# Immune Globulin (IVIG and SCIG)

**Policy Number**: 2026D0035AV
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➲ Instructions for Use

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**Related Commercial Policies**

- Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs
- Provider Administered Drugs – Site of Care

**Community Plan Policy**

- Immune Globulin (IVIG and SCIG)

## Coverage Rationale

➲ See Benefit Considerations

**Alyglo™ (IV), Asceniv™ (IV), Panzyga® (IV), Qivigy (IV), and Yimmugo (IV) are typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan.** Refer to the Medical Benefit Drug Policy titled Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs and the corresponding excluded drug list with preferred alternatives.

**Note**: For requests that require medical necessity review, refer to the General Requirements and Diagnosis-Specific Requirements sections below. *(For Medicare reviews, refer to the CMS section.***)

**Coverage for the following preferred immune globulin products Bivigam® (IV), Cutaquig® (SC), Cuvitru® (SC), Flebogamma® DIF (IV), Gammagard® Liquid (IV, SC), Gammagard® S/D (IV), Gammaked™ (IV, SC), Gammaplex® (IV), Gamunex®-C (IV, SC), Hizentra® (SC), HyQvia® (SC), Octagam® (IV), Privigen® (IV), and Xembify® (SC) is contingent on criteria in the General Requirements and Diagnosis-Specific Requirements sections.**

**Any U.S. Food and Drug Administration (FDA)–approved immune globulin product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare.**

### Diagnoses Addressed in This Policy

- Acute disseminated encephalomyelitis
- Autoimmune bullous diseases
- Bone marrow transplantation (BMT)
- Chronic inflammatory demyelinating polyneuropathy
- Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL
- Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants
- Dermatomyositis or polymyositis
- Encephalitis, immune checkpoint inhibitor-induced, severe, or progressive
- Feto-neonatal alloimmune thrombocytopenia
- Guillain-Barré syndrome (GBS)
- HIV-infection, prevention of bacterial infection in pediatric HIV
- IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy
- Immune thrombocytopenia
- Kawasaki disease
- Lambert-Eaton myasthenic syndrome (LEMS)
- Lennox Gastaut syndrome
- Lymphoproliferative disease, treatment of bacterial infections
- Measles (rubeola) post-exposure prophylaxis
- Multifocal motor neuropathy (MMN)
- Multiple myeloma, prevention of infection


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- Multiple sclerosis, relapsing forms
- Myasthenia Gravis
- Neuromyelitis optica
- Paraproteinemic neuropathy
- Parvovirus B19 infection, treatment, immunocompromised host (solid organ transplant recipient or HIV-related)
- Post B-cell targeted therapies
- Posttransfusion purpura
- Primary immunodeficiency syndromes
- Rasmussen syndrome
- Solid organ transplantation, desensitization, prevention, or treatment of acute humoral rejection
- Staphylococcal toxic shock
- Stiff-person syndrome
- Thrombocytopenia, secondary to HCV, HIV, or pregnancy
- Toxic epidermal necrolysis or Stevens-Johnson syndrome
- Warm autoimmune hemolytic anemia
- Unproven uses

## The Following Information Pertains to Medical Necessity Review

### *General Requirements (Applicable to all Medical Necessity Requests)*

- For **initial therapy**, **all** of the following:
  - Diagnosis; **and**
  - Medical records documenting **both** of the following:
    - History and physical examination documenting the severity of the condition, including frequency and severity of infections where applicable; **and**
    - Laboratory results or diagnostic evidence supporting the indication for which immune globulin is requested **and**
  - **One** of the following:
    - Prescriber attests dosing is in accordance with the FDA-approved labeling; **or**
    - For indications without FDA-approved dosing, prescriber attests there is published clinical evidence to support the dosing
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Documentation of positive clinical response to immune globulin therapy; **and**
  - **One** of the following:
    - Prescriber attests dosing is in accordance with the FDA-approved labeling; **or**
    - For indications without FDA-approved dosing, prescriber attests there is published clinical evidence to support the dosing
  - Authorization will be for no more than 12 months

### *Diagnosis-Specific Requirements*

The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

**Immune globulin is proven for:**

### *Dermatology*

- **Autoimmune bullous diseases** [pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, linear IgA bullous dermatosis]
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of autoimmune bullous diseases when all of the following criteria are met:**
  - Diagnosis of an autoimmune bullous disease; **and**
  - Extensive and debilitating disease; **and**
  - History of failure, contraindication, or intolerance to systemic corticosteroids with concurrent immunosuppressive treatment (e.g., azathioprine, cyclophosphamide, mycophenolate mofetil)

- **Toxic epidermal necrolysis or Stevens-Johnson syndrome**

### *Hematology*

- **Feto-neonatal alloimmune thrombocytopenia (AIT)**
  Additional information to support medical necessity review where applicable:


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**Immune globulin is medically necessary for the treatment of feto-neonatal alloimmune thrombocytopenia when one of the following criteria are met:**

**For Pregnant Women**

- Diagnosis of feto-neonatal alloimmune thrombocytopenia (AIT); **and**
- **One** or more of the following:
  - Previously affected pregnancy
  - Family history of the disease
  - Platelet alloantibodies found on screening

**For Newborns**

- Diagnosis of feto-neonatal alloimmune thrombocytopenia; **and**
- Thrombocytopenia that persists after transfusion of antigen-negative compatible platelets

- **Immune thrombocytopenia [Idiopathic thrombocytopenic purpura (ITP)]**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of idiopathic thrombocytopenic purpura when one of the following criteria is met:**
  - **Both** of the following:
    - Diagnosis of **acute** thrombocytopenic purpura (ITP); **and**
    - Documented platelet count < 50 x $10^9$ / L (obtained within the past 30 days)

    **or**
  - **Both** of the following:
    - Diagnosis of **chronic** thrombocytopenic purpura (ITP); **and**
    - History of failure, contraindication, or intolerance to at least **one** of the following:
      - Corticosteroids
      - Splenectomy

- **Posttransfusion purpura**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of posttransfusion purpura when both of the following criteria are met:**
  - Diagnosis of posttransfusion purpura; **and**
  - IVIG dose does not exceed 2 days

- **Thrombocytopenia, Secondary to Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), or pregnancy**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of thrombocytopenia when both of the following criteria are met:**
  - **One** of the following:
    - **Both** of the following:
      - Diagnosis of thrombocytopenia secondary to HCV infection
      - Patient is receiving concurrent antiviral therapy, unless contraindicated

      **or**
    - **Both** of the following:
      - Diagnosis of thrombocytopenia secondary HIV infection
      - Patient is receiving concurrent antiviral therapy, unless contraindicated

      **or**
    - Diagnosis of thrombocytopenia secondary to pregnancy

    **and**
  - Documented platelet count < 50 x $10^9$ / L (obtained within the past 30 days)

- **Warm autoimmune hemolytic anemia**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of warm autoimmune hemolytic anemia when all of the following criteria are met:**
  - Diagnosis of warm autoimmune hemolytic anemia; **and**
  - Other types of autoimmune hemolytic anemia have been ruled out; **and**
  - History of failure, contraindication, or intolerance to glucocorticoids (e.g., prednisone, methylprednisolone); **and**
  - History of failure, contraindication, or intolerance to at least **one** of the following:
    - Rituximab; **or**


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- Immunosuppressive agent [e.g., azathioprine, cyclophosphamide, cyclosporin A, danazol, mycophenolate mofetil (MMF), sirolimus, Tavalisse (fostamatinib)]

**and**

- Patient is still transfusion-dependent at a minimum of two weeks after initiation of rituximab or a second-line immunosuppressive agent; **and**
- Immune globulin will be used as an adjunct to other therapies

## *Infectious Disease*

- **Chronic lymphocytic leukemia (CLL), prevention of infection in B-cell CLL**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the prevention of infection in B-cell chronic lymphocytic leukemia when both of the following criteria are met:**
  - Diagnosis of B-cell chronic lymphocytic leukemia (CLL); **and**
  - **One** of the following:
    - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
    - History of bacterial infection(s) associated with B-cell CLL

- **Cytomegalovirus (CMV) induced pneumonitis in solid organ transplants**

- **HIV-infection, prevention of bacterial infection in pediatric HIV**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the prevention of bacterial infection in pediatric HIV when all of the following criteria are met:**
  - Diagnosis of HIV disease; **and**
  - Patient age ≤ 13 years; **and**
  - **One** of the following criteria:
    - Documented hypogammaglobulinemia (IgG < 400 mg/dL); **or**
    - Functional antibody deficiency as demonstrated by either poor specific antibody titers or recurrent bacterial infections

- **Lymphoproliferative disease, treatment of bacterial infections**

- **Measles (rubeola) post-exposure prophylaxis**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the prevention of measles (rubeola) post-exposure prophylaxis when all of the following criteria are met:**
  - Patient has been exposed to measles (rubeola) less than 6 days previously; **and**
  - Patient weight is greater than 30 kg (for patients ≤ 30 kg, administer Intramuscular immune globulin); **and**
  - **One** of the following nonimmune or severely immunocompromised individuals who are not already receiving immune globulin therapy:
    - Patient is a pregnant woman without evidence of measles immunity; **or**
    - Patient has received hematopoietic stem cell transplant (HSCT) and is currently receiving immunosuppressive treatment or has finished immunosuppressive treatment regimen within the past 12 months; **or**
      Patient is a HSCT recipient with chronic graft-versus-host disease (GVHD); **or**
    - Patient has received chimeric antigen receptor T-cell (CAR T) therapy within 12 months; **or**
    - Patient has acute lymphoblastic leukemia (ALL) and is completing or has completed chemotherapy within the last 6 months; **or**
    - Patient with HIV infection and severe immunosuppression defined as a current CD4+ T-lymphocyte percentage < 15% (all ages) or a CD4+ T-lymphocyte count < 200 lymphocyte cells/$mm^3$ (age > 5 years only); **or**
    - Patient with a primary immunodeficiency (Refer to the disease list linked below)

  **and**

  - Request is for an initial, one-time dose, not to exceed 400 mg/kg

- **Multiple myeloma, prevention of infection in multiple myeloma**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the prevention of infection in multiple myeloma when both of the following criteria are met:**


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- Diagnosis of multiple myeloma; **and**
- **One** of the following:
  - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
  - History of bacterial infection(s) associated with multiple myeloma

- **Parvovirus B19 infection, treatment, immunocompromised host (Solid organ transplant recipient or HIV-related)**

- **Post B-cell targeted therapies**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the prevention of infection secondary to B-cell targeted therapy when both of the following criteria are met:**
  - Documentation confirming previous treatment of B-cell targeted therapy within the last 100 days [e.g., CAR-T (e.g., Kymriah), Rituxan (rituximab), Besponsa (inotuzumab ozogamicin)]; **and**
  - **Both** of the following:
    - Documented hypogammaglobulinemia (IgG < 500 mg/dL)
    - History of bacterial infection(s) associated with B-cell depletion

- **Staphylococcal toxic shock**

## *Neurology*

- **Acute disseminated encephalomyelitis (ADEM)**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of acute disseminated encephalomyelitis (ADEM) when both of the following criteria are met:**
  - Diagnosis of acute disseminated encephalomyelitis (ADEM); **and**
  - History of failure, contraindication, or intolerance to intravenous glucocorticoids

- **Chronic inflammatory demyelinating polyneuropathy**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of chronic inflammatory demyelinating polyneuropathy when all of the following criteria are met:**
  **Initial Therapy**
  - Diagnosis of chronic inflammatory demyelinating polyneuropathy as confirmed by **all** of the following:
    - Progressive symptoms present for at least 2 months; **and**
    - Symptomatic polyradiculoneuropathy as indicated by progressive or relapsing motor or sensory impairment of more than one limb; **and**
    - Electrodiagnostic findings (consistent with EFNS/P S guidelines for definite CIDP) indicating at least **one** of the following criteria are present:
      - Motor distal latency prolongation in 2 nerves
      - Reduction of motor conduction velocity in 2 nerves
      - Prolongation of F-wave latency in 2 nerves
      - Absence of F-waves in at least 1 nerve
      - Partial motor conduction block of at least 1 motor nerve
      - Abnormal temporal dispersion in at least 2 nerves
      - Distal CMAP duration increase in at least 1 nerve

    **and**
  - Prescribed by or in consultation with a neurologist

  **Continuation of Therapy**
  - Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]

- **Encephalitis, immune checkpoint inhibitor-induced, severe, or progressive**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of encephalitis, immune checkpoint inhibitor-induced, severe, or progressive, when all of the following criteria are met:**
  - Diagnosis of encephalitis, immune checkpoint inhibitor-induced, severe, or progressive; **and**
  - History of failure, contraindication, or intolerance to glucocorticoids (e.g., methylprednisolone); **and**
  - The use of the immune checkpoint inhibitor has been interrupted; **and**


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- Prescribed by or in consultation with a neurologist

- **Guillain-Barré syndrome (GBS)**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of Guillain-Barré syndrome when all of the following criteria are met:**
  - Diagnosis of Guillain-Barré Syndrome; **and**
  - Severe disease requiring aid to walk; **and**
  - Onset of neuropathic symptoms within the last four weeks; **and**
  - Prescribed by or in consultation with a neurologist

- **IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy**

- **Lambert-Eaton myasthenic syndrome (LEMS)**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of Lambert-Eaton myasthenic syndrome when all of the following criteria are met:**
  - Diagnosis of Lambert-Eaton myasthenic syndrome (LEMS); **and**
  - History of failure, contraindication, or intolerance to immunomodulator monotherapy (e.g., azathioprine, corticosteroids); **and**
  - Concomitant immunomodulator therapy (e.g., azathioprine, corticosteroids), unless contraindicated, will be used for long-term management of LEMS; **and**
  - Prescribed by or in consultation with a neurologist
- **Lennox Gastaut syndrome**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of Lennox Gastaut syndrome when both of the following criteria are met:**
  - History of failure, contraindication, or intolerance to initial treatment with traditional anti-epileptic pharmacotherapy (e.g., lamotrigine, phenytoin, valproic acid); **and**
  - Prescribed by or in consultation with a neurologist

- **Multifocal motor neuropathy (MMN)**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of multifocal motor neuropathy when both of the following criteria are met:**
  **Initial Therapy**
  - Diagnosis of multifocal motor neuropathy as confirmed by **all** of the following:
    - Weakness with slowly progressive or stepwise progressive course over at least one month; **and**
    - Asymmetric involvement of two or more nerves; **and**
    - Absence of motor neuron signs and bulbar signs

    **and**
  - Prescribed by or in consultation with a neurologist

  **Continuation of Therapy**
  - Documentation of positive clinical response to therapy as measured by an objective scale [e.g., Rankin, Modified Rankin, Medical Research Council (MRC) scale]

- **Multiple sclerosis, relapsing forms**
  **Note**: Treatment of any other type of multiple sclerosis with immune globulin is not supported by clinical evidence.
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of relapsing forms of multiple sclerosis when all of the following criteria are met:**
  **Initial Therapy**
  - Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); **and**
  - Documentation of an MS exacerbation or progression (worsening) of the patient's clinical status from the visit prior to the one prompting the decision to initiate immune globulin therapy; **and**
  - History of failure, contraindication, or intolerance to at least **two** of the following agents:
    - Cladribine (Mavenclad)
    - Dimethyl fumarate (Tecfidera®)


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- Fingolimod (Gilenya®)
- Glatiramer acetate (Copaxone® or Glatopa®)
- Interferon β-1a (Avonex® or Rebif®)
- Interferon β-1b (Betaseron® or Extavia®)
- Monomethyl fumarate (Bafiertam)
- Natalizumab (Tysabri®)
- Natalizumab-sztn (Tyruko®)
- Ocrelizumab (Ocrevus®)
- Ofatumumab (Kesimpta®)
- Ozanimod (Zeposia®)
- Peginterferon beta-1a (Plegridy™)
- Rituximab (Riabni®, Rituxan®, Ruxience®, & Truxima®)
- Siponimod (Mayzent®)
- Teriflunomide (Aubagio®)
- Ublituximab (Briumvi®)

**and**

- Prescribed by or in consultation with a neurologist

- **Myasthenia Gravis**
  **Note**: Evidence does not support the use of immune globulin maintenance therapy for ocular myasthenia.
  - **Myasthenia Gravis exacerbation**
    Additional information to support medical necessity review where applicable:
    **Immune globulin is medically necessary for the treatment of myasthenic exacerbation when all of the following criteria are met:**
    - Diagnosis of generalized myasthenia gravis; **and**
    - Evidence of myasthenic exacerbation, defined by at least **one** of the following symptoms in the last month:
      – Difficulty swallowing
      – Acute respiratory failure
      – Major functional disability responsible for the discontinuation of physical activity
      – Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)]

      **and**
    - **One** of the following:
      – History of failure, contraindication, or intolerance to immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine) for long-term management of myasthenia gravis
      – Currently receiving immunomodulator therapy (e.g., azathioprine, mycophenolate mofetil, cyclosporine) for long-term management of myasthenia gravis

      **and**
    - Prescribed by or in consultation with a neurologist
  - **Myasthenia Gravis, refractory**
    Additional information to support medical necessity review where applicable:
    **Immune globulin is medically necessary for the treatment of refractory myasthenia gravis when all of the following criteria are met:**
    - Diagnosis of refractory generalized myasthenia gravis by or in consultation with a physician or center with expertise in management of myasthenia gravis; **and**
    - Documentation that the disease status is unchanged or worsening (persistent or worsening symptoms that limit functioning) despite failure, contraindication, or intolerance to **both** of the following (used in adequate doses and duration):
      – Corticosteroids; **and**
      – **Two** immunomodulator therapies (e.g., azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus)

      **and**
    - Currently receiving immunomodulator therapy (e.g., corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, tacrolimus), used in adequate doses, for long-term management of myasthenia gravis; **and**
    - Prescribed by or in consultation with a neurologist

- **Neuromyelitis optica**
  Additional information to support medical necessity review where applicable:


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**Immune globulin is medically necessary for the treatment of neuromyelitis optica when all of the following criteria are met:**

**Initial Therapy**

- Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming all of the following:
  - Serologic testing for anti-aquaporin-4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies has been performed; **and**
  - Past medical history of (if AQP4-IgG/NMO-IgG positive **one** of the following, if negative **two** of the following):
    - Optic neuritis
    - Acute myelitis
    - Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
    - Acute brainstem syndrome
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    - Symptomatic cerebral syndrome with NMOSD-typical brain lesions

    **and**
  - Diagnosis of multiple sclerosis or other diagnoses have been ruled out

  **and**
- History of failure, contraindication, or intolerance to at least **three** of the following:
  - Azathioprine
  - Corticosteroids
  - Mycophenolate mofetil
  - Complement inhibitors [e.g., Soliris (eculizumab), Ultomiris (ravulizumab)]
  - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab-mwge)]
  - Anti-CD19 therapy [e.g., Uplizna (inebilizumab-cdon)]
  - Anti-CD20 therapy (e.g., rituximab)

  **and**
- Patient is not receiving immune globulin in combination with any of the following:
  - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
  - Complement inhibitors [e.g., Soliris (eculizumab), Ultomiris (ravulizumab)]
  - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Enspryng (satralizumab-mwge)]
  - Anti-CD19 therapy [e.g., Uplizna (inebilizumab-cdon)]
  - Anti-CD20 therapy (e.g., rituximab)

  **and**
- Prescribed by or in consultation with a neurologist

- **Paraproteinemic neuropathy**

- **Rasmussen syndrome**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of Rasmussen syndrome when all of the following criteria are met:**
  - Documentation of **one** of the following demonstrating that:
    - Short term amelioration of encephalitis is needed prior to definitive surgical therapy; **or**
    - Disease symptoms (e.g., seizures) persist despite surgical treatment; **or**
    - The patient is not a candidate for surgical treatment

- **Stiff-person syndrome**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of stiff-person syndrome when all of the following criteria are met:**
  **Initial Therapy**
  - Diagnosis of stiff-person syndrome; **and**
  - History of failure, contraindication, or intolerance to GABAergic medication (e.g., baclofen, benzodiazepines); **and**
  - Prescribed by or in consultation with a neurologist

## *Primary Immunodeficiency*

- **Primary immunodeficiency syndromes** (Refer to the disease list linked below.)
  Additional information to support medical necessity review where applicable:


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**Immune globulin is medically necessary for the treatment of primary immunodeficiency syndromes when all of the following criteria are met:**
- Diagnosis of primary immunodeficiency; **and**
- Clinically significant functional deficiency of humoral immunity as evidenced by **one** of the following:
  - Documented failure to produce antibodies to specific antigens; **or**
  - History of significant recurrent infections

## *Rheumatology*

- **Dermatomyositis or polymyositis**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of dermatomyositis or polymyositis when both of the following criteria are met:**
  - Diagnosis of dermatomyositis or polymyositis; **and**
  - History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g., azathioprine, corticosteroids, cyclophosphamide, methotrexate)
- **Kawasaki disease**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary for the treatment of Kawasaki disease when both of the following criteria are met:**
  - Diagnosis of Kawasaki disease; **and**
  - IVIG treatment does not exceed five consecutive days

## *Transplantation*

- **Bone marrow transplantation (BMT)**
  Additional information to support medical necessity review where applicable:
  **Immune globulin is medically necessary after allogeneic BMT when all of the following criteria are met:**
  - **One** of the following uses:
    - Prevention of acute graft vs. host disease (GVHD); **or**
    - Prevention of infection

    **and**
  - Confirmed allogeneic bone marrow transplant within the last 100 days; **and**
  - Documented severe hypogammaglobulinemia (IgG < 400 mg/dL)

- **Solid organ transplantation, desensitization, prevention, or treatment of acute antibody-mediated rejection (i.e., B-cell mediated or humoral rejection)**

**Immune globulin is unproven and not medically necessary for:**
- Acquired hemophilia
- Adrenoleukodystrophy
- Alzheimer's disease
- Amyotrophic lateral sclerosis (ALS)
- Antiphospholipid antibody syndrome (APS) in pregnancy
- Asthma
- Atopic dermatitis
- Autism spectrum disorders
- Autoimmune liver disease
- Autoimmune neutropenia
- Bone marrow transplantation (BMT), prevention of acute graft vs. host disease (GVHD) after autologous BMT
- Bone marrow transplantation (BMT), prevention of chronic graft vs. host disease (GVHD) after autologous BMT
- Bone marrow transplantation (BMT), prevention of infection after autologous BMT
- Campylobacter species-induced enteritis
- Cerebral infarctions with antiphospholipid antibodies
- Chronic fatigue syndrome
- Demyelinative brain stem encephalitis
- Demyelinating neuropathy associated with monoclonal IgM
- Diabetes mellitus
- Dilated cardiomyopathy
- HIV infection, to reduce viral load


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- HTLV-1-associated myelopathy
- Idiopathic dysautonomia, acute
- Inclusion body myositis
- Isolated IgA deficiency
- Isolated IgE deficiency
- Isolated IgG4 deficiency
- Isolated IgM deficiency
- Lumbosacral or brachial plexitis
- Monoclonal gammopathy
- Myocarditis, acute
- Neonatal isoimmune hemolytic jaundice
- Neonatal sepsis, prevention
- Ocular myasthenia
- Opsoclonus myoclonus
- Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy
- Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
- POEMS syndrome
- Postinfectious cerebellar ataxia
- Postoperative sepsis
- Pseudomembranous colitis
- Rheumatic fever, acute
- Sjogren's syndrome
- Spontaneous recurrent abortions, prevention
- Urticaria, chronic
- Urticaria, delayed pressure
- Vasculitides and antineutrophil antibody syndromes

Efficacy for these conditions has not been described in adequately designed studies. The available evidence is limited to case reports or case series, anecdotal reports, and open-label trials, or the available studies have failed to demonstrate a positive treatment effect. Further well-designed studies are needed to establish the role of immune globulin in these conditions.

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

| CPT Code | Description |
|---|---|
| 90283 | Immune globulin (IgIV), human, for intravenous use |
| 90284 | Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each |

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| HCPCS Code | Description |
|---|---|
| J1459 | Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg |
| J1551 | Injection, immune globulin (Cutaquig), 100 mg |
| J1552 | Injection, immune globulin (Alyglo), 500 mg |
| J1553 | Injection, immune globulin (Yimmugo), 100 mg |
| J1554 | Injection, immune globulin (Asceniv), 500 mg |
| J1555 | Injection, immune globulin (Cuvitru), 100 mg |
| J1556 | Injection, immune globulin (Bivigam), 500 mg |
| J1557 | Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg |


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| HCPCS Code | Description |
|---|---|
| J1558 | Injection, immune globulin (Xembify), 100 mg |
| J1559 | Injection, immune globulin (Hizentra), 100 mg |
| J1561 | Injection, immune globulin, (Gamunex-C/Gammaked), 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/Gammagard Liquid ERC), 500 mg |
| J1572 | Injection, immune globulin, (Flebogamma/Flebogamma DIF), intravenous, nonlyophilized (e.g., liquid), 500 mg |
| J1575 | Injection, immune globulin/hyaluronidase, (Hyqvia), 100 mg immune globulin |
| J1576 | Injection, immune globulin (Panzyga), intravenous, non-lyophilized (e.g., liquid), 500 mg |
| J1577 | Injection, immune globulin (Qivigy), 100 mg |
| J1599 | Injection, immune globulin, intravenous, nonlyophilized (e.g., liquid), not otherwise specified, 500 mg |

| Diagnosis Code | Description |
|---|---|
| A48.3 | Toxic shock syndrome |
| A49.9 | Bacterial infection, unspecified |
| A87.8 | Other viral meningitis |
| A87.9 | Viral meningitis, unspecified |
| A88.8 | Other specified viral infections of central nervous system |
| B05.0 | Measles complicated by encephalitis |
| B05.1 | Measles complicated by meningitis |
| B05.2 | Measles complicated by pneumonia |
| B05.3 | Measles complicated by otitis media |
| B05.4 | Measeles with intestinal complications |
| B20 | Human immunodeficiency virus [HIV] disease |
| B25.0 | Cytomegaloviral pneumonitis |
| B34.3 | Parvovirus infection, unspecified |
| B97.35 | Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere |
| C90.00 | Multiple myeloma not having achieved remission |
| C90.01 | Multiple myeloma in remission |
| C90.02 | Multiple myeloma in relapse |
| C91.10 | Chronic lymphocytic leukemia of B-cell type not having achieved remission |
| C91.11 | Chronic lymphocytic leukemia of B-cell type in remission |
| C91.12 | Chronic lymphocytic leukemia of B-cell type in relapse |
| D47.9 | Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified |
| D59.11 | Warm autoimmune hemolytic anemia |
| D69.3 | Immune thrombocytopenic purpura |
| D69.51 | Posttransfusion purpura |
| D69.59 | Other secondary thrombocytopenia |
| D80.0 | Hereditary hypogammaglobulinemia |
| D80.1 | Nonfamilial hypogammaglobulinemia |
| D80.3 | Selective deficiency of immunoglobulin G [IgG] subclasses |
| D80.4 | Selective deficiency of immunoglobulin M [IgM] |
| D80.5 | Immunodeficiency with increased immunoglobulin M [IgM] |


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| Diagnosis Code | Description |
|---|---|
| D80.6 | Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia |
| D80.7 | Transient hypogammaglobulinemia of infancy |
| D81.0 | Severe combined immunodeficiency [SCID] with reticular dysgenesis |
| D81.1 | Severe combined immunodeficiency [SCID] with low T- and B-cell numbers |
| D81.2 | Severe combined immunodeficiency [SCID] with low or normal B-cell numbers |
| D81.6 | Major histocompatibility complex class I deficiency |
| D81.7 | Major histocompatibility complex class II deficiency |
| D81.82 | Activated Phosphoinositide 3-kinase Delta Syndrome [APDS] |
| D81.89 | Other combined immunodeficiencies |
| D81.9 | Combined immunodeficiency, unspecified |
| D82.0 | Wiskott-Aldrich syndrome |
| D82.1 | Di George's syndrome |
| D82.4 | Hyperimmunoglobulin E [IgE] syndrome |
| D83.0 | Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function |
| D83.1 | Common variable immunodeficiency with predominant immunoregulatory T-cell disorders |
| D83.2 | Common variable immunodeficiency with autoantibodies to B- or T-cells |
| D83.8 | Other common variable immunodeficiencies |
| D83.9 | Common variable immunodeficiency, unspecified |
| D84.81 | Immunodeficiency due to conditions classified elsewhere |
| D84.821 | Immunodeficiency due to drugs |
| D84.822 | Immunodeficiency due to external causes |
| D84.89 | Other immunodeficiencies |
| D89.2 | Hypergammaglobulinemia, unspecified |
| D89.810 | Acute graft-versus-host disease |
| D89.812 | Acute on chronic graft-versus-host disease |
| D89.82 | Autoimmune lymphoproliferative syndrome [ALPS] |
| D89.9 | Disorder involving the immune mechanism, unspecified |
| E05.00 | Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm |
| E05.01 | Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm |
| E31.0 | Autoimmune polyglandular failure |
| G04.00 | Acute disseminated encephalitis and encephalomyelitis, unspecified |
| G04.01 | Postinfectious acute disseminated encephalitis and encephalomyelitis (postinfectious ADEM) |
| G04.81 | Other encephalitis and encephalomyelitis |
| G04.90 | Encephalitis and encephalomyelitis, unspecified |
| G05.3 | Encephalitis and encephalomyelitis in diseases classified elsewhere |
| G05.4 | Myelitis in diseases classified elsewhere |
| G11.3 | Cerebellar ataxia with defective DNA repair |
| G25.82 | Stiff-man syndrome |
| G35.A | Relapsing-remitting multiple sclerosis |
| G35.B0 | Primary progressive multiple sclerosis, unspecified |
| G35.B1 | Active primary progressive multiple sclerosis |
| G35.B2 | Non-active primary progressive multiple sclerosis |
| G35.C0 | Secondary progressive multiple sclerosis, unspecified |
| G35.C1 | Active secondary progressive multiple sclerosis |
| G35.C2 | Non-active secondary progressive multiple sclerosis |


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| Diagnosis Code | Description |
|---|---|
| G35.D | Multiple Sclerosis, unspecified |
| G36.0 | Neuromyelitis optica [Devic] |
| G40.811 | Lennox-Gastaut syndrome, not intractable, with status epilepticus |
| G40.812 | Lennox-Gastaut syndrome, not intractable, without status epilepticus |
| G40.813 | Lennox-Gastaut syndrome, intractable, with status epilepticus |
| G40.814 | Lennox-Gastaut syndrome, intractable, without status epilepticus |
| G61.0 | Guillain-Barre syndrome |
| G61.81 | Chronic inflammatory demyelinating polyneuritis |
| G61.89 | Other inflammatory polyneuropathies |
| G61.9 | Inflammatory polyneuropathy, unspecified |
| G62.89 | Other specified polyneuropathies |
| G62.9 | Polyneuropathy, unspecified |
| G65.0 | Sequelae of Guillain-Barre syndrome |
| G70.00 | Myasthenia gravis without (acute) exacerbation |
| G70.01 | Myasthenia gravis with (acute) exacerbation |
| G70.80 | Lambert-Eaton syndrome, unspecified |
| G70.81 | Lambert-Eaton syndrome in disease classified elsewhere |
| G73.1 | Lambert-Eaton syndrome in neoplastic disease |
| L10.0 | Pemphigus vulgaris |
| L10.2 | Pemphigus foliaceous |
| L12.0 | Bullous pemphigoid |
| L12.1 | Cicatricial pemphigoid |
| L12.30 | Acquired epidermolysis bullosa, unspecified |
| L12.35 | Other acquired epidermolysis bullosa |
| L13.8 | Other specified bullous disorders |
| L51.1 | Stevens-Johnson syndrome |
| L51.2 | Toxic epidermal necrolysis [Lyell] |
| L51.3 | Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome |
| M30.3 | Mucocutaneous lymph node syndrome [Kawasaki] |
| M33.00 | Juvenile dermatomyositis, organ involvement unspecified |
| M33.01 | Juvenile dermatomyositis with respiratory involvement |
| M33.02 | Juvenile dermatomyositis with myopathy |
| M33.03 | Juvenile dermatomyositis without myopathy |
| M33.09 | Juvenile dermatomyositis with other organ involvement |
| M33.10 | Other dermatomyositis, organ involvement unspecified |
| M33.11 | Other dermatomyositis with respiratory involvement |
| M33.12 | Other dermatomyositis with myopathy |
| M33.13 | Other dermatomyositis without myopathy |
| M33.19 | Other dermatomyositis with other organ involvement |
| M33.20 | Polymyositis, organ involvement unspecified |
| M33.21 | Polymyositis with respiratory involvement |
| M33.22 | Polymyositis with myopathy |
| M33.29 | Polymyositis with other organ involvement |
| M33.90 | Dermatopolymyositis, unspecified, organ involvement unspecified |
| M33.91 | Dermatopolymyositis, unspecified with respiratory involvement |


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| Diagnosis Code | Description |
|---|---|
| M33.92 | Dermatopolymyositis, unspecified with myopathy |
| M33.93 | Dermatopolymyositis, unspecified without myopathy |
| M33.99 | Dermatopolymyositis, unspecified with other organ involvement |
| M36.0 | Dermato(poly)myositis in neoplastic disease |
| O26.40 | Herpes gestationis, unspecified trimester |
| O26.41 | Herpes gestationis, first trimester |
| O26.42 | Herpes gestationis, second trimester |
| O26.43 | Herpes gestationis, third trimester |
| O98.511 | Other viral disease complicating pregnancy, first trimester |
| O98.512 | Other viral disease complicating pregnancy, second trimester |
| O98.513 | Other viral disease complicating pregnancy, third trimester |
| O98.519 | Other viral disease complicating pregnancy, unspecified trimester |
| O98.711 | Human immunodeficiency virus [HIV] disease complicating pregnancy, first trimester |
| O98.712 | Human immunodeficiency virus [HIV] disease complicating pregnancy, second trimester |
| O98.713 | Human immunodeficiency virus [HIV] disease complicating pregnancy, third trimester |
| O98.719 | Human immunodeficiency virus [HIV] disease complicating pregnancy, unspecified trimester |
| O98.72 | Human immunodeficiency virus [HIV] disease complicating childbirth |
| O98.73 | Human immunodeficiency virus [HIV] disease complicating the puerperium |
| T45.AX5A | Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, initial encounter |
| T45.AX5D | Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, subsequent encounter |
| T45.AX5S | Adverse effect of immune checkpoint inhibitors and immunostimulant drugs, sequela |
| P61.0 | Transient neonatal thrombocytopenia |
| T86.00 | Unspecified complication of bone marrow transplant |
| T86.01 | Bone marrow transplant rejection |
| T86.02 | Bone marrow transplant failure |
| T86.03 | Bone marrow transplant infection |
| T86.09 | Other complications of bone marrow transplant |
| T86.10 | Unspecified complication of kidney transplant |
| T86.11 | Kidney transplant rejection |
| T86.12 | Kidney transplant failure |
| T86.13 | Kidney transplant infection |
| T86.19 | Other complication of kidney transplant |
| Z21 | Asymptomatic human immunodeficiency virus [HIV] infection status |
| Z29.89 | Encounter for other specified prophylactic measures |
| Z29.9 | Encounter for prophylactic measures, unspecified |
| Z48.290 | Encounter for aftercare following bone marrow transplant |
| Z86.19 | Personal history of other infectious and parasitic diseases |
| Z86.2 | Personal history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism |
| Z92.22 | Personal history of monoclonal drug therapy |
| Z92.26 | Personal history of immune checkpoint inhibitor therapy |
| Z92.29 | Personal history of other drug therapy |
| Z94.0 | Kidney transplant status |
| Z94.1 | Heart transplant status |
| Z94.2 | Lung transplant status |


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| Diagnosis Code | Description |
|---|---|
| Z94.3 | Heart and lungs transplant status |
| Z94.4 | Liver transplant status |
| Z94.81 | Bone marrow transplant status |
| Z94.82 | Intestine transplant status |
| Z94.83 | Pancreas transplant status |
| Z94.84 | Stem cells transplant status |

# Background

Immune globulin, whether intravenous (IV) or subcutaneous (SC), is a sterile, purified preparation of human immunoglobulin derived from pooled human plasma from thousands of donors. Consisting primarily of immunoglobulin G, one of 5 classes of immunoglobulin (Ig), each batch of immune globulin (typically referred to as IVIG) provides immunomodulating peptides and antibodies against most exogenous antigens, many normal human proteins, and Fab, the antigen-binding region of autoantibodies. All currently available products contain high concentrations of IgG with subclass distribution corresponding to that of normal serum.

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

# Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

# Clinical Evidence

## Proven

### *Autoimmune Diseases*

IVIG is beneficial for treatment of a number of autoimmune diseases based upon U.S. Food and Drug Administration (FDA) approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include immune thrombocytopenic purpura and dermatomyositis and polymyositis.

### *Dermatology*

A group of autoimmune diseases characterized by intraepidermal bullae formation (e.g., pemphigus vulgaris, bullous pemphigoid, dermatitis herpetiformis) are collectively referred to as autoimmune blistering skin disease. These are very fragile lesions that can rupture easily, leaving erosions. Autoimmune blistering skin diseases are prone to serious complications and in some cases can be fatal. The most common type of blistering skin disease is pemphigus vulgaris, which often affects the oral mucosa, and subsequent skin involvement. Immune globulin therapy is often needed for an extended period of time, often several months or years due to its chronic nature. According to ISBI practice guidelines, intravenous immune globulin (IVIG) is often given to patients who are hospitalized for Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) is often treated with IVIG due to the serious, life-threatening nature of these conditions.

### *Hematology*

IVIG is a first-line therapy for fetomaternal alloimmune thrombocytopenia and is recommended in international consensus guidelines. An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions. The guidelines recommended IVIG use in the following: fetal-neonatal alloimmune thrombocytopenia; hemolytic disease of the newborn; HIV-associated thrombocytopenia; idiopathic thrombocytopenic purpura; and posttransfusion purpura.


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## *Infectious and Infection-Related Diseases*

IVIG is beneficial for a number of infectious and infection-related diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include treatment of CMV-induced pneumonitis in solid organ transplants, treatment of staphylococcal toxic shock, treatment of bacterial infections in lymphoproliferative diseases, prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia (CLL). IVIG is also beneficial in chronic lymphocytic leukemia and multiple myeloma with reduced IgG and history of infections and prevention of bacterial infection in HIV-infected children. IVIG is also beneficial in patients with reduced IgG and history of infections for the prevention of infection following B-cell targeted therapies. Despite the lack of randomized controlled trials demonstrating that immune globulin (IG) therapy prevents infection in patients with hypogammaglobulinemia secondary to B-cell targeted therapies, Immune globulins may still be appropriate in certain cases depending on the degree of IgG deficiency, history and risk of infection, recency of B-cell targeted therapy, and other factors. Some experts recommend considering IVIG therapy when serum IgG is below 400 mg/dl or when it is 400 to 600 mg/dl and accompanied by serious, persistent, unusual, or recurrent infections.

Additionally, the Centers of Disease Control and Prevention (CDC) recommends the use of immune globulins for post-exposure prophylaxis (PEP) of a measles (rubeola) exposure. If administered within six days of an initial measles exposure, immune globulins may provide some protection against measles or change the clinical course of the disease in patients that are severely immunocompromised or that have no immunity. CDC guidance is to consider therapy in patient groups that are at risk for severe disease and complications from measles. This is defined as infants aged < 12 months, pregnant women without evidence of measles immunity, and severely immunocompromised persons. For infants and individuals less than 30 kg, intramuscular immune globulins are indicated in this clinical setting. For patients over 30 kg, intravenous or subcutaneous immune globulins are the preferred formulations. According to the CDC, severely immunocompromised patients include patients with severe primary immunodeficiency; patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in patients who have developed graft-versus-host disease; patients on treatment for acute lymphoblastic leukemia (ALL) within and until at least 6 months after completion of immunosuppressive chemotherapy; and patients with a diagnosis of AIDS or HIV-infected persons with severe immunosuppression defined as CD4 percent < 15% (all ages) or CD4 count < 200 lymphocytes/mm3 (aged > 5 years) and those who have not received a measles, mumps, and rubella (MMR) vaccine since receiving effective antiretroviral therapy (ART).

## *Rheumatology*

Due to the rarity of dermatomyositis and polymyositis, treatment recommendations supporting immune globulin have relied more on case reports and case series than on controlled However, a randomized controlled trial comparing intravenous immune globulin (IVIG) to placebo demonstrated that IVIG treatment significantly improved dermatological symptoms in patients with Dermatomyositis, regardless of disease severity prior to treatment, suggesting that IVIG is effective, even in severe cases of dermatomyositis. Current treatment recommendations also recognize IVIG as the standard-of-care therapy for the initial treatment of Kawasaki Disease to reduce the rate of cornonary artery aneurysms as well as the duration of fever and other symptoms.

## *Neuroimmunologic Disorders*

Acute disseminated encephalomyelitis (ADEM), or postinfectious encephalomyelitis, is an autoimmune demyelinating disease that causes inflammation of myelin sheaths surrounding neurons in the brain. It is most common in children and young adults, and onset usually occurs after an infection. Signs and symptoms may include fever, headache, vomiting, lethargy, confusion, seizures, vision loss, weakness, or ataxia. The diagnosis is typically confirmed with cerebrospinal fluid analysis and MRI. First-line therapy for ADEM typically consists of corticosteroids, which are usually well-tolerated and effective. Expert consensus guidelines recommend IVIG and/or plasmapheresis as a viable second-line treatment option.

In 2016, the Myasthenia Gravis Foundation of America published consensus-based guidance for the management of myasthenia gravis (MG). Guidance statements were developed for symptomatic and immunosuppressive treatments, IV immunoglobulin and plasma exchange, management of impending and manifest myasthenic crisis, thymectomy, juvenile MG, MG associated with antibodies to muscle-specific tyrosine kinase, and MG in pregnancy. In regard to the use of IVIG, the task force concluded:

- Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to immunosuppressant agents, chronic IVIG may also be used.
- IVIG is appropriately used as short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations.


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- IVIG and PLEX are probably equally effective in the treatment of severe generalized MG.
- The efficacy of IVIG is less certain in milder MG or in ocular MG.
- PLEX may be more effective than IVIG in MuSK-MG.
- The use of IVIG as maintenance therapy can be considered for patients with refractory MG or for those in whom IS agents are relatively contraindicated.

In 2010, the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) published clinical guidelines for the management of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In regard to the diagnosis and treatment of CIDP with IVIG, the task force concluded:

- For induction of treatment, IVIG should be considered in sensory and motor CIDP in the presence of disabling symptoms (level A recommendation).
- For maintenance treatment, there is no sufficient evidence to recommend any particular drug. If response to IVIG is inadequate or result in adverse events, then other first-line treatment alternatives should be considered before combination treatments.
- **Electrodiagnostic criteria:**
  - Definite: at least one of the following:
    - Motor distal latency prolongation ≥ 50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome); or
    - Reduction of motor conduction velocity ≥ 30% below LLN in two nerves; or
    - Prolongation of F-wave latency ≥ 30% above ULN in two nerves (≥ 50% if amplitude of distal negative peak CMAp < 80% of LLN values); or
    - Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥ 20% of LLN+ ≥ 1 other demyelinating parameter in ≥ 1 other nerve; or
    - Partial motor conduction block: ≥ 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parametera in ≥ 1 other nerve; or
    - Abnormal temporal dispersion (> 30% duration increase between the proximal and distal negative peak CMAP) in ≥ 2 nerves; or
    - Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥ 1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)b + ≥ 1 other demyelinating parametera in ≥ 1 other nerve
- **Clinical diagnostic criteria:**
  - Inclusion criteria:
    - **Typical CIDP**
      - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
      - Absent or reduced tendon reflexes in all extremities
    - **Atypical CIDP** (still considered CIDP but with different features)
      One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
      - Predominantly distal (distal acquired demyelinating symmetric), DADS; or
      - Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis–Sumner syndrome]; or
      - Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb); or
      - Pure motor; or
      - Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)
  - Exclusion criteria:
    - Borrelia burgdorferi infection (Lyme disease), diphtheria, drug, or toxin exposure probably to have caused the neuropathy
    - Hereditary demyelinating neuropathy
    - Prominent sphincter disturbance
    - Diagnosis of multifocal motor neuropathy
    - IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
    - Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis may occasionally have demyelinating features

IVIG is beneficial for treatment of a number of neuroimmunologic diseases based upon FDA approval, published practice guidelines, professional society evidence reviews, and/or randomized, controlled clinical trials. These include chronic


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inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, multifocal motor neuropathy, Lambert-Eaton myasthenic syndrome, IgM antimyelin-associated glycoprotein paraprotein-associated peripheral neuropathy, paraproteinemic neuropathy, stiff-person syndrome, myasthenia gravis, Lennox-Gastaut, and Rasmussen syndrome.

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions states that IVIG should be reserved as an option for patients with relapsing-remitting MS who fail, decline, or are not able to take standard immunomodulatory therapies. Based on consensus by the expert panel, IVIG is not recommended for treatment of primary or secondary progressive MS or for acute exacerbations of MS.

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Associations (EFNA) states that IVIG could be considered as a second or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated because of side effects or concomitant diseases, and in particular in pregnancy where other therapies may not be used. IVIG cannot be recommended for treatment in secondary progressive MS. IVIG does not seem to have any valuable effect as add-on therapy to methylprednisolone for acute exacerbations and cannot be recommended as treatment for chronic symptoms in MS. In clinically isolated syndromes and in primary progressive MS, the EFNS Task Force concluded that there is not sufficient evidence to make any recommendations.

Similar findings were reported in a review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI. The Committee concluded that IVIG might provide benefit for relapsing-remitting multiple sclerosis. A meta-analysis and a review of multiple sclerosis clinical trials also found that evidence supports the use of IVIG for reduction of relapses in relapsing-remitting MS. The use of IVIG in relapsing-remitting MS should only be considered when other established therapies have failed or cannot be utilized.

In their review of relapse therapy and intermittent long-term therapy, the Neuromyelitis Optica Study Group (NEMOS) suggests IVIG therapy as an alternative for patients with contraindication to one of the other treatments (azathioprine and rituximab) or, particularly, in children.

The use of intravenous immunoglobulin (IVIG) as treatment for acute relapses in NMO was reported in a retrospective review of 10 patients. In the majority of cases, IVIG was used due to lack of response to steroids with/without plasma exchange. Improvement was noted in five of 11 (45.5%) events; the remaining had no further worsening.

In a case series of eight Spanish patients with neuromyelitis optica (NMO), positive results were observed from bimonthly IVIG treatment (0.7 g/kg body weight/day for 3 days). The primary outcome measure in the study was the occurrence of serious adverse effects. Secondary outcome measures were changes in the yearly rate of attacks and in the degree of neurological disability measured with the Expanded Disability Status Scale (EDSS). All 8 patients were treated with IVIG; 5 had relapsing optic neuritis with or without myelitis and 3 had recurrent longitudinally extensive transverse myelitis (LETM). The mean age of onset was 20.5 years (range, 7-31 years) and 87.5% were female. The mean duration of the disease before beginning treatment was 9.0 years (range, 3-17 years). Following 83 infusions (range, 4-21 per patient) and a mean follow-up time of 19.3 months (range, 6-39 months), minor adverse events had occurred (headache in 3 patients and a mild cutaneous eruption in a single patient). The relapse rate decreased from 1.8 in the previous year to 0.006 during follow-up ($z = -2.5$, $p = 0.01$). The EDSS score fell from 3.3 (SD 1.3) to 2.6 (SD 1.5) ($z = -2.0$, $p = 0.04$). The investigators concluded that treatment with IVIG is safe and well-tolerated, and it may be used as a treatment alternative for NMO spectrum disorders.

## *Primary and Secondary Immune Deficiencies*

IVIG is FDA-approved and indicated as replacement therapy in primary immune deficiencies.

## *Transplantation*

Desensitization protocols that include intravenous immune globulin to eliminate antibodies in the blood prior to transplantation can increase the likelihood of transplantation success. Following solid organ (e.g., kidney, liver) transplantation, the possibility of an antibody-mediated organ rejection (AMR) that occurs through complement-mediated activation of macrophages and neutrophils causing, resulting in tissue damage and coagulation. Patients that are highly sensitized to human leukocyte antigens (HLAs) or ABO blood group antigens are more likely to have transplantation failure via AMR. Intravenous immune globulin (IVIG) therapy, as an adjunct to glucocorticoids, is used in most treatment protocols and is the standard of care for treating antibody-mediated rejection (AMR) in solid organ transplant recipients. Although randomized controlled studies are lacking, IVIG is recommended via expert opinion and community standards due to the seriousness of the condition and the lack of alternatives that have been proven effective.


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## Unproven

### *Acquired Hemophilia*

An article by Anderson et al. summarized the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions. In the opinion of the expert panel, there is no convincing evidence of clinical benefit of IVIG in this disorder, and routine use is not recommended.

### *Adrenoleukodystrophy (ALD)*

This is one of a group of genetic disorders called the leukodystrophies that cause damage to the myelin sheath surrounding nerve cells in the brain and progressive dysfunction of the adrenal gland. In one very small, randomized trial 6 patients received IVIG in addition to the dietary therapy while 6 received dietary therapy alone. No treatment effect of IVIG was demonstrated in this study. MRI findings and clinical status deteriorated in both groups. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for ALD.

### *Alzheimer's Disease*

An open label dose-ranging study was conducted in 8 mild Alzheimer's disease (AD) patients. IVIG was added to approved AD therapies for 6 months, discontinued, and then resumed for another 9 months. Anti-Aβ antibodies in the serum from AD patients increased in proportion to IVIG dose and had a shorter half-life than anti-hepatitis antibodies and total IgG. Plasma Aβ levels increased transiently after each infusion. Cerebrospinal fluid Aβ decreased significantly at 6 months, returned to baseline after washout and decreased again after IVIG was re-administered for an additional 9 months. Mini-mental state scores increased an average of 2.5 points after 6 months, returned to baseline during washout and remained stable during subsequent IVIG treatment. This study did not include an adequate number of AD patients to establish whether IVIG altered cognitive status.

Devi et al. reported on a retrospective investigation of patients (n = 10) with Alzheimer's disease treated with IVIG. Eight of the patients completed 6 months of treatment; two completed 3.5 months of treatment. Two patients developed a pruritic, maculopapular, generalized rash, resolving with appropriate treatment, but both continued with IVIG. Patients showed stability on neurocognitive scores overall, with trends toward decline on their WAIS verbal scale and full-scale intelligence scores ($p < 0.1$), as well as on the WAIS information ($p < 0.1$) subtest and the BNT ($p = 0.1$). Patients showed trends toward improvement on the WMS logical memory II recall ($p < 0.1$), WMS verbal paired associates ($p = 0.15$), and the WMS auditory delayed memory test ($p = 0.1$). It was found that IVIG was well tolerated and effective in this sample, with patients showing stability on neurocognitive test scores and trends toward improvement in some areas.

Further studies are needed to establish efficacy, to determine the optimal dosing regimen and to confirm the safety of IVIG in the general population of AD patients.

### *Amyotrophic Lateral Sclerosis (ALS)*

This is a disease characterized by progressive motor neuron degeneration, which manifests as weakness, spasticity, and muscle atrophy, usually beginning with the upper limbs. Two small-scale, uncontrolled studies (n = 7.9) examined the use of IVIG for treatment of ALS; neither of these studies found a positive treatment effect. During and after treatment, all patients showed progressive deterioration at a pace similar to that observed before treatment or faster. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that there is no role for IVIG in the treatment of ALS.

### *Antiphospholipid Antibody Syndrome (APS) in Pregnancy*

In their guideline for the treatment of recurrent first trimester and second-trimester miscarriage, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends against the use of IVIG[17]. There are several reports supporting a role for IVIG in the treatment of antiphospholipid antibody syndrome (APS), including in patients with APS undergoing in vitro fertilization. However, a meta-analysis of several modes of therapy (heparin, aspirin, glucocorticosteroids, and IVIG) in this clinical setting did not support any improved outcome with IVIG and a possible association with pregnancy loss or premature birth. A small randomized controlled study (n = 16) demonstrated no greater benefit from IVIG (plus heparin and aspirin) than from heparin and aspirin alone. Because the efficacy of IVIG has not been proved in appropriately designed studies, its use is not recommended for APS in pregnancy.


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## *Asthma*

Multiple randomized controlled trials have found no apparent advantage of IVIG over placebo. There have been observational studies and case reports suggesting a potential benefit, and a subgroup analysis performed in one of the RCTs did suggest that IVIG might reduce the amount of steroids needed, however, no additional research has been able to establish the usefulness of IVIG.

## *Atopic Dermatitis*

IVIG treatment has shown success in small, open, uncontrolled trials of patients not responding to standard therapies. A small, randomized, evaluator-blinded trial (n = 10) did not support the routine use of IVIG in patients with atopic dermatitis.

## *Autism Spectrum Disorders*

According to the review of evidence by members of the Primary Immunodeficiency Committee of the AAAAI, there are no formal randomized studies to evaluate the use of IVIG in autism. They found that two small, open-trial reports of autistic children placed on IVIG for 6 months showed no benefit. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated that the available evidence does not support the use of IVIG in the treatment of autism.

## *Autoimmune Neutropenia*

Improvement in neutrophil counts has been described in several small series of patients with autoimmune neutropenia treated with IVIG, and anecdotal reports also suggest utility for IVIG in post- bone marrow transplantation neutropenia, which might be autoimmune in nature. It is unclear whether IVIG offers any advantage over corticosteroid therapy for the treatment of autoimmune neutropenia. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for hematologic conditions found that "the evidence to support treatment with IVIG is sparse and of poor quality. However, there was some discussion regarding its use in rare circumstances when other options (e.g., intravenous antibiotics and G-CSF) have failed.

## *Bone Marrow Transplantation (BMT)*

### Prevention of Acute Graft-Versus-Host Disease (GVHD) After Autologous BMT

According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.

### Prevention of Chronic Graft-Versus-Host Disease (GVHD) After Either Allogeneic or Autologous BMT

The use of IVIG was studied in a randomized, double-blind, dose-effect, placebo-controlled, multicenter trial in related allogeneic marrow transplantation. The trial included 200 patients receiving HLA-identical sibling marrow. IVIG-treated patients experienced no benefit versus placebo in reduction of incidence of infection, interstitial pneumonia, GVHD, transplantation-related mortality, or overall survival. There was a statistically higher incidence of grade 3 (severe) veno-occlusive disease associated with high-dose IVIG. The patients given higher doses of IVIG also had more side effects, such as fever and chills. The data does not support a recommendation for IVIG in HLA-identical sibling bone marrow transplants.

### Prevention of Infection After Autologous BMT

According to the Centers for Disease Control and Prevention, routine use of IVIG among autologous recipients is not recommended.

## *Chronic Fatigue Syndrome*

Numerous anecdotal reports have shown subjective benefits of IVIG for chronic fatigue syndrome. However, a double-blind, placebo-controlled trial demonstrated IVIG was not effective in the treatment of typical chronic fatigue syndrome.

## *Diabetes Mellitus*

Per an update of the 2006 American Academy of Allergy, Asthma & Immunology guideline, and centers on the use of standard immunoglobulin preparations specifically manufactured for intravenous (IV) or subcutaneous (SC) administration, immunoglobulin is unlikely to be beneficial in treating autoimmune diabetes mellitus.


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## *Dilated Cardiomyopathy*

According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology, “Case reports suggest that patients with acute myocarditis benefit from high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.

## *HIV Infection, to Reduce Viral Load*

Although IVIG is FDA-approved for reducing the incidence of secondary infection in HIV-infected children, its use in treating HIV infection per se has not been as widely evaluated. A study examining the effect of a 2 g/kg IVIG dose on viral load found that p24 antigen levels and numbers of HIV RNA copies were significantly increased after treatment. Thus, IVIG might be useful for preventing bacterial infections but should not be considered an antiviral therapy in the HIV-infected patient.

## *Inclusion Body Myositis*

The treatment of inclusion body myositis (IBM) with IVIG has been studied in two randomized, double-blind, placebo-controlled trials. In the first study (n = 19), no statistically significant treatment differences were noted between IVIG and placebo. In the second study (n = 22), outcome measures showed a trend towards improvement with IVIG. Based on these studies, IVIG is not recommended as routine therapy for IBM due to the variability of response and expense of therapy.

IVIG for inclusion body myositis was also assessed in open-label trials, but generalized conclusions or recommendations are not presently possible.

The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts’ evidence-based practice guideline on the use of IVIG for neurologic conditions stated that IVIG should not be used for the treatment of IBM.

In their Guidelines for the Use of Intravenous Immunoglobulin in the Treatment of Neurological Diseases, the European Federation of Neurological Societies (EFNS) states that IVIG cannot be recommended for the treatment of sporadic IBM.

In their evidence-based guideline on IVIG in the treatment of neuromuscular disorders, the American Academy of Neurology states that there is insufficient evidence to support the use of IVIG in IBM.

## *Isolated IgA Deficiency*

This is the most common immunodeficiency disorder characterized by a deficiency of IgA with normal levels of other immunoglobulin classes. Isolated IgA deficiency is marked by recurrent sinusitis, bronchitis, and pneumonia, and recurrent diarrhea, although many patients have no symptoms. Management of selective IgA deficiency is limited to treating associated infections. Some advocate prophylactic daily doses of antibiotics for patients with multiple, recurrent infections. No intervention is available to either replace IgA via infusion or increase production of native IgA. Selective IgA deficiency is not an indication for IVIG replacement therapy, although in some cases poor specific IgG antibody production, with or without IgG2 subclass deficiency, might coexist; in these patients IVIG might be required. Intravenous administration of IVIG can pose a risk of anaphylaxis for IgA-deficient patients who have IgE anti-IgA antibodies or reactions caused by complement activation if IgG anti-IgA antibodies are present.

## *Isolated IgG4 Deficiency*

IgG4 deficiency may be found in 10-15% of the general population. The significance of isolated, or selective, IgG4 deficiency is unclear.

## *Myocarditis, Acute*

According to a review of evidence by the members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology, case reports suggest that patients with acute myocarditis benefit from high-dose IVIG. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo. High-dose IVIG might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.


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## *Neonatal Sepsis*

### Prevention

A recent meta-analysis found that there is insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection. Despite encouraging trials of IVIG as an adjunct to enhance the antibacterial defenses of premature newborn infants, there are substantial contradictory data and insufficient overall evidence to support the routine administration of IVIG in infants at risk for neonatal infection.

## *Ocular Myasthenia*

Myasthenia gravis is an autoimmune disorder in which the body's own antibodies block the transmission of nerve impulses to muscles, causing fluctuating weakness and muscles that tire easily. Approximately half of patients present with purely ocular symptoms (ptosis, diplopia), so-called ocular myasthenia. Between 50% and 60% of people who have ocular myasthenia will progress to develop generalized myasthenia gravis (GMG) and weakness affecting other muscles. The aims of treatment for ocular myasthenia are to return the person to a state of clear vision and to prevent the development or limit the severity of GMG. Treatments proposed for ocular myasthenia include drugs that suppress the immune system including corticosteroids and azathioprine, thymectomy, and acetylcholinesterase inhibitors. There are retrospective, but no prospective, data, which indicate that immunosuppressive treatment of ocular myasthenia may decrease the likelihood of developing GMG. It is not clear from these studies whether treatment actually reduces the incidence of GMG, delays its onset, or just masks its symptoms. Plasmapheresis and intravenous immune globulin are used for the short-term management of severe GMG, but available evidence does not indicate that either therapy has a role in patients with ocular myasthenia.

## *Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS)*

Pediatric acute-onset neuropsychiatric syndrome (PANS) is a clinical diagnosis based on a collection of symptoms with an abrupt onset, including obsessions, compulsions, or restricted food intake, often accompanied with other neuropsychiatric symptoms such as anxiety, depression, tics, or personality changes. Although it has been suggested to be related to infection or autoimmune processes, no specific biomarker has yet been identified for diagnosing this condition. Similarly, streptococcal infections have also been correlated with induced exacerbation of symptoms in some children with obsessive-compulsive and tic disorders, also possibly on an autoimmune basis. The correlated syndrome is referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). There have been limited high quality evidence to support the use of immune globulins for PANS/PANDAS. The American Academy of Pediatrics (AAP) has developed a clinical report on PANS and PANDAS based on a comprehensive literature review and an analysis of its findings. The AAP considers the use of IgG an unproven treatment that is not recommended. If used, its use should be limited to carefully controlled clinical trials in order to improve our understanding of, and evidence for, effective treatment for PANS. A separate 2018 systematic review of treatments for PANS was done by Sigra and colleagues. The review concluded that the evidence for the benefit of IgG therapy was inconclusive due to a variety of reasons, including, but not limited to, poor study designs, small numbers of trial participants, a high risk of bias, and conflicting results. Additionally, the authors noted that rigorously conducted research regarding treatments for PANDAS is scarce, and higher quality studies that do exist indicate low support for its use. One high-quality randomized, double-blind, placebo-controlled trial studied the efficacy of IVIG in children diagnosed with PANS/PANDAS. The primary outcome measures were the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) and the Clinical Global Impressions-Improvement (CGI-I) rating. During the double-blind phase, the mean decrease in CY-BOCS score was 24% ±31% in the IVIG group (n = 17) and 12% ±27% in the placebo group (n = 18), with six responders in the IVIG group (35%) versus four (22%) in the placebo group; these differences were not statistically significant. Several recent studies have been published studying the efficacy of IVIG in PANS/PANDAS. These studies, despite their promising results, have several notable limitations, yielding low-quality evidence that is not considered reliable. Most notably, these studies are not blinded, randomized, nor placebo controlled. Other limitations include poor study design, inconsistent results comparing averages of all participants, small sample size, lack of a control group, inherent risk for bias, inconsistent assessments across and within the studies, and a heterogeneous patient population with differing durations of illness and treatment protocols. Further research, specifically high-quality trials, i.e., randomized, double-blinded, and placebo controlled, are needed before immune globulin becomes a standard of therapy.

## *POEMS Syndrome*

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome also known as Crow-Fukase syndrome or osteosclerotic myeloma is a unique multisystem disorder strongly associated with plasma cell dyscrasia. Only anecdotal experience is available for assessing IVIG as treatment for POEMS syndrome. The National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services panel of national experts' evidence-based practice guideline on the use of IVIG for neurologic conditions stated there is no role for


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IVIG in the treatment of POEMS syndrome. Per an update of the 2006 American Academy of Allergy, Asthma & Immunology guideline, and centers on the use of standard immunoglobulin preparations specifically manufactured for intravenous (IV) or subcutaneous (SC) administration, immune globulin is not recommended for use in POEMS syndrome. In addition, polyneuropathy associated with IgM monoclonal gammopathy is an example of a disease in which IVIG was ineffective or even had negative effects.

### *Rotaviral Enterocolitis*

Only small studies and case reports have suggested that oral immune globulin may have a beneficial effect on diarrhea related to rotaviral enterocolitis in infants and young children. Intravenous and/or subcutaneous immune globulins were not studied.

### *Sjogren's Syndrome*

IVIG has shown some efficacy in Sjogren's syndrome. Most of the reports have focused on associated dysautonomia or neuropathy although they have been very small case studies. One case study was of a 41-year-old man with severe sympathetic and parasympathetic autonomic dysfunction as a consequence of acetylcholine receptor antibodies and Sjogren's syndrome who failed to respond to IVIG. Larger, blinded, and controlled studies of IVIG are required regarding its efficacy for Sjogren's syndrome.

### *Spontaneous Recurrent Abortions, Prevention*

Results of treatment with IVIG have been conflicting. While prospective studies have suggested that the use of IVIG in pregnant women with a history of recurrent abortions imparted a protective benefit, other studies suggested no benefit. The members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology assessed a review from a number of high-quality randomized, placebo-controlled, multicenter studies and found that, "Given the review of randomized trials, cumulative current evidence does not presently support the use of IVIG for the prevention of recurrent spontaneous abortions.

### *Urticaria*

An autoimmune process is implicated in about one third of patients with chronic urticaria. Most case reports of successful treatment of chronic urticaria occur in those in whom an autoimmune mechanism is involved. However, in other case reports, patients did not respond or relapsed shortly after the completion of therapy. Delayed-pressure urticaria is a variant of chronic urticaria that is also difficult to treat. The use of IVIG in patients with delayed-pressure urticaria was conducted as an open-label trial; one third of the enrolled patients experienced remission, another third experienced some benefit, and the rest did not respond. Per an update of a 2006 American Academy of Allergy, Asthma & Immunology guideline, there is no clear evidence that the use of IVIG benefits patients with chronic urticaria, and additional placebo-controlled studies with long-term follow-up are needed.

### *Vasculitides and Antineutrophil Antibody Syndromes*

The efficacy of IVIG in the treatment of anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) was assessed in a randomized, placebo-controlled trial. Thirty-four patients (24 diagnosed with Wegener's granulomatosis, 10 diagnosed with microscopic polyangiitis) were randomized to a single course of either 400 mg/kg/day IVIG or placebo for 5 days. A therapeutic response was defined as a 50% decrease in the Birmingham Vasculitis Activity Score (BVAS) at 3 months. A therapeutic response was found in 14/17 patients who received IVIG and 6/17 patients who received placebo (OR = 8.56, 95% CI = 1.74 - 42.2, p = 0.015). The C-reactive protein (CRP) level decrease was significantly greater at 2 weeks and one month in the IVIG group compared to the placebo group. After 3 months, there was no difference in disease activity or CRP level between the IVIG and placebo groups. In addition, small open label trials of IVIG found some clinical benefit as an alternative therapeutic agent. Results were reported as transient in several of these. Additional randomized controlled trials will need to be conducted to determine its place in therapy.

## Professional Societies

### *Immune Deficiency Foundation (IDF)*

There are more than 300 primary immunodeficiency diseases (PIDs) recognized by the World Health Organization. The following diseases are PIDs are thus proven indications for immune globulin (list not all inclusive). Additional PID information can be found at the IDF website: primaryimmune.org. Back to criteria.

- Autosomal recessive agammaglobulinemia
- Autosomal recessive hyperimmunoglobulin M syndrome (HIM)
- Bruton's disease
- Chronic mucocutaneous moniliasis (CMC or APCED)


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- Combined immunodeficiency disorders:
  - Ataxia-telangiectasia
  - DiGeorge syndrome
  - Nijmegen breakage syndrome
  - WHIM (warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis) syndrome
  - Wiskott Aldrich syndrome
- Common variable immunodeficiency (CVID)
- Congenital hypogammaglobulinemia late onset, ICOS impaired
- Congenital/X-linked agammaglobulinemia
- Good syndrome (immunodeficiency with thymoma)
- Hyperimmunoglobulinemia E syndrome
- Hypogammaglobulinemia
- ICF syndrome
- Polyendocrinopathy and enteropathy (IPEX)
- Selective IgG subclass deficiencies (persistent absence of IgG1, IgG2, and/or IgG3)
- Selective IgM deficiency
- Severe combined immunodeficiency
- Specific antibody deficiency
- Transient hypogammaglobulinemia of infancy, short-term treatment of recurrent severe bacterial infections
- X-linked immunodeficiency with hyperimmunoglobulin M

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. U.S. Food and Drug Administration (FDA)–approval alone is not a basis for coverage.

There are currently eight clinical indications for which IVIG has been licensed by the FDA. The indications can be summarized as follows:

- Treatment of primary immunodeficiencies such as common variable immunodeficiency (CVID), X-linked agamma-globulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies
- Prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia
- Prevention of coronary artery aneurysms in Kawasaki disease (KD)
- Prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation
- Reduction of serious bacterial infection in children with human immunodeficiency virus (HIV)
- Increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding
- Improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in chronic inflammatory demyelinating polyneuropathy (CIDP)
- Maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy

Subcutaneous human immune globulin products are FDA approved for the treatment of patients with primary immune deficiency. This includes but not is limited to diagnoses such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

## Centers for Medicare and Medicaid Services (CMS)

Medicare may cover intravenous (IV) and subcutaneous (SC) immune globulin (IG) products when criteria are met. Refer to the National Coverage Determinations (NCDs) for Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3) and Lymphocyte Immune Globulin, Anti-Thymocyte Globulin (Equine) (260.7). Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) exist; refer to the LCDs/LCAs for Intravenous Immune Globulin (L35891), Immune Globulin (L34007), Off-Label Use of Intravenous Immune Globulin (IVIG) (L39314),


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Immune Globulin Intravenous (IVIg) (L34074), Immune Globulin Intravenous (IVIg) (L34314), Immune Globulin (L35093), Intravenous Immunoglobulin (IVIG) (L34580) and Immune Globulins (L34771).

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.
(Accessed October 10, 2025)

**For preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 10/01/2026 | **Coverage Rationale**<br>• Removed reference link to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* for Qivigy (immune globulin intravenous, human-kthm)<br>• Removed content/language pertaining to preferred products<br>**Supporting Information**<br>• Updated *References* section to reflect the most current information<br>• Archived previous policy version 2026D0035AU |

# Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.


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