) package insert. Research Triangle Park, NC: Talecris Biotherapeutics. October 2010.
82. Tanyer G, SiklarZ, Dallar Y, Yildirmak Y, Tiras U. Multiple dose IVIG treatment in neonatal immune hemolytic jaundice. J Trop Pediatr. Feb 2001;47(1):50-53.
83. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. Arch Dermatol. Jan 2003;139(1):39-43.
84. Wetter DA, Davis MD, Yiannias JA, et al. Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. Mayo Clin Proc. Jan 2005;80(1):41-47.
85. ZLB Behring. Immune globulin intravenous (Human) (Carimune<sup>®</sup> NF Nanofiltered, Lyophilized Preparation) package insert. Kankakee, IL: ZLB Behring; January 2005.
86. ZLB Behring. Immune globulin intravenous (Human) (Panglobulin NF Nanofiltered) package insert. Washington, DC: American Red Cross Blood Services; 2003.
87. ZLB Behring. Immune globulin intravenous (Human) 5% (Gammar-P I.V.)package insert. Kankakee, IL: Aventis Behring LLC. 2003.

---

## Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	8/15/2008	5026	Immune Globulin Intravenous (Human) (IVIG)
Great-West Healthcare	12/2007	P02.104.2	Immune Globulins

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.