Reference number(s)
1985-A

Standard Medicare Part B Management Intravenous Immune Globulin (IVIG)

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name
Alyglo
Asceniv
Bivigam
Flebogamma DIF
Gammagard Liquid
Gammagard Liquid ERC
Gammagard S/D
Gammaked
Gammaplex
Gamunex-C
Octagam
Panzyga
Privigen
Qivigy
Yimmugo

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

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FDA-approved Indications[1-16,127,129,134,135]

- Primary immunodeficiency
- Idiopathic thrombocytopenic purpura (ITP)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy
- Kawasaki syndrome
- B-cell chronic lymphocytic leukemia (CLL)
- Dermatomyositis

Compendial Uses[17-19,45]

- Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
- Acquired thrombocytopenia
- Antiphospholipid syndrome
- Asthma
- Autoimmune hemolytic anemia
- Autoimmune necrotizing myopathy
- Autoimmune neutropenia
- Bone marrow transplant/hematopoietic stem cell transplant
- Cerebellar ataxia due to Epstein-Barr virus infection
- Clostridium difficile colitis
- Adjunct to Crohn's disease treatment
- Cytomegalovirus treatment and prophylaxis
- Desensitization therapy – heart transplant
- Diabetic amyotrophy
- Hopkins' syndrome
- Acute disseminated encephalomyelitis
- Prophylaxis of enteritis due to rotavirus
- Epilepsy
- Gastroenteritis
- Granulomatosis with polyangiitis
- Guillain-Barre syndrome
- Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
- Hemophagocytic syndrome
- Induction of Factor VIII immune tolerance
- Measles (Rubeola) prophylaxis
- Moderate and severe immune checkpoint inhibitor-related toxicities
- Hypogammaglobulinemia from CAR-T therapy
- Herpes gestationis
- Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)

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- Prevention of bacterial infections in HIV infected patients
- Prevention of bacterial infections in post-surgical or ICU patients
- Isaacs syndrome
- Japanese encephalitis virus disease
- Severe IgA nephropathy
- Lambert-Eaton myasthenic syndrome
- Linear IgA dermatosis
- Lysinuric protein intolerance
- Prevention of bacterial infections in patients with multiple myeloma
- Multiple sclerosis
- Myasthenia gravis
- Myocarditis
- Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
- Neonatal jaundice
- Otitis media
- Paraneoplastic visual loss
- Polyarteritis nodosa
- Polymyositis
- Post-transplant lymphoproliferative disorder
- Pure red cell aplasia
- Pyoderma gangrenosum
- Renal transplant rejection
- Retinocochleocerebral vasculopathy, Central nervous system-predominant
- Respiratory syncytial virus infection
- Sepsis
- Stevens-Johnson syndrome
- Stiff-person syndrome
- Systemic lupus erythematosus
- Systemic onset juvenile chronic arthritis
- Systemic vasculitis
- Tetanus treatment and prophylaxis
- Fetal or neonatal thrombocytopenia
- Toxic epidermal necrolysis
- Toxic necrotizing fasciitis
- Toxic shock syndrome
- Heart transplant rejection
- Desensitization of highly sensitized patients awaiting renal transplantation
- Uveitis
- Varicella prophylaxis
- Von Willebrand disorder

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Nationally Covered Indication[58]

Centers for Medicare and Medicaid Services guidelines provide coverage for IG for the following autoimmune mucocutaneous conditions pursuant to the criteria in the coverage criteria section:

- Pemphigus vulgaris
- Pemphigus foliaceus
- Bullous pemphigoid
- Mucous membrane pemphigoid (cicatricial pemphigoid)
- Epidermolysis bullosa acquisita

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Documentation

The following documentation must be available, upon request, for all submissions (where applicable):

Myasthenia Gravis

- Clinical records describing standard treatments tried and failed

Secondary Hypogammaglobulinemia (e.g., CLL, BMT/HSCT recipients)

- Copy of laboratory report with pre-treatment serum IgG level

Multifocal Motor Neuropathy (MMN)

- Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])

Dermatomyositis and Polymyositis

- Clinical records describing standard treatments tried and failed

Lambert-Eaton Myasthenic Syndrome (LEMS)

- Neurophysiology studies (e.g., electromyography)
- A positive anti- P/Q type voltage-gated calcium channel antibody test

Idiopathic Thrombocytopenic Purpura

- Laboratory report with pre-treatment/current platelet count

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- Chronic/persistent ITP: copy of medical records supporting trial and failure with corticosteroid or anti-D therapy (unless contraindicated)

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)

- Medical records confirming the diagnosis and previous treatment with systemic corticosteroids for those initiating the IG therapy
- Medical records documenting that other causes of symptoms have been ruled out
- Medical records documenting objective assessment of baseline symptoms
- Medical records documenting a clinical response for those continuing with IG therapy

Stiff-Person Syndrome

- Anti-glutamic acid decarboxylase (GAD) antibody testing results
- Clinical records describing standard treatments tried and failed

Toxic Shock Syndrome or Toxic Necrotizing Fasciitis due to Group A Streptococcus

- Documented presence of fasciitis (toxic necrotizing fasciitis due to group A streptococcus only)
- Microbiological data (culture or Gram stain)

Coverage Criteria - Home Administration

Primary Immune Deficiency Disorder

Authorization of 6 months may be granted for treatment of primary immune deficiency disorder when the following criteria are met:

- The requested intravenous immune globulin preparation will be administered in the home with an infusion pump.
- The treating practitioner has determined that administration of the requested intravenous immune globulin in the member's home is medically necessary and appropriate.
- The member has a primary immune deficiency disorder and has one of the following ICD-10 codes as their diagnosis: D80.0 (hereditary hypogammaglobulinemia), D80.2 (selective deficiency of immunoglobulin A), D80.3 (selective deficiency of immunoglobulin G subclasses), D80.4 (selective deficiency of immunoglobulin M), D80.5 (immunodeficiency with increased

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immunoglobulin M), 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 (SCID with low T- and B-cell numbers), D81.2 (SCID with low or normal B-cell numbers), D81.5 (purine nucleoside phosphorylase deficiency), D81.6 (major histocompatibility complex class I deficiency), D81.7 (major histocompatibility complex class II deficiency), D81.82 (activated phosphoinositide 3-kinase delta syndrome), 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 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), G11.3 (cerebellar ataxia with defective DNA repair).

Coverage Criteria

Primary Immunodeficiency[1-12,14-16,127,129,134,135]

Initial authorization of 6 months may be granted for members with primary immunodeficiency.

Myasthenia Gravis[17,23-25]

- Authorization of 1 month may be granted to members who are prescribed IG for worsening weakness, acute exacerbation, or in preparation for surgery.[22-24]
    - Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure
    - Pre-operative management (e.g., prior to thymectomy)
- Authorization of 6 months may be granted to members with refractory myasthenia gravis who have tried and failed 2 or more standard therapies (e.g., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, rituximab).

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)[23-25,38]

Authorization of 3 months may be granted for treatment of chronic inflammatory demyelinating polyneuropathy.

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Dermatomyositis or Polymyositis[13,23-25,41]

Authorization of 3 months may be granted when the following criteria are met:

- Member has at least 4 of the following:
  - Proximal muscle weakness (upper or lower extremity and trunk)
  - Elevated serum creatine kinase (CK) or aldolase level
  - Muscle pain on grasping or spontaneous pain
  - Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
  - Positive for anti-synthetase antibodies (e.g., anti-Jo-1, also called histadyl tRNA synthetase)
  - Non-destructive arthritis or arthralgias
  - Systemic inflammatory signs (fever: more than 37°C at axilla, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method),
  - Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen), and
- Standard first-line treatments (corticosteroids) and second-line treatments (immunosuppressants) have been tried but were unsuccessful or not tolerated, or
- Member is unable to receive standard first-line and second-line therapy because of a contraindication or other clinical reason.

Idiopathic Thrombocytopenic Purpura (ITP)/Immune Thrombocytopenia[3,4,7-13,15,16]

- Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met:[42,43]
  - Children (< 18 years of age)
    - Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or
    - High risk for bleeding (see Appendix B), or
    - Rapid increase in platelets is required (e.g., surgery or procedure)
  - Adults (≥ 18 years of age)
    - Platelet count < 30,000/mcL, or
    - Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required, and
    - Corticosteroid therapy is contraindicated and IG will be used alone or IG will be used in combination with corticosteroid therapy
- Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:[42,43]
  - Platelet count < 30,000/mcL, or
  - Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required, and

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    - Relapse after previous response to IG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
- Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:[42]
    - Platelet count < 30,000/mcL, or
    - Significant bleeding symptoms
- ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.[42]

The member's risk factor(s) for bleeding (see Appendix B) or reason requiring a rapid increase in platelets must be provided.

B-cell Chronic Lymphocytic Leukemia (CLL)[37]

Authorization of 6 months may be granted for treatment of B-cell chronic lymphocytic leukemia (CLL) when all of the following criteria are met:

- IG is prescribed for prophylaxis of bacterial infections.
- Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
- Member has a pretreatment serum IgG level <500 mg/dL.

Bone Marrow Transplant/Hemopoietic Stem Cell Transplant (BMT/HSCT)[17,18,22]

Authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:

- Therapy will be used to prevent the risk of acute graft-versus-host disease, associated interstitial pneumonia (infectious or idiopathic), septicemia, and other infections (e.g., cytomegalovirus infections [CMV], recurrent bacterial infection).
- Either of the following:
    - IG is requested within the first 100 days post-transplant.
    - Member has a pretreatment serum IgG < 400 mg/dL.

Multifocal Motor Neuropathy (MMN)[17,18,39,40]

Authorization of 3 months may be granted for treatment of multifocal motor neuropathy when the following criteria are met:

- Member experienced progressive, multifocal, asymmetrical weakness without objective sensory loss in 2 or more nerves for at least 1 month
- The diagnosis was confirmed by electrodiagnostic studies

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Guillain-Barre syndrome (GBS)[17,23-25]

Authorization of 1 month total may be granted for GBS when the following criteria are met:

- Member has severe disease with significant weakness (e.g., inability to stand or walk without aid, respiratory weakness)
- Onset of neurologic symptoms occurred less than 4 weeks from the anticipated start of therapy

Lambert-Eaton Myasthenic Syndrome (LEMS)[18,23,24,26]

Authorization of 6 months may be granted for LEMS when the following criteria are met:

- Diagnosis has been confirmed by either of the following:
  - Neurophysiology studies (e.g., electromyography)
  - A positive anti- P/Q type voltage-gated calcium channel antibody test
- Anticholinesterases (e.g., pyridostigmine) and amifampridine (e.g., 3,4-diaminopyridine phosphate, Firdapse) have been tried but were unsuccessful or not tolerated
- Weakness is severe or there is difficulty with venous access for plasmapheresis

Kawasaki Syndrome[7,8]

Authorization of 1 month may be granted for treatment of Kawasaki syndrome in pediatric patients.

Stiff-person Syndrome[17,18,23-25]

Authorization of 6 months may be granted for stiff-person syndrome when the following criteria are met:

- Diagnosis has been confirmed by anti-glutamic acid decarboxylase (GAD) antibody testing
- Member had an inadequate response to first-line treatment (benzodiazepines and/or baclofen)

Management of Immune Checkpoint Inhibitor-Related Toxicities[45]

Authorization of 1 month may be granted for management of immune checkpoint-inhibitor toxicities when all of the following criteria are met:

- Member has experienced a moderate or severe adverse event to a PD-1 or PD-L1 inhibitor (e,g., pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab)
- The offending medication has been held or discontinued
- Member experienced one or more of the following adverse events: myocarditis, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, myasthenia gravis, peripheral neuropathy, encephalitis, transverse myelitis, severe inflammatory arthritis, Guillain-Barre syndrome, or steroid-refractory myalgias or myositis

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Acute Disseminated Encephalomyelitis[17]

Authorization of 1 month may be granted for acute disseminated encephalomyelitis in members who have had an insufficient response or a contraindication to intravenous corticosteroid treatment.

Autoimmune Mucocutaneous Blistering Disease[58]

Authorization of 6 months may be granted for treatment of biopsy proven autoimmune mucocutaneous blistering diseases when all of the following criteria are met:

- Member has one of the following diagnoses: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid), or epidermolysis bullosa acquisita.
- At least one of the following criteria is met regarding prior treatment with conventional therapy:
    - Member has failed conventional therapy
    - Member has a contraindication to conventional therapy
    - Member has rapidly progressive disease and a clinical response could not be affected quickly enough using conventional agents, and IG will be given in combination with conventional treatment.
- IG will be used for short-term control of the member's condition and will not be used as maintenance therapy.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS) (See Appendix C)[132]

Initial Authorization of 6 months may be granted when the following criteria are met:

- Child meets PANS Research Consortium Diagnostic Criteria for PANS/PANDAS:
    - Documentation of abrupt, dramatic onset (within less than one month) of obsessive-compulsive disorder or severely restricted food intake; and
    - Documentation of concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories:
        - Anxiety
        - Emotional lability and/or depression
        - Irritability, aggression, and/or severely oppositional behaviors
        - Behavioral (developmental) regression
        - Deterioration in school performance (related to attention deficit/hyperactivity disorder (ADHD)-like symptoms, memory deficits, cognitive changes)
        - Sensory or motor abnormalities
        - Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency; and
    - Onset of symptoms occurs between 3 years of age and puberty; and

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    - Documentation that other causes of symptoms have been ruled out.
- Child has tried and failed treatment with systemic corticosteroids.
- Documented objective assessment of baseline symptoms has been submitted (e.g., Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS], Clinical Global Impression of Severity [CGIS], Parent-Rated Pediatric Acute Neuropsychiatric Symptom Scale [PANS Scale]).

Autoimmune Hemolytic Anemia[17]

Authorization of 6 months may be granted for treatment of autoimmune hemolytic anemia in members who do not respond or have a contraindication to corticosteroids or splenectomy.

Autoimmune Neutropenia[17,29]

Authorization of 6 months may be granted for treatment of autoimmune neutropenia where treatment with G-CSF (granulocyte colony stimulating factor) is not appropriate.

Acquired Thrombocytopenia[17]

Authorization of 1 month may be granted for acquired thrombocytopenia.

Prevention of Bacterial Infections in Patients with Multiple Myeloma[17,29]

Authorization of 6 months may be granted for multiple myeloma in members who have recurrent, serious infections despite the use of prophylactic antibiotics.

Japanese Encephalitis Virus Disease[17]

Authorization of 1 month may be granted for Japanese encephalitis virus disease

Measles (Rubeola) Prophylaxis[18]

Authorization of 1 month may be granted for postexposure prophylaxis to prevent or modify symptoms of measles (rubeola) in susceptible members exposed to the disease less than 6 days previously.

Multiple Sclerosis[17]

Authorization of 6 months may be granted for treatment of relapsing-remitting multiple sclerosis (RRMS).

Stevens-Johnson Syndrome[17]

Authorization of 1 month may be granted for severe cases of Stevens-Johnson syndrome.

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Tetanus Treatment and Prophylaxis[18]

Authorization of 1 month may be granted for treatment or postexposure prophylaxis of tetanus as an alternative when tetanus immune globulin (TIG) is unavailable.

Toxic Epidermal Necrolysis[17]

Authorization of 1 month may be granted for severe cases of toxic epidermal necrolysis.

Toxic Shock Syndrome[17]

Authorization of 1 month may be granted for staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the member has persistent oliguria with pulmonary edema.

Systemic Lupus Erythematosus (SLE)[17]

Authorization of 6 months may be granted for severe, active SLE in members who have experienced inadequate response, intolerance or have a contraindication to first and second line therapies (e.g., hydroxychloroquine, glucocorticoids, anifrolumab, rituximab).

Toxic Necrotizing Fasciitis Due to Group A Streptococcus[17]

Authorization of 1 month may be granted for members with fasciitis due to invasive streptococcal infection.

Varicella Prophylaxis[18]

Authorization of 1 month may be granted for postexposure prophylaxis of varicella in susceptible individuals when varicella-zoster immune globulin (VZIG) is unavailable.

Other Indications[17,18,45, 52]

Authorization of 6 months may be granted for the following indications:

- Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy or CAR-T therapy
- Antiphospholipid syndrome
- Asthma
- Autoimmune necrotizing myopathy
- Cerebellar ataxia due to Epstein-Barr virus infection
- Clostridium difficile colitis
- Adjunct to Crohn's disease treatment

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- Cytomegalovirus treatment and prophylaxis when the member is undergoing a transplant
- Desensitization therapy – heart transplant
- Diabetic amyotrophy
- Hopkins' syndrome
- Prophylaxis of enteritis due to rotavirus
- Epilepsy
- Fetal or neonatal thrombocytopenia
- Gastroenteritis
- Granulomatosis with polyangiitis
- Hemolytic disease of fetus or newborn due to RhD isoimmunization
- Hemophagocytic syndrome
- Induction of Factor VIII immune tolerance
- Herpes gestationis
- Prevention of bacterial infections in HIV infected patients
- Prevention of bacterial infections in post-surgical or ICU patients
- Isaacs syndrome
- Severe IgA nephropathy
- Linear IgA dermatosis
- Lysinuric protein intolerance
- Myocarditis
- Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
- Neonatal jaundice
- Otitis media
- Paraneoplastic visual loss
- Polyarteritis nodosa
- Post-transplant lymphoproliferative disorder
- Pure red cell aplasia
- Pyoderma gangrenosum
- Renal transplant rejection
- Retinocochleocerebral vasculopathy, Central nervous system-predominant
- Respiratory syncytial virus infection
- Sepsis
- Systemic onset juvenile chronic arthritis
- Systemic vasculitis
- Heart transplant rejection
- Desensitization of highly sensitized patients awaiting renal transplantation
- Uveitis
- Von Willebrand disorder

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Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Acquired Thrombocytopenia, Acute disseminated encephalomyelitis, Guillain-Barre syndrome, Japanese encephalitis virus disease, Kawasaki syndrome, Measles prophylaxis, Moderate and severe immune checkpoint inhibitor-related toxicities, Steven's Johnson syndrome, Tetanus treatment and prophylaxis, Toxic epidermal necrolysis, Toxic shock syndrome, Toxic Necrotizing Fasciitis Due To Group A Streptococcus, Varicella prophylaxis

Authorization for members who are requesting authorization for continuation of therapy of IG must meet all requirements in the coverage criteria.

Primary Immune Deficiency

Authorization of 12 months may be granted when ALL of the following criteria are met:

- The member is currently receiving therapy with IG
- The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)

Authorization of 6 months maybe granted when documentation of objective clinical response to therapy has been submitted (e.g., Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS], Clinical Global Impression of Severity [CGIS], Parent-Rated Pediatric Acute Neuropsychiatric Symptom Scale [PANS Scale]).

All Other Indications

Authorization of 6 months may be granted when ALL of the following criteria are met:

- The member is currently receiving therapy with IG
- IG is being used to treat an indication listed in the coverage criteria section

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- The member is receiving benefit from therapy, such as a reduction in the frequency of infections, improvement in disability, stabilization of condition.

Appendix

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine[31,32]

- Age 2 years and older: impaired antibody response demonstrated to vaccination with a pneumococcal polysaccharide vaccine
- Not established for children less than 2 years of age
- Excludes the therapy initiated in the hospital setting

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)[42,43]

- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (e.g., peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to trauma (e.g., construction worker, fireman, professional athlete)

Appendix C[132]

- Members suspected of having PANS/PANDAS should be evaluated with the following tests, as indicated:
    - Complete blood cell counts with manual differential
    - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
        - If there are elevated inflammatory markers, fatigue, rashes, or joint pain, antinuclear antibody (ANA) or fluorescent antinuclear antibody (FANA) should be obtained (if ANA is elevated, the member should be evaluated for lupus)
    - Comprehensive metabolic panel
        - If liver function tests are abnormal or Kayser–Fleisher rings are present, the member should be evaluated for Wilson's disease with ceruloplasmin and 24 urine copper tests.
    - Throat culture, anti-streptolysin O (ASO) and anti-DNAse B
    - Urinalysis (to assess hydration) and to rule out inflammation for children with urinary complaints
        - If urinalysis reveals pyuria, clean-catch urine culture
    - Antiphospholipid antibody work up if the member has chorea, petechiae, migraines, stroke, thrombosis, thrombocytopenia, or levido rash. Workup should include:
        - anticardiolipin antibody,

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    - dilute Russell's viper venom time (dRVVT),
    - b 2-glycoprotein I antibodies.
- Members should be evaluated for other causes of symptoms, including:
    - Autism/Autistic Spectrum Disorder
    - Developmental Delay/Mental Retardation
    - Cerebral palsy
    - Genetic conditions and syndromes (such as Down Syndrome, Fragile X, Rett Syndrome, etc.)
    - Cerebral malformation syndromes
    - Inborn errors of metabolism
    - CNS infections
    - Toxic cerebral insults (such as kernicterus, chemo-radiation, etc.)
    - Obsessive compulsive disorder
    - Anorexia nervosa
    - Avoidant/restrictive food intake disorder (ARFID)
    - Tourette syndrome
    - Transient tic disorder
    - Bipolar disorder
    - Sydenham chorea
    - Autoimmune encephalitis
    - Systemic autoimmune disease
    - Wilson's disease

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Alyglo, Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, Privigen, and Yimmugo
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service- Drug Information (AHFS-DI)
    - Lexi-Drugs
    - Clinical Pharmacology
- NCCN Guideline: Chronic lymphocytic leukemia/Small lymphocytic lymphoma
- NCCN Guideline: Management of immunotherapy-related toxicities
- Update on the use of immunoglobulin in human disease: a review of evidence by Work Group Report of the American Academy of Allergy, Asthma, and Immunology.

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- Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services.
- Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective.
- Guidelines on the use of intravenous immune globulin for neurologic conditions.
- Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee.
- EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases.
- Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.
- Guidelines on the use of intravenous immune globulin for hematologic conditions.
- Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency.
- Practice parameter for the diagnosis and management of primary immunodeficiency.
- Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest section of the American Academy of Allergy, Asthma and Immunology.
- European Society for Immunodeficiencies. Diagnostic criteria for Primary Immune Deficiency (PID).
- Immune Deficiency Foundation. Diagnostic and Clinical Care Guidelines for Primary Immunodeficiency Diseases. 3rd edition.
- European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – second revision.
- Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Societies guideline on management of multifocal motor neuropathy.
- Consensus criteria for the diagnosis of multifocal motor neuropathy.
- The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia.
- Updated international consensus report on the investigation and management of primary immune thrombocytopenia.
- Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience.
- Working Group on Antiretroviral Therapy of the National Pediatric HIV Resource Center. Antiretroviral therapy and medical management of pediatric HIV infection.

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- Center for Medicare and Medicaid Services (CMS). Intravenous immune globulin for autoimmune mucocutaneous blistering diseases. Decision Memorandum.
- Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA)Consensus Task Force recommendations for evaluation and management.
- Staphylococcus aureus. American Academy of Pediatrics. Red Book: 2018 Report of the Committee on Infectious Diseases.
- British Society for Rheumatology guideline on management of systemic lupus erythematosus in adults
- Guidelines on the use of intravenous immune globulin for hematologic conditions.
- Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care.
- European Guidelines (S1) on the use of high-dose intravenous immunoglobulin in dermatology.
- Surviving sepsis campaign: international guidelines for management of sepsis and septic shock.
- British Association of Dermatologists' guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people.
- 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus.
- NCD 250.3: Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases.

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Alyglo, Asceniv, Bivigam, Flebogamma DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam, Panzyga, Privigen, and Yimmugo are covered in addition to the following:

- Prevention of infections in patients with acquired hypogammaglobulinemia secondary to malignancy
- Acquired thrombocytopenia
- Antiphospholipid syndrome
- Asthma
- Autoimmune hemolytic anemia
- Autoimmune necrotizing myopathy
- Autoimmune neutropenia
- Bone marrow transplant/hematopoietic stem cell transplant
- Cerebellar ataxia due to Epstein-Barr virus infection
- Clostridium difficile colitis
- Adjunct to Crohn’s disease treatment
- Cytomegalovirus treatment and prophylaxis
- Desensitization therapy – heart transplant
- Dermatomyositis
- Diabetic amyotrophy
- Hopkins’ syndrome
- Acute disseminated encephalomyelitis

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- Prophylaxis of enteritis due to rotavirus
- Epilepsy
- Gastroenteritis
- Granulomatosis with polyangiitis
- Guillain-Barre syndrome
- Hemolytic disease of fetus or newborn due to RhD isoimmunization, prophylaxis
- Hemophagocytic syndrome
- Induction of Factor VIII immune tolerance
- Measles (Rubeola) prophylaxis
- Moderate and severe immune checkpoint inhibitor-related toxicities
- Hypogammaglobulinemia from CAR-T therapy
- Herpes gestationis
- Prevention of bacterial infections in HIV infected patients
- Prevention of bacterial infections in post-surgical or ICU patients
- Isaacs syndrome
- Japanese encephalitis virus disease
- Severe IgA nephropathy
- Lambert-Eaton myasthenic syndrome
- Linear IgA dermatosis
- Lysinuric protein intolerance
- Prevention of bacterial infections in patients with multiple myeloma
- Multiple sclerosis
- Myasthenia gravis
- Myocarditis
- Prevention and treatment of bacterial infections in high-risk, preterm, low-birth-weight neonates
- Neonatal jaundice
- Otitis media
- Paraneoplastic visual loss
- Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS)
- Polyarteritis nodosa
- Polymyositis
- Post-transplant lymphoproliferative disorder
- Pure red cell aplasia
- Pyoderma gangrenosum
- Renal transplant rejection
- Retinocochleocerebral vasculopathy, Central nervous system-predominant
- Respiratory syncytial virus infection
- Sepsis
- Stevens-Johnson syndrome
- Stiff-person syndrome

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- Systemic lupus erythematosus
- Systemic onset juvenile chronic arthritis
- Systemic vasculitis
- Tetanus treatment and prophylaxis
- Fetal or neonatal thrombocytopenia
- Toxic epidermal necrolysis
- Toxic necrotizing fasciitis
- Toxic shock syndrome
- Heart transplant rejection
- Desensitization of highly sensitized patients awaiting renal transplantation
- Uveitis
- Varicella prophylaxis
- Von Willebrand disorder
- Idiopathic thrombocytopenic purpura (ITP)
- Multifocal motor neuropathy
- Kawasaki syndrome
- B-cell chronic lymphocytic leukemia (CLL)

Explanation of Rationale

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

This policy considers subcutaneous administration of immune globulin as an alternative to intravenous therapy and intramuscular therapy in members who meet medical necessity criteria for intravenous immune globulin or intramuscular immune globulin.

Support for using immune globulin to treat acquired thrombocytopenia can be found in a several small studies. Hartert and colleagues reported that intravenous immune globulin provided a sustained response in a man with severe thrombocytopenia following a mismatched, related allogeneic stem cell transplant (SCT). Nine months after SCT, the man presented with papular cutaneous lesions, diarrhea, and pancytopenia. Tests for cytomegalovirus were positive. Within a few days he developed fever, arthralgia, severe pancytopenia, generalized edema, polyserositis with pericardial and pleural effusions, and nephrotic syndrome. Skin and bowel symptoms were interpreted as graft-versus-host disease. Anemia was refractory to red cell transfusion. Autoantibody testing suggested a lupus-like syndrome. He was treated with prednisolone and mycophenolate mofetil (MMF) before IVIG treatment was begun at 0.4 mg/kg on 5 consecutive days. A total of 4 cycles were given. At 2 months after symptom onset, his renal function had improved, and body weight had normalized. Hemoglobin (Hb) and platelet count were still low at the time of discharge, but there were no clinical signs of anemia or bleeding. Several weeks later, the patient was readmitted with arthralgia and decreases in platelet count and Hb associated with a slight reduction in steroid therapy. Cytomegalovirus tests were again positive, and he was treated with foscarnet and ganciclovir. IVIG was given at 0.4 mg/kg for 5 days, resulting in a marked increase in platelet count. Hb rose slowly after discharge. IVIG was repeated 2 weeks later at a reduced dose of 5 g/day for 5 days

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and repeated every 4 weeks thereafter. Hb stabilized at greater than 9 g/dL, and the platelet count was maintained at greater than 80 x 10(9)/liter. The patient had no signs of graft-versus-host disease. He continued immunosuppressive therapy with prednisolone 3 mg/day and MMF 750 mg/day. Chute et al treated trimethoprim-sulfamethoxazole thrombocytopenia in a 21-year-old patient with intravenous immune globulin (IVIG) treatment. The patient did not respond to methylprednisolone and was treated with IVIG 0.4 g/kg and a platelet transfusion. Within 1 hour, resolution of the acutely progressive disorder was measured. The proposed mechanism is an immunoglobulin-mediated reticuloendothelial Fc receptor blockade. Guzzi et al used IVIG 0.2 g/kg for 7 days, in combination with corticosteroids, to treat secondary thrombocytopenia to sarcoidosis in a 22-year-old male. Corticosteroids alone were not effective; the platelet count did not increase substantially until IV immune globulin was added to therapy.

Support for using immune globulin to treat antiphospholipid syndrome can be found in a study by Gordon and Kilby. Therapy with intravenous immune globulin 2 g/kg in divided doses over 2 to 5 days resulted in marked clinical benefits in 4 pregnant patients (including one twin pregnancy) who developed, in the second half of pregnancy, intrauterine growth restriction (IUGR) associated with systemic lupus erythematosus and/or antiphospholipid syndrome. There were 2 early date fetal deaths. All pregnant patients had been receiving aspirin and high-dose subcutaneous heparin in the second trimester.

Support for using immune globulin to treat asthma can be found in a study by Salmun et al. Therapy with intravenous immune globulin (IVIG) 400 mg/kg every 3 weeks significantly decreased the oral steroid required by 9 patients with severe asthma that participated in a double-blind, placebo-controlled, randomized trial over 9 months. The median oral steroid required after IVIG went down to 3 mg/day from a median dose of 16.4 mg/day before IVIG treatment (p=0.0078).

Mazer and Gelfand investigated the use of IVIG in pediatric patients with asthma. Immune globulin was found to reduce the dose of corticosteroids needed and improve pulmonary function tests and symptoms in 8 children with asthma. The dose of immune globulin was 1 g/kg/day for 2 consecutive days repeated every 4 weeks for 6 months.

Support for using immune globulin to treat autoimmune hemolytic anemia can be found in a study by Flores et al (1993). Of 72 patients with warm-antibody autoimmune hemolytic anemia, approximately 40% responded to intravenous immune globulin (IVIG) treatment. Those with hepatomegaly and a low pretreatment hemoglobin had the best response to IVIG. The investigators suggest IVIG as adjunctive treatment only in select cases.

Support for using immune globulin to treat autoimmune necrotizing myopathy can be found in several published studies. A study by Kocoloski et al. found that in a longitudinal case series in adults with immune-mediated necrotizing myopathy (IMNM, N=20), intravenous immune globulin (IVIG) was associated with significant reduction in mean creatine kinase (CK) level from 4765 IU/L at baseline to 1463 IU/L at 3 months and 558 IU/L at 6 months. The standard IVIG dosage was 2 g/kg of actual body weight, administered every 4 weeks. Eighty-five percent of patients had a greater than 50% absolute decline in CK levels at 3 months and 90% at 6 months. Manual muscle testing (MMT-8, maximum score is 80 for unilateral measures) showed significant improvement from the beginning of IVIG treatment compared with 3 months (52 vs 63.9) and 6 months (52 vs 68.9) with 85% of patients having greater than 10% absolute improvement in MMT-8 at 6 months. There was a significant reduction in the mean dose of

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prednisone at 6 months (31.5 mg vs 11.1 mg;). Immune-mediated necrotizing myopathy was defined as elevated serum CK, proximal muscle weakness, and anti-SRP or anti-HMGCR autoantibodies. Autoantibody-negative IMNM patients were included if they had an elevated CK, proximal muscle weakness, and had necrotizing myopathy on muscle biopsy. Necrotizing myopathy was defined as the presence of necrotic muscle fibers in scattered distribution with different stages of necrosis, myophagocytosis and regeneration, and macrophage predominant, pauci-lymphocytic infiltrates without secondary causes (ie, malignancy, viral infection, or drug toxicity). Patients with non-statin drug-induced and toxin-induced myopathies were excluded. Mean patient age was 58 years, 55% were female, and 100% were White. The most common adverse event was headache (25% of patients). Thirty five percent of patients continued at the initial IVIG starting dose/frequency, and 20% were on a lower dose than initially started. Three patients were started on rituximab due to IVIG treatment failure.

Support for using immune globulin to treat autoimmune neutropenia can be found in guidelines for the use of intravenous immune globulin for hematologic conditions from the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services. In general, immune globulin is not recommended for routine care but can be used in life-threatening circumstances.

Support for using immune globulin in patients who have received bone marrow transplants or hematopoietic stem cell transplants can be found in several published studies. A meta-analysis published by Bass et al (1993) found IVIG prophylaxis was associated with a significant reduction in posttransplant complications. Winston et al (1993) found IVIG reduces the incidence and severity of graft versus host disease. The recommended dose of immune globulin is 500 mg/kg IV 7 days and 2 days before transplantation, then weekly for 90 days following the transplant. Abdel-Mageed and colleagues (1999) conducted a comparison of two doses of intravenous immune globulin (IVIG), 250 mg/kg or 500 mg/kg given weekly from day -8 to day +111, the higher dose was associated with less acute graft-versus-host disease (p=0.03).

Support for using immune globulin to treat cerebellar ataxia due to Epstein-Barr infection can be found in a study by Daaboul, Vern, and Blend (1998). Intravenous immune globulin (IVIG) dosed at 2 g/kg over 3 days (total 144 g) may have contributed to the recovery of a 19-year-old male with acute post-infectious (Epstein-Barr virus or EBV) cerebellar ataxia. The patient presented with nausea, vomiting, unsteady gait and cervical lymphadenopathy. The presence of anti-EBV capsid IgM antibody, elevated serum EBV IgG antibody and cerebellar hyperperfusion on single-photon emission tomography led to the diagnosis. Within 2 weeks of empiric initiation of IVIG therapy, the patient recovered completely.

Support for using immune globulin to treat clostridium difficile colitis can be found in a study by Leung et al. Intravenous immune globulin was shown to be effective in preventing recurrence of colitis induced by Clostridium difficile toxin in 5 children. C difficile produces 2 types of exotoxin: toxin A and toxin B; toxin A produces diarrhea. These children, with chronically recurrent C difficile-induced colitis were found to have lower circulating levels of antitoxin A immunoglobulins than normal subjects. Administration of IV immune globulin 400 mg/kg every 3 weeks promoted resolution of gastrointestinal symptoms of colitis in all patients. However, colitis recurred in 1 patient after discontinuing the IV immune globulin; therapy was not interrupted in the other patients.

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Support for using immune globulin as an adjunct to Crohn's disease treatment can be found in a study by Knoflach, Muller, and Eible (1990). The study reported transient improvement in the symptoms of Crohn disease in six patients after administration of IV immune globulin 400 mg/kg/day for 5 days. A reduction in abdominal pain and loss of fever was obtained in all patients, in 2 to 3 days after treatment. However, three patients relapsed after 2 weeks and required an additional course of immune globulin.

Support for using immune globulin to treat cytomegalovirus infection and as prophylaxis against cytomegalovirus infection can be found in two meta-analyses conducted by Glowaki (1994) and Ratko (1995). The use of intravenous immune globulin (IVIG) as passive immunization for the prevention of symptomatic cytomegalovirus disease in the transplant population.

Support for using immune globulin as desensitization therapy in patients undergoing a heart transplant can be found in guidelines published by the Canadian Cardiovascular Society/Canadian Cardiac Transplant Network. Immune globulin, targeted B cell (rituximab), and plasma cell therapies (bortezomib) form the foundation of desensitization treatments. Immunoglobulin and rituximab have increased transplantation rates, reduced wait list time, and reported graft outcomes similar to those of non-sensitized patients. However, there are no randomized trials on efficacy of desensitization therapy in heart transplant.

Support for using immune globulin to treat dermatomyositis can be found in a guideline published by the European Dermatology Forum/European Academy of Dermatology and Venereology. High dose IVIG is indicated in all severe forms of dermatomyositis. Immune globulin should generally be used as adjunctive therapy.

Support for using immune globulin to treat diabetic amyotrophy can be found in a case report by Ogawa et al. Treatment with immune globulin (IVIG) restored the ability to walk in a 49-year-old woman with diabetic amyotrophy (DA) of the thighs. The woman did not receive antidiabetic treatment for 14 years after diagnosis of diabetes mellitus. Three years after starting treatment, she began hemodialysis because of the diabetic nephropathy. A year later she began noticing weakness and atrophy of both thighs, though without pain or sensory disturbance, and she began to walk with a cane. In a short time, she became confined to a wheelchair and was diagnosed with DA. Treatment with an aldose reductase inhibitor and vitamin B12 were ineffective. She was given a 3-day course of IVIG 400 mg/kg/day (a reduced dose because of concern for congestive heart failure). On the following day, she could walk with a cane. Four weeks later she was given a second course of IVIG. Three days later she could walk unassisted. Follow-up needle electromyography suggested inactivation of proximal neuropathy. The patient experienced no adverse effects.

Support for using immune globulin to treat Hopkin's syndrome can be found in a case report published by Cohen et al (1998). A 15-year-old child experienced near complete recovery of muscle paralysis and atrophy after treatment with IV gamma globulin. Patient was diagnosed with poliomyelitis-like syndrome after an asthmatic attack. Moderate improvement in muscle strength was seen 3 weeks after patient received IV gamma globulin 1 g/kg/day for 2 consecutive days. A second treatment course was given 3 weeks later. Two years later this patient reported minimal weakness of the left deltoid muscle and he is able to play basketball.

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Support for using immune globulin to treat acute disseminated encephalomyelitis (ADEM) can be found in a case series by Nishikawa et al (1999). Intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days was effective in the treatment of 3 pediatric cases (ages 2 to 5 years) of ADEM. Signs and symptoms included fever, headache, vomiting and somnolence with elevated myelin basic protein in the cerebrospinal fluid (CSF) and increased signal intensity (white matter lesions) on T2-weighted magnetic resonance imaging. Each patient recovered fully within 1 to 3 weeks of IVIG therapy. Although corticosteroids have been the drug of choice for ADEM, they should be avoided in viral encephalitis. Therefore, the authors recommend IVIG therapy for suspected ADEM, reserving steroids for those who fail IVIG.

Support for using immune globulin as prophylaxis against enteritis due to rotavirus can be found in a study by Barnes et al. During the first week of life, 75 low-birth-weight neonates received oral human IgG or placebo with each feeding. IgG or placebo was given in doses of 4 mL 4 times daily during the first 7 days of life starting with the first feeding following birth. Each 4 mL of IgG contained approximately 500 mg of IgG. Twenty-five of 75 babies excreted rotavirus during the first 2 weeks of life. In babies with rotavirus, IgG was associated with delayed excretion of rotavirus and with milder symptoms of the infection. Six of 11 babies given placebo and 1 of 14 babies given IgG required low lactose feeds to alleviate rotavirus associated diarrhea. Oral human IgG protects low-birth-weight infants from diarrhea caused by rotavirus, especially in infants unprotected by other means (i.e., breastfeeding, rooming in).

Support for using immune globulin to treat epilepsy can be found in a study by Ariizumi et al. High doses of an immune globulin preparation (97% IgG and 3% IgA) were effective in producing complete clinical and electroencephalogram remission in 4 of 8 children with intractable epilepsy with attacks for 2 years or less. The probability of a successful response appeared to correspond to a short duration of illness and low serum IgA level.

Support for using immune globulin to treat gastroenteritis can be found in a study by Guarino et al. A prospective, double-blind placebo-controlled trial was conducted in 98 children with gastroenteritis (mean age 15 months +/- 8 months). Children randomized to receive a single oral dose of intravenous immune globulin (IVIG) 300 mg/kg had significantly faster improvement in stool pattern and clinical symptomatology than those receiving placebo (duration of diarrhea was 76 vs 131 hours in the placebo groups; hospital stay was 4 days in the IVIG group and 6 days in the placebo group.

Support for using immune globulin to treat granulomatosis with polyangiitis can be found in a guideline published by Groh et al. IVIG can be considered as second-line therapy for patients on glucocorticoids with or without other immunosuppressants with EGPA flares refractory to other treatments or during pregnancy. In the context of drug-induced hypogammaglobulinemia with severe and/or recurrent infections, immune globulin replacement may be considered.

Support for using immune globulin to treat Guillain-Barre syndrome can be found in two published studies. Intravenous immune globulin (IVIG) was at least as effective as plasma exchange (PE) in altering the course of Guillain-Barré syndrome (GBS) (van der Meche, 1994). One hundred forty-seven patients who were unable to walk 10 meters independently, were randomized to receive either PE (200 mL/kg in 5 sessions) over 7 to 14 days or IVIG (0.4 g/kg/day) for 5 days. In 12 patients, 1 session or more of PE had to be discontinued due to hypotension and problems with venous flow; 1 patient required discontinuation

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due to transient elevation of liver enzymes. In the PE group 34% of patients improved 1 functional grade or more after 4 weeks, compared with 53% in the IVIG group. This was a statistically significant difference. The median time to improvement of at least one grade was quicker in the IVIG group (27 days) when compared to the PE group (41 days). This was also a statistically significant difference. Sixty-eight complications occurred in the PE group and 39 in the IVIG group (eg, 27% of the IVIG patients required artificial ventilation in the second week vs 42% of the PE group. The investigators conclude that IVIG is at least as effective as PE.

Intravenous immune globulin (IVIG) therapy produced similar results as plasma exchange (PE) in a multicenter, randomized, controlled trial of 225 patients with Guillain-Barré syndrome conducted by the Plasma/Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. When IVIG was combined with PE therapy, results were similar compared to PE or IVIG therapy alone. All patients, regardless of the treatment regimen received, exhibited similar ability to walk unaided, median times to hospital discharge and return to work, and ability to walk at 48 weeks after therapy. Patients in the study who had a longer delay from onset to randomization had significantly more improvement after 4 weeks than those with short delays (p less than 0.001). Patients received 5 or 6 PEs of 50 mL/kg; IVIG (Sandoglobulin(R)) was dosed at 0.4 g/kg/day for 5 days.

Support for using immune globulin as prophylaxis against hemolytic disease of fetus or newborn due to RhD isoimmunization can be found in a study by de la Camara et al. IV immune globulin was effective as prenatal therapy following severe Rh immunization, improving the outcome of pregnancy, in two patients.

Support for using immune globulin to treat hemophagocytic syndrome can be found in a study by Freeman et al. Three pediatric patients with hemophagocytic syndrome were successfully treated with intravenous immune globulin (IVIG) 1 g/kg followed by packed RBCs. All patients had significant increases in their RBC counts and decreasing tissue enzyme values soon after infusion. While some investigators caution that IVIG should not be considered sole therapy for hemophagocytic syndrome, successful treatment of a 4 1/2-year-old patient with IVIG has also been reported.

Support for using immune globulin to induce factor VIII immune intolerance can be found in a study by Nilsson et al. Successful induction of immune tolerance was achieved with a combination of factor VIII, cyclophosphamide, and high-dose IV immune globulin, in patients with hemophilia A who had developed antibodies to factor VIII. Cyclophosphamide was given from day 1 of treatment in doses of 12 to 15 mg/kg/day IV for 2 days (first dose given immediately prior to infusion of factor A), followed by oral administration of 2 to 3 mg/kg/day for 8 to 10 days. Factor VIII was given initially in doses sufficient to neutralize the inhibitor and then to raise factor VIII coagulant activity to a concentration of 40 to 100 international units/dL; factor VIII was then administered in intervals of 8 to 12 hours to maintain factor VIII coagulant activity at a level of 30 to 80 international units/dL. When decreases in factor VIII coagulant activity were observed, the daily dose of factor VIII was increased by administration of highly purified commercial virus-inactivated factor VIII concentrates at shorter intervals. Immune globulin was given initially in doses of 2.5 to 5 g IV, immediately after the first loading dose of factor VIII; beginning on day 4 of treatment, immune globulin was administered in doses of 0.4 g/kg/day for 5 days. In addition, when concentrations of factor VIII inhibitors were high initially (greater than 3 Malmo inhibitor units/mL), the antibodies were first removed by extracorporeal adsorption to protein A. With this regimen, factor VIII coagulant antibodies disappeared in 9 of 11 patients with hemophilia A following 2 to 3 weeks of combined

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therapy, with the half-life of infused factor VIII normalizing in 8 of these 9 patients. Stabilization of the tolerant state was observed for a median of 30 months. These data suggest that the combination of all 3 components (cyclophosphamide, factor VIII and immune globulin) are required to achieve successful induction of tolerance to factor VIII. Prior therapy in the above patients with factor VIII and cyclophosphamide and with factor VIII and immune globulin had been ineffective.

Support for using immune globulin to treat moderate and severe immune checkpoint inhibitor-related toxicities can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

- As a further intervention for myocarditis if no improvement within 24-48 hours of starting high-dose methylprednisolone
- As an adjunct to rituximab for severe (G3) or life-threatening (G4) bullous dermatitis
- For Stevens-Johnson syndrome, or toxic epidermal necrolysis
- For moderate, severe, or life-threatening steroid-refractory myositis (proximal muscle weakness, neck flexor weakness, with or without myalgias) for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids
- As treatment for severe (G3-4) myasthenia gravis
- As treatment for moderate (G2) or severe (G3-4) Guillain-Barré Syndrome or severe (G3-4) peripheral neuropathy in combination with high-dose methylprednisolone
- As treatment for encephalitis in combination with high-dose methylprednisolone if severe or progressing symptoms (strongly consider if progressing over 24 hours)
- For demyelinating disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis)
- For moderate (G3) pneumonitis if no improvement after 48-72 hours of corticosteroids or severe (G3-4) pneumonitis if no improvement after 48 hours of methylprednisolone

Support for using immune globulin to treat hypogammaglobulinemia from CAR-T therapy can be found in the National Comprehensive Cancer Network's guideline for Management of Immunotherapy-Related Toxicities. The NCCN Guideline supports the use of immune globulin for the management of the below toxicities:

- For the management of G4 cytokine release syndrome that is refractory to high-dose corticosteroids and anti-IL-6 therapy
- After anti-CD19 CAR T-cell therapy as replacement for hypogammaglobulinemia in select patients (those with serum IgG levels <400-600 mg/dL and serious or recurrent infections [particularly bacterial]) until serum IgG levels normalize and infections resolve

Support for using immune globulin to treat herpes gestationis can be found in a study by Harman and Black. When administered as two courses over 5 weeks, intravenous immune globulin (IVIG) 400 mg/kg/day for 5 consecutive days induced a short-term remission and decreased the autoantibody titer in a 17-year-old female who was 6 months postpartum. Intolerant to corticosteroids, the patient required cyclosporine for long-term maintenance.

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Support for using immune globulin to prevent bacterial infections in HIV-infected patients can be found a report from the American Academy of Pediatrics. Intravenous immune globulin may be used for prevention of serious bacterial infections in HIV-infected pediatric patients with hypogammaglobulinemia. Use may also be considered in HIV-infected pediatric patients experiencing recurrent, serious bacterial infections (meningitis, bacteremia, pneumonia) over a 1-year period. However, in children receiving trimethoprim-sulfamethoxazole for Pneumocystis jiroveci infection (PCP) prophylaxis, IV immune globulin may not provide any additional benefit.

Support for using immune globulin to prevent bacterial infections in post-surgical or ICU patients can be found in a several studies. Siber et al conducted a double-blind, randomized, 3-arm study involving 329 ICU patients (Anon, 1992) to assess the prophylactic efficacy of hyperimmune anti-lipopolysaccharide intravenous immune globulin (IVIG) (400 mg/kg every week) or standard IVIG (400 mg/kg every week) to placebo. The adult patients were stratified by surgery type and were randomized to 1 of the 3 treatment groups. The number of patients in whom late onset infections developed was significantly lower in the standard IVIG group than in placebo (30 of 109 vs 53 of 112 patients, respectively), as was the incidence of pneumonia (15 vs 30). The number of days spent in ICU was also lower in the standard IVIG group. In contrast, the hyperimmune IVIG preparation had no detectable, prophylactic effect on infection. Investigators have commented that the inconsistent benefit of IVIG to prevent nosocomial infections is due to variable levels of antibodies in standard preparations.

Pilz and colleagues found early intravenous immune globulin (IVIG) treatment improves disease severity and may improve prognosis in prospectively score-identified high-risk postcardiac surgical patients. Patients (n=1341) at risk for sepsis after cardiac surgery were compared to 881 matched historical control patients. Patients were stratified according to risk for sepsis using a proven scoring system, APACHE (the Acute Physiology and Chronic Health Evaluation). They were treated with IVIG (Psomaglobin N: day 1 (8 mL/kg), day 2 (4 mL/kg); or Pentaglobin: days 1, 2, and 3 (5 mL/kg). Following IVIG administration, prompt and marked improvements in disease severity (i.e., a fall in APACHE score) were reported. Significantly higher score response rates, and a reduction in mortality as compared to control groups was noted, especially in the high-risk group. For the high-risk group receiving IVIG, the mean survival time of the nonsurvivors was 18.3 days as opposed to 8.3 days in the matched control group.

Support for using immune globulin to treat Isaacs syndrome can be found in a study by Ishii et al. Intravenous immune globulin (200 mg/kg/day; total 50 g) was found to worsen the symptoms of Isaac syndrome while an initial and repeat plasma exchange in a 41-year-old patient allowed symptoms to disappear for 2 to 3 weeks.

Support for using immune globulin to treat Japanese encephalitis virus disease can be found in a study by Caramello et al. In a case report, a 49-year-old man recovered from Japanese encephalitis (JE) following a 5-day course of intravenous immune globulin (IVIG). The patient was stuporose, somnolent, disoriented, febrile and had mild meningismus, photophobia and mild conjunctival hyperemia symptoms following a 3-week trip to rural Vietnam. Serologic tests via immunofluorescence were positive for JE. Saline and noncorticosteroid antiinflammatory therapy did not improve the patient's worsening confusion and agitation. On day 6 of hospitalization, a 5-day course of IVIG was initiated at 400 mg/kg, which generated symptom improvement after the first infusion. On day 23, the patient was discharged with no residual

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lesions and an EEG showed regression of theta-delta waves. One month later during follow-up, there was only a slight deficit in recent memory.

Support for using immune globulin to treat severe IgA nephropathy can be found in a study by Rostoker et al. A small, open prospective cohort study involving 11 patients with severe IgA nephropathy (9 with idiopathic disease and 2 with Henoch-Schonlein purpura) found a substantial decrease in proteinuria (5.2 g/day vs 2.25 g/day), hematuria and leukocyturia after intervention with IV immune globulin (2 g/kg/month x 3 months) and IM immune globulin (0.35 mL of 16.5%/kg every 15 days x 6 months). The decrease in GFR slowed or stopped and the staining intensity of glomerular IgA and C3 deposits also decreased.

Support for using immune globulin to treat lysinuric protein intolerance can be found in a case study by Dionisi-Vici et al. A 10-year-old boy with lysinuric protein intolerance, an autosomal recessive disease of defective intracellular protein transport, recovered after a single IV immune globulin dose of 1 g/kg. No relapses occurred over 2 years of follow-up.

Intravenous immunoglobulin (IVIG) has been shown to be ineffective for the prophylaxis of, and as a treatment adjunct in, infections in some high-risk, preterm, low-birth-weight neonates (USPDI, 2002). Studies published before 1990 suggested that prophylactic IVIG reduced nosocomial infections in low-birth-weight infants. However, these studies enrolled small numbers of patients; employed varied designs, preparations, and doses; and included diverse study populations. The National Institute of Child Health and Human Development (NICHHD) Neonatal Research Network therefore performed a prospective, multi-center, randomized trial to test the hypothesis that the intravenous administration of immune globulin to infants with birth weights between 501 and 1,500 grams would reduce the incidence of nosocomial infections (Fanaroff et al, 1994). In this trial, the repeated prophylactic administration of IVIG failed to reduce the incidence of nosocomial infections significantly in premature infants weighing 501 to 1,500 grams at birth. Furthermore, there were no significant differences in morbidity, mortality, or the duration of hospitalization between infants given IVIG and infants given no infusion or an infusion and placebo.

Support for using immune globulin to treat neonatal jaundice can be found in a study by Tanyer et al. Infants with isoimmune hemolytic jaundice who received multiple doses of intravenous immune globulin (IVIG) required less phototherapy than similar infants receiving a single dose or no IVIG. Sixty-one full-term babies with blood group incompatibility received multiple doses of IVIG 500 mg/kg, a single dose, or no IVIG, within 2 to 4 hours after admission for neonatal jaundice. All infants received phototherapy. Phototherapy was stopped when the bilirubin had decreased to a safe limit. In the multiple-dose group, there was no need for exchange transfusion (multiple dose vs single dose, p less than 0.05). Twelve percent of the babies in the single-dose group and 33% in the group without IVIG required exchange transfusions (p less than 0.05 and p less than 0.01, respectively compared to the multiple dose group). The duration of phototherapy was significantly less for the treated groups than for the untreated group (p less than 0.05).

Support for using immune globulin to treat otitis media can be found in a study by Ishikaza et al. Mean pneumococcal IgG and IgG2 antibody levels were significantly lower in 7 patients with recurrent acute otitis media as compared to healthy controls. They further found that following treatment with IV immune

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globulin (200 mg/kg every 4 weeks for 6 months), the antibody levels increased, and episodes of infection decreased. Gray conducted a 5-year, double-blind, multicenter trial. Hyperimmune bacterial polysaccharide immune globulin (BPIG) demonstrated some efficacy in children (less than 24 months) with 1 to 3 prior episodes of acute otitis media. The 76 children were randomized to receive either BPIG (0.5 mL/kg) or saline IM at entry into the study and 30 days later. During the 120-day follow-up period, the incidence of acute otitis media infections, documented by aspiration and culture of middle ear fluid, were similar in the BPIG and placebo groups. As expected, pneumococcal acute otitis media was significantly less frequent in the BPIG recipients (0.21 vs 0.45 episode/patient), and the time spent free of acute otitis media was longer in BPIG patients (51 vs 35 days). This study demonstrated that circulating antibody, even without stimulation of specific local immunity, may prevent infection of the middle ear.

Support for using immune globulin to treat paraneoplastic visual loss can be found in a study by Guy and Aptsiauri. In 2 out of 3 cases, patients with paraneoplastic visual loss benefited from intravenous immune globulin (IVIG) therapy. Marked improvement in visual acuity and visual field reported in a 62-year-old woman diagnosed with metastatic adenocarcinoma after treatment with IVIG therapy for a total dose of 2 g/kg over 5 days. Mixed results are seen in the following two cases: a 77-year-old woman presented with loss of vision on her left eye. She received IVIG 400 mg/kg over 5 days resulting in no change in light perception. A search for an occult malignant neoplasm revealed uterine cancer. A 71-year-old man diagnosed with adenocarcinoma of the pancreas with progressive loss of vision in his right eye received a dose of IVIG 400 mg/kg. He reported an improvement in the visual field defect in the right eye, with no change in visual acuity. Patient declined further treatment due to shortness of breath and itching.

Support for using immune globulin to treat pediatric Acute-onset Neuropsychiatric Syndrome (PANS)/pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS) can be found in a study by Melamed et al. Statistically significant improvements following IVIG treatment were demonstrated in all psychometric assessments and parent questionnaires including CY-BOCS (obsessive compulsive scale), YGTSS (tic scale) and a parent PANS rating scale (for all scales $p<0.001$). The fraction of pro-inflammatory monocytes and dendritic cells decreased from pre-IVIG treatment levels. The proportional reductions were not compensated by increases in total white blood cells; pro-inflammatory monocytes post-IVIG were decreased as a proportion of CD14+ myeloid cells and in absolute number.

Support for using immune globulin to treat polyarteritis nodosa can be found in a case report by Viguier, Guillevin and Laroche. Immune globulin therapy brought complete regression of parvovirus B19-associated polyarteritis nodosa in a 33-year-old woman. The women presented with asthenia, fever, palpable purpura, intense myalgia, paresthesias, and polyarthritis of the hand joints. Biopsies showed small- and medium-vessel vasculitis. Parvovirus B19-specific IgM and IgG antibodies and parvovirus DNA were found in serum. The patient was given IV immune globulin 1 g/kg/day for 2 days. Her condition had improved dramatically within a week, and a month later she was in complete clinical remission, although parvovirus B19 DNA was still detectable in her serum. Three years later she remained well.

Support for using immune globulin to treat polymyositis can be found in the guidelines published by European Federation of Neurological Societies (EFNS). As second-line treatment, IVIG can be considered as a treatment option in polymyositis.

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Support for using immune globulin to treat post-transplant lymphoproliferative disorder can be found in a study by Cantarovich et al. Two patients recovered from post-transplantation lymphoproliferative disorder (PTLD) after receiving a combination of intravenous immune globulin (IVIG) and interferon alpha-2b. A 60-year-old female initially developed this complication 2 months after cardiac transplant. The manifestations of PTLD over the next 5 months included liver, spleen, lung and nasopharyngeal nodules. A 65-year-old male experienced onset of PTLD 8 months after liver transplant, including subQ and liver nodules. Both patients received the combination of IVIG (0.5 g/kg every 15 days) and interferon-alpha-2b (2 million units subcutaneously 3 times/week) for a total of 4 to 12 months. Their times to complete recovery from PTLD were 3 and 7 months, respectively. Corresponding lengths of remission were 47 and 33 months, respectively.

Support for using immune globulin to treat pure red cell aplasia can be found in a study by McGuire et al. Intravenous immune globulin was used to treat a 12-month-old girl with antibody-medicated pure red cell aplasia. The response was gradual with a rise in reticulocyte count from 0.1% to 3.8% at 3 weeks and a peak count of 10.5% five weeks after initiation of therapy.

Support for using immune globulin to treat pyoderma gangrenosum can be found in a study published by Herberger and colleagues. The authors observed that corticosteroids and cyclosporine A are frequently ineffective as 1st-line therapies in the treatment of pyoderma gangrenosum (PG) and associated with a number of AEs. In a retrospective, dual-center, cohort study, these investigators examined the safety and effectiveness of biologics and IVIGs in the treatment of PG. A total of 52 patients (mean age of 58.4 years) with 75 wound episodes (mean wound size of 53.2 cm^2) were included in the study. Overall, 92.3 % of patients initially received corticosteroids (CSs; 48/52); 51.9 % cyclosporine A (CSA; 27/52). In 275 therapeutic attempts, complete remission or improvement were achieved in 63.6 % (21/33) of patients on infliximab; 57.1 % (16/28) on adalimumab; 71.4 % (5/7) on etanercept; 66.6 % (6/9) on ustekinumab, and 66.7 % (10/15) of patients who were given IVIGs. That figure was 48.8 % (38/78) for those treated with CSs and 20.0 % (7/35) for individuals on CSA. On average, AEs occurred in 18.5 % (15/81) of cases treated with biologics in 20 % (3/15) of patients receiving IVIGs, in 40 % (14/35) of individuals on CSA and in 10.4 % of those treated with CSs (5/48). The authors concluded that the present retrospective analysis suggested that both biologics (especially TNF-alpha antagonists) and IVIGs are well-tolerated and safe options in the treatment of PG. Moreover, these researchers stated that data from prospective comparative studies are highly desirable.

Support for using immune globulin to treat renal transplant rejection can be found in studies that investigated IVIG as an adjunct to plasmapheresis and IVIG alone. Lerich et al conducted a single-center, retrospective analysis of all kidney and kidney-pancreas transplant recipients (n=519) that found the 2-year graft survival was 78% in 23 patients who experienced acute humoral rejection (AHR) and treated with intravenous immune globulin (IVIG) and plasmapheresis (PP) compared with 94% in 415 patients who experienced no rejection. The review identified 23 patients (mean age, 45 years) who experienced AHR (median time to AHR, 6 days; range, 5 to 8 days) that was confirmed by biopsy (C4d positive) and/or serological evidence (donor-specific anti-human leukocyte antigen antibodies). Twenty-two of these 23 patients were treated with IVIG and PP; one patient received PP alone. Other concomitant treatments were pulse methylprednisolone (n=13) and Thymoglobulin or OKT3 (n=7). The dose of IVIG widely varied but was usually 2 g/kg administered after the last PP session. The PP session varied based on urine output

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and serum creatinine, with most patients receiving 4 (range, 3 to 6 days) daily sessions. Posttransplant maintenance immunosuppression drugs were tacrolimus or cyclosporine, in combination with mycophenolate and prednisone. The median time to rejection was 6 days (range, 3 to 14 days, except for 2 patients with AHR at days 147 and 843, respectively). Renal function improved in 20 of 23 patients after treatment. Hemodialysis was required in 2 of the remaining 3 patients and transplant nephrectomy was subsequently performed in 2 of the 3 patients who failed to respond to treatment. The 2-year graft survival rates were 78% and 94% (p=0.0002) for the AHR and no rejection groups, respectively; the corresponding 2-year patient survival rates were 95% and 98% (p=0.09), respectively. The final mean serum creatinine levels were 1.8 mg/dL (interquartile range (IQR), 1.4 to 2.6 mg/dL) and 1.6 mg/dL (IQR, 1.3 to 1.8 mg/dL) in patients with functioning grafts for the AHR and no rejection groups, respectively. No adverse reactions were reported.

Luke et al conducted a retrospective review of 17 patients who manifested steroid-resistant or anti-lymphocyte antibody-resistant rejection of renal transplants. IVIG 2 g/kg was administered over 2 to 10 days during each treatment course, according to fluid balance status of each patient. Four patients required 2 courses of IVIG, and 3 had 3 or more courses. IVIG , mycophenolate mofetil, and/or steroid cycle were administered in 10 patients and IVIG alone was administered to 7 patients. After a mean of 21 months after initiating IVIG , the patient survival rate was 95% and the graft survival rate was 71%. Nine of the 17 patients showed complete resolution of rejection and 5 showed reduced severity of rejection. Among the 4 patients with anti-lymphocyte antibody- resistant rejection, IVIG completely reversed rejection in 1 patient and reduced severity in 2 patients. Reduction or resolution of rejection was demonstrated in 6 of the 7 patients who received IVIG alone. In these 7 patients, the serum creatinine level was 2.2 +/- 0.9 mg/dL at baseline, 3.7 +/- 1.2 mg/dL during rejection, and 2.7 +/- 1.3 mg/dL 2 weeks after IVIG therapy.

Support for using immune globulin to treat central nervous system-predominant retinocochleocerebral vasculopathy (Susac syndrome (SuS)) can be found in the guidelines published by nternational Journal of Stroke. Treatment of central nervous system (CNS)-predominant SuS is dependent on initial severity. The treatment includes corticosteroid (pulse methylprednisolone (optional in mild severity), followed by oral prednisone), IVIG, one or two additional immunomodulating drugs (mycophenolate with or without tacrolimus (TAC), or cyclophosphamide (CPM) (not an option for mild severity)), and potential use of rituximab. For the treatment of extremely severe CNS SuS, IVIG provides added disease protection and reduces dependency on medications that pose greater side effect risks per the guideline view.

Support for using immune globulin to treat respiratory syncytial virus infection can be found in a study by Groothuis et al. The authors conducted a multicenter, blinded, and randomized study of respiratory syncytial virus-enriched IVIG (RSVIG) in 249 infants and children. The patients were born prematurely and were less than 6 months of age at the start of the 3-year study, had bronchopulmonary dysplasia, or congenital heart disease. During the RSV season, one group received 750 mg/kg/month, a second group received 150 mg/kg/month, and the third group received no therapy. The high-dose group had significantly fewer instances of moderate to severe RSV lower respiratory tract infections (72% less), fewer hospitalizations (63% less), fewer hospital days (63% less), fewer ICU days (97% less), and less ribavirin use than did the group receiving low-dose RSVIG or no therapy. Six deaths occurred, 3 in the low- and 3 in the high-dose group. No death, however, was attributable to RSVIG or to RSV illness.

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Support for using immune globulin to treat sepsis can be found in a meta-analysis by Turgeon et al. The authors conducted meta-analysis of randomized, controlled trials comparing intravenous immune globulin (IVIG) to either placebo or no intervention. IVIG significantly decreased mortality in critically ill adults with sepsis (n=2621). Based upon a pooled analysis of 20 systematically selected trials of IVIG verses either placebo or no intervention, IVIG significantly reduced mortality of adults with sepsis, severe sepsis, or septic shock (risk ratio (RR) 0.74, 95% CI, 0.62 to 0.89; p=0.001). Similar results were found in subanalysis of the peer-reviewed, published trials and the blinded trials. Sensitivity analysis revealed severity of sepsis, IVIG dose, and duration of therapy as sources of heterogeneity. Studies evaluating severely ill adults, with a diagnosis of severe sepsis or septic shock, achieved significantly greater mortality benefit from IVIG use (RR 0.64, CI, 0.52 to 0.79; p less than 0.001) versus either placebo or no intervention, whereas studies evaluating less severely ill subjects, with a diagnosis of sepsis, did not show a mortality benefit (RR 0.89, CI, 0.71 to 1.10; p=0.25). Doses of IVIG 1 g or more per kilogram showed a significant mortality benefit versus doses less than 1 g per kilogram (RR 0.61, CI, 0.4 to 0.94; p=0.02 and RR 0.79, CI, 0.64 to 0.97; p=0.08, respectively). Duration of IVIG therapy longer than 2 days significantly reduced mortality risk (RR 0.66, CI, 0.53 to 0.82; p less than 0.002); however, IVIG therapy duration of 2 days or less showed no survival benefit over either placebo or no intervention (RR 0.98, CI, 0.74 to 1.29; p=0.86). No difference was detected between the IVIG group and the placebo or no intervention group for the secondary endpoints of length of stay in the intensive care unit or duration of mechanical ventilation.

A recent guideline published by the Surviving Sepsis campaign states IV immunoglobulins are not suggested for patients with sepsis or septic shock (weak recommendation; low quality of evidence).

Support for using immune globulin to treat Stevens-Johnson syndrome and toxic epidermal necrolysis can be found in the European guidelines on the use of high-dose intravenous immunoglobulin in dermatology (Enk et al). High-dose IVIG can be considered for confirmed Stevens-Johnson syndrome and toxic epidermal necrolysis. IVIG should be given as soon as SJS/TEN is diagnosed. In contrast, the British Guidelines for the management of SJS/TEN indicates there is insufficient evidence to support or refute benefit of IVIG in this scenario (McPherson et al).

Support for using immune globulin to treat Stiff-person syndrome can be found in a study by Dalakas. Intravenous immune globulin (IVIG) reduced stiffness parameters and factors of heightened sensitivity in patients (N=16) with stiff-person syndrome unresponsive to other agents. The mean age of study participants was 47 years (9 women, 7 men). Patients were incompletely responding to therapies. At enrollment, all patients were receiving benzodiazepines, 6 were receiving baclofen, 3 gabapentin, and 1 patient was receiving valproic acid. Doses remained unchanged throughout the study. Patients were otherwise balanced with regard to disease duration, onset of symptoms, disease severity, and other associated conditions. Immune globulin 2 g/kg IV, divided in 2 daily doses, or placebo (half-normal saline) was administered every month for 3 months. After a washout period of 1 month, the patients crossed over to the alternative therapy for another 3 months. All patients were followed for at least 3 months after the infusions. The mean number of stiff areas in the placebo group remained constant during the first 4 months but then dropped significantly in the next 3 months, after cross over. The scores of the IVIG group dropped in the first 3 months, remained constant during the wash-out period and rebounded from months 5 through 8 but never reached baseline. There was a significant difference in changes in the stiff areas between the 2 groups for the direct treatment effect on the month following each infusion and the first

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order carry-over effect (residual effects after 3 monthly infusions). Subanalysis of each of the stiffness areas showed a significant reduction of the stiffness in the trunk, abdomen, and the face. The duration of benefit varied from 6 to 12 weeks or up to a year. Change in the scores of distribution of stiffness index (total = 6) and heightened sensitivity (total = 7) from baseline to the 2nd and 3rd month were obtained after each treatment. The net differences in the stiffness index and heightened sensitivity scores from baseline to the end of 3 months of treatment and the first or second carry-over effects were compared between the patients randomized to the 2-treatment group for each period.

Support for using immune globulin to treat systemic lupus erythematosus can be found in the EULAR guidelines (Fanouriakis et al). Immune globulin is suggested for acute treatment of systemic lupus erythematosus-associated thrombocytopenia, as well as in cases with inadequate response to high-dose glucocorticoids, or to avoid glucocorticoid-related infections.

Support for using immune globulin to treat systemic onset juvenile chronic arthritis can be found in a study by Vignes et al. An uncontrolled pilot study (n=7) reported a 71% response rate for intravenous immune globulin (IVIG) therapy of adult onset Still disease refractory to monotherapy with nonsteroidal inflammatory agents. Patients received IVIG 2 g/kg over 2 or 5 days every 4 weeks for up to 6 cycles. Two patients did not respond to IVIG but achieved remission with oral prednisone. Of 5 responders, 1 patient relapsed after 5 months. The remaining 4 patients continued in remission for 11 to 53 months without additional IVIG.

Support for using immune globulin to treat systemic vasculitis can be found in a study by Jayne et al. IV immune globulin was effective in treating systemic vasculitis in 7 patients. Immune globulin 0.4 g/kg/day for 5 days was administered. Decreases in antineutrophil cytoplasm antibodies and C-reactive protein were observed which lasted for up to 100 days. Two of these patients had their immunosuppressive therapy discontinued prior to treatment with immune globulin, 2 other patients had not been previously treated, and the remaining patients continued other therapy during the study. The effect of immune globulin was only transient in one patient.

Support for using immune globulin to treat fetal or neonatal thrombocytopenia can be found in a study by Bussel et al. Antenatal therapy with IV immune globulin (1 g/kg over 4 to 7 hours weekly), with or without dexamethasone 3 to 5 mg daily, was reported effective in increasing fetal platelet counts in severe neonatal alloimmune thrombocytopenia. In this study, 7 pregnant women were treated with immune globulin (5 also received dexamethasone). All patients had previously had infants with severe alloimmune thrombocytopenia. Periumbilical blood sampling performed in 6 fetuses demonstrated increases in platelet counts by a mean of 72.5 x 10(9)/L. Platelet counts were above 30 x 10(9)/L at birth in all 7 treated fetuses, and no cases of intracranial hemorrhage were observed; all of the 7 infants who were untreated had lower platelet counts, with 3 developing intracranial hemorrhage (antenatal in 2 infants). Mild intrauterine growth retardation was observed in 1 treated infant (whose mother received dexamethasone concurrently), and oligohydramnios occurred in 4 dexamethasone-treated patients during the third trimester. However, all 7 infants developed normally during follow-up of 2 months to 4 years following birth. Percutaneous umbilical blood sampling should be performed at 20 to 22 weeks gestation in women who have previously delivered an infant with alloimmune thrombocytopenia and a platelet count under 30 x 10(9)/L at birth; IV immune globulin therapy is recommended weekly if the fetal platelet count drops below 100 x 10(9)/L. Sampling should be repeated 4 to 6 weeks later to evaluate effects of treatment. In

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the case of treatment failure, early Caesarean section is the primary alternative, although selective platelet transfusion may also have a role.

Support for using immune globulin to treat toxic necrotizing fasciitis and toxic shock syndrome can be found in a study by Darenberg et al. In a double-blind, placebo-controlled trial of 21 patients with streptococcal toxic shock syndrome caused by severe invasive group A streptococci infection, with or without necrotizing fasciitis, there was a 3.6-fold lower mortality rate at 28 days in patients receiving adjunctive therapy of intravenous immune globulin (IVIG) compared to placebo. The study randomized patients to receive either IVIG 1 g/kg on day 1, followed by 0.5 g/kg on days 2 and 3, or to the placebo group receiving 1% albumin. Adjunctive therapy consisted of clindamycin 600 mg IV 3 times daily plus benzylpenicillin 12 g/day or cefuroxime 1.5 g 3 times per day in penicillin allergic patients. The study was terminated prematurely due to slow patient recruitment. Primary endpoint analysis demonstrated the morality rate at day 28 as 1 patient in the IVIG group (n=10), and in 4 patients in the placebo group (n=11). There were no significant differences in secondary endpoint analysis: time to resolution of shock in the survivors (mean of 88 hours vs 122 hours), or mortality at day 180 (2 vs 4 patients) in the IVIG and placebo groups, respectively.

Support for using immune globulin to treat heart transplant rejection can be found in a study by Jordan et al (1998). Rapid improvement in treating antibody-mediated allograft rejection is reported within 2 to 5 days after high-dose intravenous immune globulin (IVIG) (2 g/kg) treatment in all 10 patients in the study. IVIG also contains anti-idiopathic antibodies that are potent inhibitors of donor-specific human leukocyte antigen alloantibodies, thus preventing organ rejection episodes.

Support for using immune globulin to desensitize a highly sensitized patient awaiting renal transplantation can be found in a study by Jordan et al (2004). Successive, pretransplant treatments with high-dose intravenous immunoglobulin (IVIG) in highly sensitized patients with ESRD significantly improved the transplantation rate and time to transplantation compared with placebo in the multicenter, randomized, double-blind National Institutes of Health (NIH) IG02 trial (n=98). Highly sensitized adults (panel reactive antibody (PRA), 50% or greater every month for 3 months; mean age, 40.7 years; range, 20 to 73 years; 57% female) were randomized to receive pretransplant infusions of either IVIG 2 g/kg (maximum, 180 g; Gamimune(R) N 10% SD) (n=48; prior transplant, 73%) or placebo (n=50; prior transplant, 58%) every month for 4 months. If not transplanted after 4 months, additional infusions were given at 12 and 24 months, with follow-up until 30 months. If transplanted after 4 months, patients received additional blinded infusions monthly for 4 months. The mean PRA 1 to 3 months before study entry was approximately 80% or higher. Six patients (nonadherent group) were excluded from the analysis because they either failed to initiate therapy (n=4) or received crossover therapy (n=2; assigned to placebo but received IVIG). Among the dosing-adherent group (n=92), the transplantation rate in the IVIG group (35%; 16 of 46) was twice that in the placebo group (17%; 8 of 46) (p=0.048). Among patients who had received a previous transplant, transplantation rates were 22% (10 of 34) and 7% (3 of 28) in the IVIG and placebo groups, respectively. In addition, pretreatment with IVIG significantly reduced time to transplantation compared with placebo (p=0.049), and this improvement remained significant after adjusting for receipt of previous transplantation (p=0.034). The projected mean time to transplantation (assuming constant hazard rate) was estimated to be 4.8 years for IVIG compared with 10.3 years for placebo. Pretransplant treatment with IVIG significantly reduced mean PRA levels for IgG plus IgM (p=0.033) and IgG alone

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(p=0.007) relative to placebo; however, the mean PRA at each time point during the study period was greater than 40%. Notably, PRA levels returned to near baseline at 6 months following IVIG infusion. Among all transplant recipients (includes 3 patients from the nonadherent group), significantly more acute rejection episodes occurred in the IVIG group (9 of 17) than the placebo group (1 of 10) (p=0.042). However, among the dosing-adherent transplant recipients, graft failure rates during the 30-month follow-up period (25% vs 38%, respectively) and 2-year graft survival rates (80% vs 75%, respectively) were similar in the IVIG and placebo groups. Overall, IVIG was well tolerated; the incidence of headache was greater with IVIG compared with placebo (52% vs 30%).

Support for using immune globulin to treat uveitis can be found in a study by LeHoang et al. Use of intravenous immune globulin (IVIG) provided a safe and effective therapy for patients with birdshot retinochoroidopathy, a bilateral autoimmune posterior uveitis. For induction therapy, patients (n=18) received IVIG 0.4 g/kg/day for 4 days every 4 weeks for 6 months. Thereafter, patients received IVIG 1.2 to 1.6 g/kg over 2 to 4 days at 6 to 8 week intervals. Within the first 3 months, patients experienced visual field improvements and within 2 to 6 months, improvements in visual acuity and macular edema improved. After 6 months, in the 26 eyes with a visual acuity of 20/30 or less, 14 eyes improved by at least 2 lines and 2 eyes deteriorated. In 5 patients with an initial visual acuity of 20/25, visual acuity increased to 20/20 in 4 and remained unchanged in 1. In 5 eyes with an initial acuity of 20/20, 4 remained stable and 1 deteriorated. Initially macular edema was present in 23 eyes with 17 eyes showing a decrease in macular edema on fundus fluorescein angiograms after 6 months. After a mean follow-up period of 39 months, 33 out of 36 eyes continued to show improved or stable visual acuity.

Support for using immune globulin to treat von Willebrand disorder can be found in two case studies. Intravenous immune globulin (IVIG) was efficacious when administered to a 47-year-old man with acquired Von Willebrand syndrome (Hanley et al). A 5-day course of IVIG 400 mg/kg/day was administered prior to orthopedic surgery and anticoagulation treatment was continued following surgery. At 7 days following the IVIG course, there was normalization of clotting factors and von Willebrand factors/cofactors.

Sampson et al reported temporary restoration of von Willebrand factor with control of bleeding episodes in a 75-year-old man diagnosed with acquired type 2a von Willebrand disease. This patient has received repeated treatments of intravenous immune globulin (IVIG) 30 g/day for 5 days after each bleeding episode over the past 3 years.

Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (cicatricial pemphigoid) and epidermolysis bullosa acquisita are covered according to the conditions outlined in National Coverage Determination Manual section called Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases (250.3- Version 1).

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