AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Parenteral Immunoglobulins

Number: 0206

Policy

I. Aetna considers the use of intravenous immunoglobulin (IVIG) therapy medically necessary in members with the conditions specified below:

- Acquired red cell aplasia
- Acute disseminated encephalomyelitis (see Appendix)
- Autoimmune mucocutaneous blistering diseases: IVIG is considered medically necessary for members with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (a.k.a., cicatrical pemphigoid), and epidermolysis bullosa acquisita if the member has either failed or has contraindications to conventional therapy, or the member has rapidly progressive disease in which a clinical response could not be affected quickly enough using conventional agents. When indicated for rapidly progressive disease, accepted guidelines indicate that IVIG should be given along with conventional treatment(s) and IVIG should be used only until conventional therapy could take effect. (See Appendix) Note: IVIG for the treatment of autoimmune mucocutaneous blistering disease is considered medically necessary only for short-term therapy and not as a maintenance therapy
- B-cell chronic lymphocytic leukemia (CLL): For persons with hypogammaglobulinemia associated with CLL and recurrent infections or specific antibody deficiency (see Appendix)
- Birdshot (vitiligenous) retinochoroidopathy (see Appendix)
- Chronic inflammatory demyelinating polyneuropathy (see Appendix)
- Churg-Strauss Syndrome (CSS) (allergic granulomatosis), adjunctive therapy for persons with severe active illness for whom other interventions have been unsuccessful, have become intolerable, or are contraindicated
- Dermatomyositis, adjunctive therapy in persons who have had an inadequate response to first and second line therapies (see Appendix)
- Enteroviral meningoencephalitis (see Appendix)
- Guillain-Barré syndrome (GBS) and GBS variants: IVIG is generally accepted as the treatment of choice for persons with Guillain-Barre syndrome, provided that they are so severely affected that they at least require aid to walk, that the disorder is diagnosed during the first 2 weeks of the illness, and that there are no contraindications to IVIG (see Appendix)
- Hemolytic disease of newborn, to decrease need for exchange transfusion (see Appendix)
- HIV infected children: Bacterial control or prevention (see Appendix)
■ HIV-associated thrombocytopenia, pediatric or adult: Considered medically necessary when criteria in Appendix are met (see Appendix)

■ Hyperimmunoglobulinemia E syndrome: For treatment of severe infection (see Appendix)

■ Immune or idiopathic thrombocytopenic purpura (ITP) when a rapid rise in the platelet count is required, such as prior to surgery, to control excessive bleeding, or to defer or avoid splenectomy (see Appendix for criteria for ITP in adults, ITP in children, chronic ITP, and ITP in pregnancy)

■ Kawasaki disease (see Appendix)

■ Lambert-Eaton myasthenic syndrome (see Appendix)

■ Moersch-Woltmann (Stiff-man) syndrome (unresponsive to other therapies) (see Appendix)

■ Multifocal motor neuropathy: For persons who have progressive, symptomatic multifocal motor neuropathy that has been diagnosed on the basis of electrophysiologic findings that rule out other possible conditions that may not respond to this treatment (see Appendix)

■ Multiple myeloma (see Appendix)

■ Myasthenia gravis (see Appendix)

■ Neonatal alloimmune thrombocytopenia (NAIT) (also known as fetal alloimmune thrombocytopenia or FAIT) (see Appendix)

■ Neonatal hemochromatosis, prophylaxis (see Appendix)

■ Opsoclonus-ataxia associated with neuroblastoma (see Appendix)

■ Paraneoplastic opsoclonus-ataxia associated with neuroblastoma (see Appendix)

■ Polymyositis in persons who are resistant to first and second line therapies

■ Post-transfusion purpura (see Appendix)

■ Primary humoral immunodeficiency diseases (such as congenital agammaglobulinemia (X-linked agammaglobulinemia), hypogammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyperimmunoglobulin M, Wiscott-Aldrich syndrome, immunodeficiency with thymoma (Good syndrome), hyper IgM syndromes, and severe combined immunodeficiency) (see Appendix)

■ Rasmussen encephalitis (Rasmussen's syndrome) (see Appendix)

■ Refractory autoimmune hemolytic anemia (see Appendix)

■ Relapsing-remitting multiple sclerosis (MS) when standard approaches (i.e., interferons) have failed, become intolerable, or are contraindicated (see Appendix) (See also CPB 0264 - Multiple Sclerosis)

■ Respiratory syncytial virus infection

■ Renal transplantation from live donor with ABO incompatibility or positive cross-match, where a suitable non-reactive live or cadaveric donor is unavailable (preparative regimen)

■ Secondary immunosuppression associated with major surgery (such as cardiac transplants) and certain diseases (extensive burns, or collagen-vascular diseases) (see Appendix)

■ Selective IgG subclass deficiencies with severe infection for persons meeting selection criteria (see Appendix)
■ Solid organ transplantation, for suppression of panel reactive anti-HLA antibodies in persons with high panel reactive antibody (PRA) levels to human leukocyte antigens (HLA) prior to transplantation, and for treatment of antibody mediated rejection of solid organ transplants

■ Staphylococcal toxic shock syndrome (see Appendix)

■ Stem cell or bone marrow transplantation: IVIG is indicated for prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL), who have primary immunodeficiency diseases, or who have CMV, EBV, or RSV infection (see Appendix and CPB 0544 - Immune Globulins for Post-exposure Prophylaxis). IVIG is also indicated for steroid-resistant graft-versus-host disease in bone marrow transplant recipients 20 years of age or older, in the first 100 days post-transplant, and who are hypogammaglobulinemic (IgG level less than 400 mg/dL).

■ Systemic lupus erythematosus (SLE), for persons with severe active SLE for whom other interventions have been unsuccessful, have become intolerable, or are contraindicated (see Appendix)

■ Toxic epidermal necrolysis and Steven-Johnson syndrome (see Appendix)

■ Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus (see Appendix).

II. Aetna considers subcutaneously administered immunoglobulins as an alternative to intravenous immunoglobulin therapy medically necessary for members who meet the criteria for IVIG set forth above.

III. Aetna considers intramuscularly administered immunoglobulins (e.g., GamaSTAN S/D) medically necessary as an alternative to intravenous immunoglobulin therapy for conditions associated with hypogammaglobulinemia that meet the criteria for IVIG set forth above. Intramuscular formulations of immune globulin are also considered medically necessary for the following indications: prophylaxis of hepatitis A; prevention or modification of measles (rubeola) in persons exposed fewer than 6 days previously; passive immunization against varicella in immunosuppressed patients; and prophylaxis of rubella in pregnancy when therapeutic abortion is not an option. See CPB 0544 - Immune Globulins for Post-exposure Prophylaxis.

IV. Aetna considers the use of IVIG experimental and investigational for all other clinical conditions because its effectiveness for indications other than the ones listed above has not been established. See Appendix for a current list of such indications (not an all-inclusive list).

V. Least Cost Medically Necessary Brands of Parenteral Immunoglobulins:

There are several brands of parenteral immunoglobulins on the market (see appendix). There is a lack of reliable evidence that any one brand of parenteral immunoglobulin is superior to other brands for medically necessary indications. Gammaplex brand of parenteral immunoglobulin ("least cost brand of parenteral immunoglobulin") is less costly to Aetna. Consequently, because other brands (e.g., Bivigam, Carimune, Glebogamma, Gammagard, Gammaked, Gammar, Gamunex, Hizentra, HyQvia, Ivecgam, Octogam, Panglobin, Polygam, Privigen) of parenteral immune globulin are more costly than the alternative least cost brand of parenteral immune globulin that is at least as likely to produce equivalent therapeutic results as to the treatment of the member's disease, under some Aetna plans, other brands of parenteral immune globulin will be considered not medically necessary unless the member has a contraindication or intolerance to the least cost brand of parenteral immune globulin. If the least cost brand of parenteral immune globulin does not have the labeled indication (see appendix), then Aetna considers medically necessary another brand of parenteral immune globulin that has the required labeling indication. Other brands of Parenteral Immune globulin will be allowed to be grandfathered with their previous use history.

Notes: The following criteria are considered in assessing the medical necessity of IVIG for the indications listed above.
1. Clinical monitoring takes clear precedence over laboratory monitoring. IVIG therapy should primarily be guided by clinical improvement.

2. In some situations, IVIG may be used for medically necessary indications listed above for a person that has rapidly progressive disease in which a clinical response could not be effected quickly enough using conventional agents. In these situations, IVIG therapy would be given along with conventional treatment(s) and continued administration of IVIG is not considered medically necessary once conventional therapy takes effect and the patient is stabilized.

3. Once treatment is initiated, there must be adequate documentation of progress. If there is initial improvement, and continued treatment is necessary, then some type of objective quantitative assessment to monitor the progress is required, when applicable. Any accepted metric assessment may be used for objective monitoring of progress, such as the Inflammatory Neuropathy Cause and Treatment (INCAT) scale*, the Medical Research Council (MRC) scale ** and activities of daily living (ADL) measurements. Changes in these measures should be clearly documented. Subjective or experiential improvement alone is generally insufficient to either continue IVIG, except for diseases where there is no accepted objective metric.

4. Previous treatment failures must be documented. (This would not apply to primary immunodeficiencies diagnosed at birth.)

5. The diagnosis of the disorder must be reasonably certain, and based on a thorough history and examination, and appropriate laboratory testing (e.g., electromyography (EMG), spinal fluid tests, serum tests and biopsy findings).

6. There should be, depending on the diagnosis and clinical circumstances, an attempt made to decrease/wean the dosage when improvement has occurred. There should be, when clinically appropriate for the diagnosis, an attempt to stop the IVIG infusion if improvement is sustained with dosage reduction. If improvement does not occur with IVIG, continued infusion may not be considered medically necessary. (This does not apply to persons with primary immune deficiency diseases.)

* The Inflammatory Neuropathy Cause and Treatment (INCAT) scale is used to access functional disability of both upper and lower extremity components in chronic inflammatory demyelinating polyneuropathy (CIDP). The INCAT scale has upper and lower extremity components, with a maximum of 5 points for the upper extremity (arm disability) and a maximum of 5 points for the lower extremity (leg disability), which add up to a maximum of 10 points (where 0 is normal and 10 is severely incapacitated). The INCAT scores may be used to evaluate the effectiveness and need for IVIG. IVIG may be discontinued when there is a lack of clear clinical improvement (i.e., a decline in INCAT disability score or failure to improve by 1 point at 6 weeks following the initial infusion or return to baseline at anytime following initial improvement of 1 point).

** The Medical Research Council (MRC) scale is used to grade muscle strength. Scale: 0 = no muscle movement; 1 = flicker of muscle movement; 2 = trace movement but not able to fully overcome gravity; 3 = just able to overcome gravity, but not against resistance; 4 = moves against resistance, but weak; 5 = full strength against resistance.

For IVIG for rubella (German measles), see CPB 0544 - Immune Globulins for Post-exposure Prophylaxis.

Background

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 (NICHD) 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.

For a discussion of IVIG for recurrent spontaneous abortion, see CPB 0348 - Recurrent Pregnancy Loss.

Several brands of IVIG have been approved by the Food and Drug Administration (FDA) (see table in Appendix). There is a lack of reliable evidence that any one brand of IVIG is more effective than other brands. However, immune globulin products may differ from each other in ways that may be important in a particular patient. Different manufacturers then use various combinations of precipitation and/or chromatography steps to obtain a final preparation that consists of greater than 95 % IgG in all currently available products. The various manufacturers also use different final purification steps and stabilizers to obtain their final products, which may then vary in storage requirement and shelf life. In several currently available products, stabilizers include sugars, such as sucrose, glucose, or maltose. Other products contain amino acids such as glycine and proline. The sodium content of different products also varies.

Most products approximate the distribution of IgG subclasses found in normal plasma. However, products are neither standardized nor routinely tested for their content of specific antibodies against different pathogens, except for measles, poliovirus, and hepatitis B surface antigen.

Thus, product-to-product and lot-to-lot variation in specific antibody titers is likely. There are also product-to-product and lot-to-lot variations in adverse effects in individual patients. Thus, generic substitution is not acceptable for many patients. In contrast, the different preparations are generally assumed to have overall equivalent therapeutic efficacy in protecting antibody deficient patients against infection.

Specific patients may require, or do better with, IGIV products with certain characteristics. Most patients tolerate most products with a minimum of adverse events, or with simple premedications. Thus, for many patients, selection of a product to conform with local dispensing or formulary preferences may not pose problems. However, some patients experience a different range and/or severity of adverse effects from different products, which may be impossible to predict.

If a patient is having adverse effects that interfere with IgG replacement, different products should be tried in the hope of finding a product that will be more acceptable. However, adverse effects may be more frequent and/or more severe whenever a patient is first started on IGIV and whenever a new product is used. For this reason, extra caution should be used when starting a naïve patient or changing the specific product used by any individual patient.

Some patients require products low in IgA, or products with relatively lower osmolarity, sucrose, or sodium. Patients with diabetes who use certain types of glucose meters must use caution with maltose-containing products, since that sugar may give false readings for glucose. Some preparations may have as much as 30 mg/ml (3 %) albumin, in addition to the IgG itself. This may be undesirable in patients who might have trouble tolerating increased intravascular volume.

The first type of IgG preparation to be used for antibody replacement, 16 % Immune Serum Globulin (ISG) for intra-muscular (IM) administration is still available. However, the IM route is rarely used at the present time because the injections are painful, the amount given is limited by the volumes that can be administered, and there is risk of local injury, such as nerve damage.

Immune globulin may also been given by the subcutaneous route. Immune globulin may be administered by a subcutaneous injection via a small, portable pump for the prevention of serious infection in children and adults with primary immunodeficiency. Many patients can be readily taught to infuse themselves at home, or parents may administer the infusions to their children.

In April 2006, the American Academy of Asthma, Allergy and Immunology (Orange et al, 2006) published evidence based guidelines on indications for intravenous immunoglobulins.

Darabi et al (2006) noted that IVIG has been approved by the FDA for use in 6 conditions: (i) immune thrombocytopenic purpura (ITP), (ii) primary immunodeficiency, (iii) secondary immunodeficiency, (iv) pediatric HIV infection, (v) Kawasaki disease, and (vi) prevention of graft-versus-host disease (GVHD) and infection in bone marrow transplant recipients. IVIG has subsequently been approved by the FDA for chronic inflammatory demyelinating polyneuropathy (CIDP). However, most usage of IVIG is for off-label indications, and for some of these comprehensive guidelines have been published. Common off-labeled uses for IVIG include chronic neuropathy (e.g., multi-focal motor neuropathy), hypogammaglobulinemia, renal transplant rejection, myasthenia gravis, Guillain-Barre syndrome,
necrotizing fasciitis, and autoimmune hemolytic anemia. The authors concluded that only a few indications account for most of the usage for IVIG. Reports concerning IVIG continue to grow at a tremendous pace but few high-quality randomized controlled studies have been reported.

In a review on autism, Levy et al (2009) stated that popular biologically based treatments include anti-infectives, chelation medications, gastrointestinal medications, hyperbaric oxygen therapy, and IVIGs. Non-biologically based treatments include auditory integration therapy, chiropractic therapy, craniosacral manipulation, interactive metronome, and transcranial stimulation. However, few studies have addressed the safety and effectiveness of most of these treatments.

Whittington and Kelly (2008) stated that neonatal hemochromatosis (NH) is the result of severe fetal liver injury that seems to result from maternal-fetal alloimmunity. Women who have had an infant affected with NH are at high-risk in subsequent pregnancies for having another affected infant. This study was designed to examine if therapy directed at limiting the severity of gestational alloimmunity can reduce the occurrence of severe NH in infants of women at risk. A secondary objective was to use a prospectively collected data set to examine questions of vital interest about NH. Women with a history of pregnancy ending in documented NH were treated with IVIG at 1 g/kg of body weight weekly from the 18th week until the end of gestation. Extensive data were prospectively collected regarding the gestational histories of the subjects. The outcomes of treated pregnancies were compared with those of previous affected pregnancies, which were used as historical controls. A total of 48 women were enrolled to be treated during 53 pregnancies. The gestational histories of these women demonstrated the high-risk of occurrence of NH: 92% of pregnancies at risk resulted in intrauterine fetal demise, neonatal death, or liver failure necessitating transplant. In contrast, with gestational therapy, the 53 at-risk gestations resulted in 3 failures and 52 infants who survived intact with medical therapy alone. When compared on a per-woman or per-infant basis, the outcome of gestation at risk for NH was improved by gestational therapy. The authors concluded that NH seems to be the result of a gestational alloimmune disease, and occurrence of severe NH in at-risk pregnancies can be significantly reduced by treatment with high-dose IVIG during gestation.

In this regard, the Australian National Blood Authority (Gibson et al, 2007) listed NH as one of the conditions for which IVIG has an established therapeutic role. According to the Australian agency, women who are pregnant or attempting to conceive and their most recent pregnancy ended in delivery of a fetus shown to have had NH are qualified for IVIG therapy. Dosage should be 1g/kg body weight weekly from the 18th week until the end of gestation.

Anderson et al (2007) noted that to help ensure IVIG use is in keeping with an evidence-based approach to the practice of medicine, the National Advisory Committee on Blood and Blood Products of Canada (NAC) and Canadian Blood Services convened a panel of national experts to develop an evidence-based practice guideline on the use of IVIG for hematologic conditions. The mandate of the expert panel was to review evidence regarding use of IVIG for 18 hematologic conditions and formulate recommendations on IVIG use for each. A panel of 13 clinical experts and 1 expert in practice guideline development met to review the evidence and reach consensus on the recommendations for the use of IVIG. The primary sources used by the panel were 3 recent evidence-based reviews. Recommendations were based on interpretation of the available evidence and where evidence was lacking, consensus of expert clinical opinion. A draft of the practice guideline was circulated to hematologists in Canada for feedback. The results of this process were reviewed by the expert panel, and modifications to the draft guideline were made where appropriate. This practice guideline provided the NAC with a basis for making recommendations to provincial and territorial health ministries regarding IVIG use management. Specific recommendations for routine use of IVIG were made for 7 conditions including acquired red cell aplasia; acquired hypogammaglobulinemia (secondary to malignancy); fetal-neonatal alloimmune thrombocytopenia; hemolytic disease of the newborn; HIV-associated thrombocytopenia; idiopathic thrombocytopenic purpura; and post-transfusion purpura. Intravenous immune globulin was not recommended for use, except under certain life-threatening circumstances, for 8 conditions including acquired hemophilia; acquired von Willebrand disease; autoimmune hemolytic anemia; autoimmune neutropenia; hemolytic transfusion reaction; hemolytic transfusion reaction associated with sickle cell disease; hemolytic uremic syndrome/thrombotic thrombocytopenic purpura; and viral-associated hemophagocytic syndrome. Intravenous immune globulin was not recommended for 2 conditions (aplastic anemia and hematopoietic stem cell transplantation) and was contraindicated for 1 condition (heparin-induced thrombocytopenia). For most hematologic conditions reviewed by the expert panel, routine use of IVIG was not recommended.
Goebel et al (2010) evaluated the effectiveness of IVIG in patients with longstanding complex regional pain syndrome (CRPS) under randomized, controlled conditions. Patients who had pain intensity greater than 4 on an 11-point (0 to 10) numerical rating scale and had CRPS for 6 to 30 months that was refractory to standard treatment were enrolled in this study. Subjects received IVIG (0.5 g/kg) and normal saline in separate treatments, divided by a washout period of at least 28 days. The primary outcome was pain intensity 6 to 19 days after the initial treatment and the cross-over treatment. A total of 13 eligible participants were randomly assigned and 12 completed the trial. The average pain intensity was 1.55 units lower after IVIG treatment than after saline (95% confidence interval [CI]: 1.29 to 1.82; p < 0.001). In 3 patients, pain intensity after IVIG was less than after saline by 50% or more. No serious adverse reactions were reported. The drawbacks of this study were that the trial was small, and recruitment bias and chance variation could have influenced results and their interpretation. The authors concluded that IVIG (0.5 g/kg) can reduce pain in refractory CRPS. They stated that confirmatory trials are required to ascertain the best immunoglobulin dose, the duration of effect, the need for repeat treatment, and whether treatment response varies with disease duration.

Diabetic amyotrophy usually occurs in patients with poorly controlled diabetes, either as an initial presentation or in a patient with longstanding disease. The mechanism of diabetic amyotrophy is uncertain, although peri-vascular inflammation and secondary nerve infarction are thought responsible. A recent consensus statement from the American Academy of Neurology (AAN) concluded that there is "no convincing data" to substantiate the treatment of diabetic amyotrophy using IVIG (Donofrio et al, 2009).

O’Horo and Safdar (2009) stated that Clostridium difficile (C. difficile) is the most common infectious cause of nosocomial healthcare-associated diarrhea. The increasing prevalence of C difficile, spread in the community, virulence and frequent relapse has created an urgent need to identify new effective treatments for C. difficile infection. Among these, IVIG is used for cases of severe C. difficile infection. These investigators undertook a systematic review to examine the published literature pertaining to the use of immunoglobulin for C. difficile infection. Four retrospective studies and 5 case reports that addressed the use of IVIG for the treatment of C. difficile infection were identified. One study on the use of oral immunoglobulin was identified. Although overall there appear to be benefits to using IVIG in recurrent severe disease, the small sample sizes and lack of control groups in 3 of the 4 studies do not allow recommendations to be made regarding the use of immunoglobulin in C. difficile infection. The authors stated that further research is urgently needed to clarify the role of immunoglobulin -- intravenous or oral -- for the treatment of C. difficile infection.

Abougergi et al (2010) stated that C. difficile colitis (CDC) is the most common cause of hospital-acquired diarrhea. The increase in the incidence and fatality rate of CDC over the past decade has stimulated a search for new therapies, including IVIG. These researchers reported their experience with IVIG for the treatment of 21 patients with severe CDC. The existing literature on IVIG infusion for severe CDC was also reviewed. Twenty-one of 1,230 patients with CDC were treated with IVIG. The mean age was 68 (range of 35 to 98) years, with mean hospital stay of 23 (range of 9 to 64) days. Conventional treatment was used for an average of 8 (range of 1 to 25) days before IVIG infusion. All patients had evidence of pancolitis (radiologically) or ileus (clinically). The mean Acute Physiological Assessment and Chronic Health Evaluation (APACHE II) score was 25 (range of 6 to 39) at day 1 of IVIG infusion. Nine patients (43%) survived their hospitalization with colitis resolution while 12 (57%) died. One patient developed pulmonary edema after IVIG infusion. Symptoms resolved after an average of 10 (range of 2 to 20) days for survivors. Two patients underwent urgent colectomy. The authors concluded that this is the largest case series describing IVIG use for patients with severe CDC and the one with the highest mortality rate to date. The use of IVIG in this setting does not seem to benefit all patients. Benefit appears to depend on the extent of systemic involvement. They stated that further studies are needed before adopting IVIG as routine treatment for severe CDC.

Diaz-Manera and colleagues (2009) noted that advances in the treatment of myasthenia gravis (MG) have reduced mortality rates due to the disease and improved patients’ quality of life. Nowadays, attending neurologists can choose among different treatment strategies for MG patients. An exhaustive revision of published data on the efficacy of the different therapeutic options for MG indicates that there are insufficient evidence-based results. However, recommendations based on expert opinion can be provided. Thymectomy is indicated in all patients with a thymoma or for generalized acetylcholine receptor-sero-positive patients aged 18 to 55 years. Steroids are the most widely used immunosuppressive drug for MG. They are recommended as the first-line drug in all patients with...
generalized MG without response to thymectomy, or in those patients who do not fulfill criteria for the surgery. The selection of second-line drugs may vary between protocols. The authors recommended starting with azathioprine if insufficient remission is achieved with steroids, followed by ciclosporin, mycophenolate and others. They use rituximab or cyclophosphamide only in severely drug-resistant patients. Finally, the authors recommend IVIG or plasma exchange (PE) in MG crisis, or for unstable patients before thymectomy or in clinical exacerbations.

Tranchant (2009) stated that the purpose of the treatment of MG is to improve neuromuscular transmission, and to reduce the production or presence of the nicotinic acetylcholine receptor (achR). Acetylcholinesterase inhibitors are the first line treatment with the rapid onset of effect, for all types of MG (ocular, generalized MG, sero-negative or sero-positive patients). Plasmapheresis or IVIG is the treatment for exacerbations. Their main advantage is the rapid onset of the effect; 3 to 5 PE or IVIG infusions (1.2 to 2 g/body weight administered over 2 to 5 days) are usually recommended. In case of suspected thymoma, thymectomy should be always performed. The option of thymectomy was discussed in young patients less than 50 years old with unstable MG, even if thymoma lesions are not suspected. Corticosteroids and/or immunosuppressive agents are used in severe forms of the disease. A few randomized studies have shown the effectiveness of the therapeutic agents. Corticosteroids are considered a major treatment of MG but the doses and periods of time are still being debated. The combination of corticosteroids and immunosuppressive agents are recommended early to spare corticosteroids. The treatment of MG should be modulated regularly (minimal doses for example). The use of IVIG prior to thymectomy was not discussed.

The European Federation of Neurological Societies' task force on the use of IVIG in treatment of neurological diseases (Elovaara et al, 2008) stated that IVIG is an effective treatment for acute exacerbations of MG and for short-term treatment of severe MG (level A); and IVIG is similar to PE regarding effect. This treatment is safe also for children, during pregnancy, and for elderly patients with complicating disorders. There is not sufficient evidence to recommend IVIG for chronic maintenance therapy in MG alone or in combination with other immunoactive drugs. Furthermore, the use of IVIG before thymectomy was not discussed.

Morozumi and associates (2009) evaluated the effect of IVIG therapy in the treatment of neuropathic pain associated with Sjögren's syndrome. These investigators examined 5 patients affected by painful sensory neuropathy associated with Sjögren's syndrome. All patients were treated with IVIG (0.4 g/kg/day for 5 days) and pain rating was assessed by the visual analog scale (VAS). All 5 patients showed a remarkable improvement in neuropathic pain following IVIG therapy. Pain, assessed by the determination of mean VAS score, was reduced by 73.4 % from days 2 to 14 following treatment. The observed clinical improvement persisted for 2 to 6 months. One patient, examined by quantitative sensory testing, showed an improvement of superficial sensory deficit accompanied by pain relief. The authors concluded that IVIG might be an effective treatment for pain in Sjögren's syndrome-associated neuropathy. They stated that further studies should be done in a controlled, blind study.

Ishii et al (1994) examined the clinical effects of PE and high dose IVIG in a 41-year old woman with Isaacs' syndrome. After double filtration PE, symptoms almost disappeared for 2 to 3 weeks and the recorded continuous muscle action potentials were considerably decreased. Symptoms recurred within a few months. On the other hand, IVIG worsened the symptoms of the disorder: during and after IVIG at a dose of 0.2 g/kg/day (total 50 g), widespread myokymia, pseudomyotonia, and muscle cramps gradually increased. Symptoms improved after another course of PE.

Myers and Baker (2009) noted that acquired neuromyotonia, also known as Isaacs’ syndrome, has been described in combination with a variety of other autoimmune disorders; however there has never been a report of sero-positive Isaacs’ syndrome in a patient with a history of Guillain-Barre syndrome (GBS). Both conditions involve antibody-mediated autoimmune effects on the peripheral nervous system, although the clinical manifestations are quite different. These researchers presented a man who experienced an episode of GBS at the age of 21 and subsequently developed Isaacs’ syndrome at the age of 24 which was positive for anti-voltage-gated potassium channel (VGKC) antibodies. When treated with IVIG, he developed an eczematous rash that differed markedly in pattern and duration from the usual presentation for this IVIG reaction.

Aries and colleagues (2005) stated that initially IVIGs were used as replacement therapy in primary and secondary antibody-deficiency syndromes. The clinical use of IVIG has been extended during the past decade to a wide variety of clinical conditions, such as infectious processes, neuroimmunological
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Diseases, and different systemic autoimmune diseases. The mode of action of IVIG is complex, involving modulation of the Fc receptors, interference with the complement and cytokine network, and effects on the activation and differentiation of T and B-cells. Kawasaki disease (KD) was one of the first diseases within the group of primary vasculitides in which IVIG were used. Today, there is a clear evidence of benefit for IVIG in the treatment of coronary artery abnormalities related to KD. Subsequently, various reports have suggested a beneficial effect in other vasculitides; however, there are few data from controlled studies. For anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), 1 placebo-controlled and several open-label studies have shown a beneficial effect on the disease activity in patients with Wegener's granulomatosis or microscopic polyangitis refractory to standard therapy with prednisone and cyclophosphamide. For other vasculitides, such as polyarteritis nodosa or Henoch-Schönlein purpura, only case reports have described an inhibition of a disease progression by IVIG so far. However, the effect was partly only temporary. The authors concluded that KD and AAV are the only vasculitides with a definite beneficial use of IVIG. For other vasculitides, the efficacy of IVIG has not been proven properly but may be useful in single cases.

Eleftheriou and Brogan (2009) stated that primary systemic vasculitides of the young are relatively rare diseases, but can have a significant morbidity and mortality. The purpose of this review was to provide an overview of the pediatric vasculitides. Vasculitides that predominantly affect children will be considered in more detail than vasculitic diseases that although are seen in children affect adults more commonly, such as the ANCA associated vasculitides. New classification criteria for childhood vasculitides have recently been proposed and are currently undergoing validation. Epidemiological clues continue to implicate infectious triggers in KD and Henoch Schönlein purpura. Several genetic polymorphisms have now been described in the vasculitides that may be relevant in terms of disease predisposition or development of disease complications. Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents. However new challenges are looming in regards to the role of inflammation in endothelial health and the long term cardiovascular morbidity for children with primary systemic vasculitis. International multi-center collaboration is of utmost importance in order for us to further advance the understanding and improve the treatment and outcome of systemic vasculitis in the young. Furthermore, an UpToDate review on "Management of Henoch-Schönlein purpura" (Dedeoglu et al, 2010) did not mention the use of IVIG as a therapeutic option.

Ishii and associates (2010) stated that treatment of autoimmune bullous skin diseases can often be challenging and primarily consists of systemic corticosteroids and a variety of immunosuppressants. Current treatment strategies are effective in most cases but hampered by the side effects of long-term immunosuppressive treatment. Intravenous immunoglobulin is one potential promising therapy for patients with autoimmune bullous skin diseases, and evidence of its effectiveness and safety is increasing. A number of autoimmune bullous skin diseases have been identified in which IVIG treatment may be beneficial. However, experience with IVIG in patients with autoimmune skin blistering disease is limited, where it is recommended for patients not responding to conventional therapy. The mode of action of IVIG in autoimmune diseases, including bullous diseases is far from being completely understood. These researchers summarized the clinical evidence supporting the notion, that IVIG is a promising therapeutic agent for the treatment of patients with autoimmune bullous skin disease. In addition, they reviewed the proposed modes of action. In the future, randomized controlled trials are necessary to better determine the efficacy and adverse effects of IVIG in the treatment of autoimmune bullous skin diseases.

Jolles (2011) noted that high-dose IVIG (hdIVIG) is being used increasingly for dermatological indications. Its mode of action is via a number of proposed mechanisms and it is not associated with the many side-effects of steroids and other immunosuppressive agents. The evidence for using hdIVIG in the treatment of autoimmune bullous disorders is based on uncontrolled trials and case reports. However, there are now 62 reported patients and this review aimed to make a critical assessment of the current data. This has been obtained from a Medline search of the English literature from 1966 to 2000 for pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, pemphigoid gestationis, cicatricial pemphigoid, epidermolysis bullosa acquisita and linear IgA disease. Taken together hdIVIG was effective in 81 % of the patients with blistering disease. Patients appear to be more likely to respond when hdIVIG is used as adjunctive therapy (91 % response rate) than as monotherapy (56 % response rate). The authors concluded that hdIVIG may offer a safe potential therapeutic avenue for resistant cases of the autoimmune bullous disorders but should be further assessed using double-blind placebo-controlled trials.
Parambil et al (2011) stated that small fiber neuropathy (SFN) is commonly associated with sarcoidosis and can cause significant morbidity to afflicted patients. The appropriate treatment of this condition, when associated with sarcoidosis, is not well established. These investigators described case series of 3 patients with sarcoidosis and SFN; the presenting clinical features, skin biopsy results, autonomic reflex screen and quantitative sudomotor axon reflex testing (QSART) findings, and response to therapy were delineated. They described 3 patients with biopsy-proven sarcoidosis who developed intractable neuropathic pain and/or symptoms related to associated autonomic dysfunction despite treatment with various immunosuppressive medications and narcotic analgesics. QSART showed evidence of a post-ganglionic sudomotor abnormality in 1 patient and was normal in the other 2. Skin biopsy findings were abnormal, demonstrating a non-length-dependent sensory SFN in all 3 patients. Painful neuropathic symptoms, as well as symptoms related to dysautonomia from SFN responded significantly to treatment with IVIG. The authors concluded that IVIG appears to be effective in relieving symptoms from SFN associated with sarcoidosis, suggesting an underlying immune mechanism. Moreover, they stated that larger prospective, controlled studies are needed to confirm this response to IVIG and to further elucidate the underlying pathobiology behind this association with sarcoidosis.

Isobe et al (2004) described the case of a 40-year old female diagnosed with follicular lymphoma who was treated with rituximab-combined chemotherapy. Although she achieved complete remission, she developed progressive anemia and reticulocytopenia. Bone marrow examination revealed features of pure red cell aplasia and hemophagocytosis. In addition, the appearance of large pronormoblasts suggested that she was infected with parvovirus B19. Excess viral DNA in her bone marrow confirmed that her illness was caused by persistent parvovirus B19 infection. Serum immunoglobulin levels decreased beyond the lower normal limit, which indicated that her humoral immunity was impaired after rituximab-combined chemotherapy. Although she had been infected with parvovirus B19, she was re-infected and failed to control the viral expansion. High-titer immunoglobulin against parvovirus B19 was intravenously administrated and resulted in remarkable reticulocytosis and improvement of anemia. High-titer immunoglobulin, which contained a sufficient amount of neutralizing antibodies against parvovirus B19, likely inactivated most viruses in vivo. These investigators successfully eradicated the virus after 2 courses of high-dose therapy at 0.5 g/kg/day every week followed by 8 courses of maintenance therapy at 0.1 g/kg/day every other week. It is important to consider that parvovirus B19 infection is a possible cause of progressive anemia in B-cell lymphoma patients treated with rituximab-combined chemotherapy. The authors proposed that the use of high-titer immunoglobulin against parvovirus B19 may enable such immunocompromised patients to eradicate the virus before sufficient immune system reconstruction. Also, UpToDate reviews on "Initial treatment of follicular lymphoma" (Freedman and Friedberg, 2011) and "Treatment of relapsed or refractory follicular lymphoma" (Freedman and Friedberg, 2011) do not mention the use of IVIG.

Perlmutter et al (1999) examined if plasma exchange or IVIG would be better than placebo (sham IVIG) in reducing severity of neuropsychiatric symptoms in children, exacerbations of tics and obsessive symptoms. Children with severe, infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders, including Tourette syndrome, were randomly assigned treatment with plasma exchange (5 single-volume exchanges over 2 weeks), IVIG (1 g/kg daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG). Symptom severity was rated at baseline, and at 1 month and 12 months after treatment by use of standard assessment scales for OCD, tics, anxiety, depression, and global function. A total of 30 children entered the study and 29 completed the trial. Ten received plasma exchange, 9 IVIG, and 10 placebo. At 1 month, the IVIG and plasma exchange groups showed striking improvements in obsessive-compulsive symptoms (mean improvement on children's Yale-Brown obsessive compulsive scale score of 12 [45 %] and 13 [58 %], respectively), anxiety (2.1 [31 %] and 3.0 [47 %] improvement on National Institute of Mental Health anxiety scale), and overall functioning (2.9 [33 %] and 2.8 [35 %] improvement on National Institute of Mental Health global scale). Tic symptoms were also significantly improved by plasma exchange (mean change on Tourette syndrome unified rating scale of 49 %). Treatment gains were maintained at 1 year, with 14 (82 %) of 17 children *much* or "very much" improved over baseline (7 of 8 for plasma exchange, 7 of 9 for IVIG). The authors concluded that plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders. They stated that further studies are needed to determine the active mechanism of these interventions, and to determine which children with OCD and tic disorders will benefit from immunomodulatory therapies.

In a double-blind placebo-controlled study, Hoekstra et al (2004) studied the effects of IVIG on tics. A total of 30 patients with a DSM-IV tic disorder were randomly assigned to IVIG (1 g/kg on 2 consecutive
days; mean age = 28.71 years; range of 14 to 53 years) or placebo (mean age = 30.73 years; range of 14 to 63 years). Symptoms were rated with the Yale Global Tic Severity Scale, the Yale-Brown Obsessive Compulsive Scale, and the Clinical Global Impressions scale of symptom change with regard to tic severity. These were used at baseline and on weeks 2, 4, 6, 10, and 14 post-treatment, after which blinding was broken. The study was conducted from March through August 2002. These researchers observed no significant differences between both treatment groups regarding post-treatment changes in tic severity. Severity of obsessions and compulsions, which was in the subclinical range, decreased significantly in the IVIG group compared with the placebo group at week 6 (p = 0.02). Then, there was a 32.3% improvement in the IVIG group compared with baseline. Though this improvement was maintained over the following 8 weeks, no statistically significant differences between the IVIG and the placebo group with regard to improvements in obsessions and compulsions were detected at subsequent assessments. IVIG treatment was associated with significantly more side effects than placebo, most notably headache. The authors concluded that based on the present results, IVIG can not be recommended in tic disorders.

Trucco et al (2011) evaluated the outcome of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis following IVIG and corticosteroid therapy. These researchers have previously shown that 85% of fetuses and infants with maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis suffer demise or need for transplant. In an attempt to improve this outcome, in 1998, they began to empirically treat affected patients with IVIG and corticosteroids. These investigators reviewed the clinical records and echocardiograms of 20 affected patients encountered in their institutions and treated with IVIG and corticosteroids from 1998 to 2009. All 20 were initially referred at a median gestational age of 23 weeks (range of 18 to 38 weeks); 19 mothers were anti-Ro antibody positive, 8 anti-La antibody positive, and 7 had clinical autoimmune disease. Endocardial fibroelastosis was seen in 16 and was not obvious in 4 others with reduced ventricular function, and 16 (80%) had reduced or borderline ventricular shortening fraction (less than or equal to 30%) before or after birth. Eighteen had atrioventricular block at referral (16 in 3°). During pregnancy, maternal IVIG was given in 9 and dexamethasone in 17. After birth, 17 infants received IVIG (n = 14) and/or corticosteroids (n = 15). Twelve underwent pacemaker implantation. Four with hydrops at presentation died perinatally, despite initial improvement in function in 3. At a median follow-up of 2.9 years (1.1 to 9.8 years), 16 (80%) patients are currently alive with normal systolic ventricular function and 6 are not paced. The authors concluded that treatment of maternal autoantibody-mediated fetal cardiomyopathy/endocardial fibroelastosis with IVIG and corticosteroids potentially improves the outcome of affected fetuses. They stated that further studies (prospective, multi-center randomized trials including the evaluation of maternal and neonatal titers before and after therapy) are needed to determine the optimal dose and timing of IVIG administration.

In a Cochrane review, Ohlsson et al (2010) evaluated the effect of IVIG on mortality/morbidity caused by suspected infection in neonates and in those neonates who had suspected infection on study entry and later were confirmed as being infected. These investigators searched MEDLINE, EMBASE, The Cochrane Library, the reference lists of identified studies, meta-analyses and personal files in December 2009. They selected randomized or quasi-randomized controlled trials of IVIG for the treatment of suspected bacterial/fungal infection compared to placebo or no intervention in newborn infants (less than 28 days old). Statistical analyses included Typical Relative Risk (RR), Risk Difference (RD), weighted mean difference (WMD), the number needed to treat to benefit (NNTB) (all with with 95% CI and the I(2) statistic to examine statistical heterogeneity. The updated search identified 1 new study; 10 studies of variable quality undertaken in 8 countries are included in this review. Mortality in infants with clinically suspected infection was reduced following IVIG treatment [7 studies (n = 378); typical RR 0.58 (95% CI: 0.38, 0.89); typical RD -0.10 (95% CI: -0.18, -0.03); NNTB 10 (95% CI: 6, 33); I(2) = 0%]. Mortality in cases of subsequently proven infection was reduced [7 trials (n = 262); typical RR 0.55 (95% CI: 0.31, 0.98); I(2) = 0%]. The authors concluded that because of concerns about study quality, there is still insufficient evidence to support the routine administration of IVIG to prevent mortality in infants with suspected or subsequently proved neonatal infection. A large study of the effectiveness of IVIG in neonates with suspected infection has recently been completed. Results of the International Neonatal Immunotherapy Study (INIS trial), which enrolled 3,493 infants, are expected to be published in 2010. The results of that trial should establish the usefulness of IVIG for suspected infection in newborns.

The INIS Collaborative Group (2011) stated that neonatal sepsis is a major cause of death and complications despite antibiotic treatment. Effective adjunctive treatments are needed. Newborn infants are relatively deficient in endogenous immunoglobulin. Meta-analyses of trials of IVIG for suspected or proven neonatal sepsis suggest a reduced rate of death from any cause, but the trials have been small.
and have varied in quality. At 113 hospitals in 9 countries, these investigators enrolled 3,493 infants receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive 2 infusions of either polyvalent IgG immune globulin (at a dose of 500 mg/kg body weight) or matching placebo 48 hours apart. The primary outcome was death or major disability at the age of 2 years. There was no significant between-group difference in the rates of the primary outcome, which occurred in 686 of 1,759 infants (39.0%) who received IVIG and in 677 of 1,734 infants (39.0%) who received placebo (relative risk, 1.00; 95% CI: 0.92 to 1.08). Similarly, there were no significant differences in the rates of secondary outcomes, including the incidence of subsequent sepsis episodes. In follow-up of 2-year-old infants, there were no significant differences in the rates of major or non-major disability or of adverse events. The authors concluded that therapy with IVIG had no effect on the outcomes of suspected or proven neonatal sepsis.

Kim and colleagues (2011) stated that the prognosis of MG has improved dramatically due to advances in critical-care medicine and symptomatic treatments. Its immunopathogenesis is fundamentally a T-cell-dependent autoimmune process resulting from loss of tolerance toward self-antigens in the thymus. Thymectomy is based on this immunological background. For MG patients who are inadequately controlled with sufficient symptomatic treatment or fail to achieve remission after thymectomy, remission is usually achieved through the addition of other immunotherapies. These immunotherapies can be classified into 2 groups: (i) rapid induction and (ii) long-term maintenance. Rapid induction therapy includes IVIG and PE. These produce improvement within a few days after initiation, and so are useful for acute exacerbation including myasthenic crisis or in the peri-operative period. High-dose prednisone has been more universally preferred for remission induction, but it acts more slowly than IVIG and PE, commonly only after a delay of several weeks. Slow tapering of steroids after a high-dose pulse offers a method of maintaining the state of remission. However, because of significant side effects, other immunosuppressants (ISs) are frequently added as “steroid-sparing agents”. The currently available ISs exert their immunosuppressive effects by 3 mechanisms: (i) blocking the synthesis of DNA and RNA. (ii) inhibiting T-cell activation and (iii) depleting the B-cell population. In addition, newer drugs including antisense molecule, tumor necrosis factor alpha receptor blocker and complement inhibitors are currently under investigation to confirm their effectiveness. Until now, the treatment of MG has been based primarily on experience rather than gold-standard evidence from randomized controlled trials. It is hoped that well-organized studies and newer experimental trials will lead to improved treatments.

A review of treatment of IgG subclass deficiencies (Lemmon & Knutsen, 2012) explains that, “in patients receiving immune globulin replacement therapy, treatment should periodically be held after one to two years for immunologic and clinical reassessment. When discontinuing immune globulin, it is advisable to do so during the spring months to minimize exposure to viral infections. We generally wait three or four months after discontinuation before performing immune testing.” The authors explain, as a rationale for this reassessment, that some people do not respond to IgG replacement therapy, and also that, especially in younger patients, immune responsiveness and IgG subclass levels may normalize over time.

The American College of Obstetricians and Gynecologists’ practice bulletin on “Antiphospholipid syndrome” (ACOG, 2011) indicated that IVIG was considered but not recommended for pregnant women with APS.

Also, the British Committee for Standards in Haematology’s guidelines on “The investigation and management of antiphospholipid syndrome” (Keeling et al, 2012) does not mention the use of IVIG.

Alijotas-Reig (2013) stated that currently there are no reliable data regarding the actual treatment received by women with refractory obstetric APS (OAPS). These researchers evaluated current clinical evidence and new trends in the treatment of refractory OAPS. A non-systematic but comprehensive literature search using relevant keywords was made to identify relevant articles published in English from different computerized databases: PubMed (Medline), Google Scholar electronic database search and The Cochrane Library, from January 2000 to March 2012. Studies on the treatment of poor obstetric outcomes in women with OAPS were included. Prospective randomized clinical trials, cohort studies, reviews, systematic reviews and meta-analysis were retrieved. A total of 130 articles were finally selected for this review, including 17 randomized clinical trials and 4 meta-analyses. The majority of articles were non-randomized original papers and basic and clinical reviews. The authors concluded that up to 20% of women with OAPS do not receive the currently recommended therapeutic regimen. Unfortunately, well-designed studies regarding the usefulness of new drugs in refractory OAPS are
scarce. Hydroxychloroquine and low-dose prednisolone appear to be useful when added to standard therapy. Current data do not support the use of IVIG in this field.

The American Academy of Child and Adolescent Psychiatry’s practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder (AACAP, 2012) stated that “Therapeutic plasma exchange and intravenous immunoglobulin remain experimental interventions with substantial risk and potential morbidity”.

Also, UpToDate reviews on “Attention deficit hyperactivity disorder in children and adolescents: Treatment with medications” (Krull, 2012a), “Attention deficit hyperactivity disorder in children and adolescents: Overview of treatment and prognosis” (Krull, 2012b), and “Adult attention deficit hyperactivity disorder” (Searight and Burke, 2012) do NOT mention the use of IVIG as a therapeutic option.

UpToDate reviews on “Initial treatment of depression in adults” (Katon and Ciechanowski, 2012a) and “Treatment of resistant depression in adults” (Katon and Ciechanowski, 2012b) do NOT mention the use of IVIG as a therapeutic option.

An UpToDate review on “The diffuse alveolar hemorrhage syndromes” (Schwarz, 2012) states that “The possible role of intravenous immunoglobulin (IVIG) in patients with DAH due to vasculitis or other connective tissue disease is unknown”.

An UpToDate review on “PANDAS: Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci” (Pichichero, 2012) states that “Routine administration of immunomodulatory therapy (e.g., glucocorticoids, plasma exchange, intravenous immunoglobulin [IVIG]) is not indicated for children who meet PANDAS criteria”.

Perlmutter et al (1999) reported on 29 children who were randomized to one of three groups: plasma exchange (n = 10), IVIG (n = 9), or placebo (n = 10). They found that at 1 month, the IVIG and plasma-exchange groups showed striking improvements in obsessive-compulsive symptoms (mean improvement on children’s Yale-Brown obsessive compulsive scale score of 12 [45 %] and 13 [58 %], respectively), anxiety (2·1 [31 %] and 3·0 [47 %] improvement on National Institute of Mental Health anxiety scale), and overall functioning (2·9 [33 %] and 2·8 [35 %] improvement on National Institute of Mental Health global scale). The investigators concluded that plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection triggered OCD and tic disorders. The investigators stated that further studies are needed to determine the active mechanism of these interventions, and to determine which children with OCD and tic disorders will benefit from immunomodulatory therapies. This 3-armed trial with 10 or less participants per arm has limited statistical power.

Martino et al (2009) stated that despite their empirical use in community settings, there is still a lack of conclusive, evidence-based data regarding the usefulness of antibiotic and immuno-modulatory treatments in children with PANDAS.

Shulman (2009) noted that the relationship between obsessive-compulsive disorder (OCD) or tics/Tourette’s syndrome in childhood to antecedent group A streptococci (GAS) is unclear. One recent prospective cohort study found that more than 85 % of clinical exacerbations in OCD/tic behavior in patients who met criteria for PANDAS had no relationship to GAS infection. Another study found no correlation between clinical exacerbations and changes in a variety of markers of brain autoimmunity, the proposed pathogenesis of PANDAS. A third recent study concluded that, compared with specialty clinic diagnoses, patients diagnosed with tics or Tourette's by physicians in the community were significantly more likely to be diagnosed with PANDAS without meeting the proposed criteria, most lacked supporting laboratory evidence of GAS infection, and they were more likely to be treated with unjustified short-term to chronic antibiotic and/or immuno-modulatory therapy.

Marconi et al (2009) stated that the use of treatment strategies, such as therapeutic plasmapheresis or IVIG, has been proposed to explain the autoimmune process responsible for the pathogenesis of PANDAS. Moreover, they stated that further research is still necessary in order to understand the role of streptococcal infection in the pathogenesis of PANDAS.

Tan et al (2012) posed the question “I have heard about children who have tic disorders that seem to be exacerbated by group A β-hemolytic streptococcal infection. Should children presenting with this phenomenon receive treatment with antibiotics, receive prophylactic treatment, or use
immunomodulators to treat the symptoms?” They noted the answer to be: “Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) constitute a condition that includes neuropsychiatric symptoms, mainly obsessive-compulsive disorder or tic disorders, temporally associated with an immune-mediated response to streptococcal infections. The actual existence of PANDAS as a unique clinical entity is still up for debate, as a temporal association between group A β-hemolytic streptococcal infections and symptom exacerbations has been difficult to prove thus far. Based on only a few studies, positive results have been found using antibiotic prophylaxis and immunomodulatory therapy in children with PANDAS. At this time, however, evidence does not support a recommendation for long-term antibiotic prophylaxis or immunomodulatory therapy.”

The AAN's evidence-based guideline on “Intravenous immunoglobulin in the treatment of neuromuscular disorders” (Patwa et al, 2012) states that IVIG is as efficacious as plasmapheresis and should be offered for treating Guillain-Barré syndrome (GBS) in adults (Level A). IVIG is effective and should be offered in the long-term treatment of chronic inflammatory demyelinating polyneuropathy (Level A). IVIG is probably effective and should be considered for treating moderate-to-severe myasthenia gravis and multifocal motor neuropathy (Level B). IVIG is possibly effective and may be considered for treating non-responsive dermatomyositis in adults and Lambert-Eaton myasthenic syndrome (Level C). Evidence is insufficient to support or refute use of IVIG in the treatment of immunoglobulin M paraprotein-associated neuropathy, inclusion body myositis, polymyositis, diabetic radiculoplexoneuropathy, or Miller Fisher syndrome, or in the routine treatment of post-polio syndrome or in children with GBS (Level U). IVIG combined with plasmapheresis should not be considered for treating GBS (Level B). More data are needed regarding IVIG efficacy as compared with other treatments/treatment combinations.

In a Cochrane review, Gajdos et al (2012) examined the effectiveness of IVIG for treating exacerbations of MG or for chronic MG. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register (October 11, 2011), CENTRAL (2011, Issue 3), MEDLINE (January 1966 to September 2011) and EMBASE (January 1980 to September 2011) using 'myasthenia gravis' and 'intravenous immunoglobulin' as the search terms. All randomized controlled trials (RCTs) or quasi-RCTs in which IVIG was compared with no treatment, placebo or plasma exchange, in people with MG. One review author extracted the data and 2 others checked these data. For methodological reasons, no formal meta-analysis was performed. These researchers identified 7 RCTs. These trials differ in inclusion criteria, comparison with alternative treatment and outcomes. In a trial comparing IVIG with placebo, including 51 participants with MG worsening, the mean difference (MD) in quantitative MG score (QMGS) (MD 95 % CI) after 14 days was: -1.60 (95 % CI: - 3.23 to 0.03) this result being borderline statistically significant in favor of IVIG. In an unblinded study of 87 participants with exacerbation comparing IVIG and PE there was no difference in myasthenic muscle score (MMS) after 15 days (MD -1.00; 95 % CI: -7.72 to 5.72). In a study of 84 participants with worsening MG there was no difference in change in QMGS 14 days after IVIG or PE (MD -1.50; 95 % CI: -3.43 to 0.43). In a study of 12 participants with moderate or severe MG, which was at high-risk of bias from skewed allocation, the mean fall in QMGS both for IVIG and PE after 4 weeks was significant (p < 0.05). A study with 15 participants with mild or moderate MG found no difference in change in QMGS 42 days after IVIG or placebo (MD 1.60; 95 % CI: -1.92 to 5.12). A study included 33 participants with moderate exacerbations of MG and showed no difference in change in QMGS 14 days after IVIG or methylprednisolone (MD -0.42; 95 % CI: -1.20 to 0.36). All these 3 smaller studies were underpowered. The last trial, including 168 people with exacerbations, showed no evidence of superiority of IVIG 2 g/kg over IVIG 1 g/kg on the change of MMS after 15 days (MD 3.84; 95 % CI: -0.98 to 8.66). Adverse events due to IVIG were moderate (fever, nausea, headache), self-limiting and subjectively less severe than with PE (although, given the available data, no statistical comparison was possible). Other than where specific limitations were mentioned the trials were generally at low-risk of bias. The authors concluded that in exacerbation of MG, 1 RCT of IVIG versus placebo showed some evidence of the efficacy of IVIG and 2 did not show a significant difference between IVIG and PE. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIG. A further, but under-powered, trial showed no significant difference between IVIG and oral methylprednisolone. They stated that in chronic MG, there is insufficient evidence from RCTs to determine whether IVIG is effective.

The Ad Hoc Committee of the Croatian Society for Neurovascular Disorders/Croatian Medical Association’s guidelines for the use of IVIG in the treatment of neurologic diseases (Basci-Kes et al, 2012) stated that the use of IVIG in the management of patients with neuroimmune disorders has shown a progressive trend over the last few years. Despite the wide use of IVIG, consensus on its optimal use is deficient. The European Federation of Neurological Societies (EFNS) guidance regulations offered consensus recommendations for optimal use of IVIG. The effectiveness of IVIG has been proven in
Guillain-Barre syndrome (level A), chronic inflammatory demyelinating polyradiculoneuropathy (level A), multi-focal mononeuropathy (level A), acute exacerbations of MG and short-term treatment of severe MG (level A). As a second-line treatment, the use of IVIG is recommended in dermatomyositis in combination with prednisone (level B) and is considered as a treatment option in polymyositis (level C). As a 2nd- or even 3rd-line therapy, the use of IVIG should be considered in patients with RRMS if conventional immunomodulatory therapies are not tolerated (level B) and in relapses during pregnancy or post-partum period (good clinical practice point). Finally, it appears that the use of IVIG has a beneficial effect also in stiff-person syndrome (level A), some paraneoplastic neuropathies (level B), and some acute-demyelinating diseases and childhood refractory epilepsy (good practice point). The guideline did not mention the use of IVIG as a maintenance therapy for MG.

Also, an UpToDate review on “Treatment of myasthenia gravis” (Bird, 2013) did not mention the use of IVIG as maintenance therapy for MG.

In a Cochrane review, Lunn and Nobile-Orazio (2012) evaluated the effects of immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated demyelinating peripheral neuropathy. These investigators searched the Cochrane Neuromuscular Disease Group Specialized Register June 6, 2011), CENTRAL (2011, Issue 2), MEDLINE (January 1966 to May 2011) and EMBASE (January 1980 to May 2011) for controlled trials. They also checked bibliographies and contacted authors and experts in the field. These researchers included randomized or quasi-randomized controlled trials involving participants of any age treated with any type of immunotherapy for anti-myelin-associated glycoprotein antibody-associated demyelinating peripheral neuropathy with monoclonal gammopathy of undetermined significance and of any severity. The primary outcome measure was change in the Neuropathy Impairment Scale or Modified Rankin Scale at 6 months after randomization. Secondary outcome measures were: Neuropathy Impairment Scale or the Modified Rankin Score at 12 months after randomization; 10-meter walk time, subjective clinical scores and electrophysiological parameters at 6 and 12 months after randomization; IgM paraprotein levels and anti-myelin-associated glycoprotein antibody titers at 6 months after randomization; and adverse effects of treatments. The 2 authors independently selected studies; and 2 authors independently assessed the risk of bias in included studies. These investigators identified 7 eligible trials (182 participants), which tested IVIG, alfa-interferon alfa-2a, PE, cyclophosphamide and steroids, and rituximab. Only 2 trials, of IVIG (with 33 participants, including 20 with antibodies against myelin-associated glycoprotein), had comparable interventions and outcomes, but both were short-term trials. There were no clinical or statistically significant benefits of the treatments used on the outcomes pre-defined for this review, but not all the predefined outcomes were used in every included trial. Intravenous immunoglobulin showed a statistical benefit in terms of improvement in Modified Rankin Scale at 2 weeks and 10-meter walk time at 4 weeks. Cyclophosphamide failed to show any benefit in the trial’s primary outcome, and showed a barely significant benefit in the primary outcome specified here, but some toxic adverse events were identified. A trial of rituximab was of poor methodological quality with a high risk of bias and a further larger study is awaited. Serious adverse events were few in the other trials. The authors concluded that there is inadequate reliable evidence from trials of immunotherapies in anti-myelin-associated glycoprotein paraproteinemic neuropathy to form an evidence base supporting any particular immunotherapy treatment. There is very low quality evidence of benefit from rituximab. They stated that large, well-designed, randomized trials of at least 6 to 12 months duration are needed to evaluate existing or novel therapies, preferably employing unified, consistent, well-designed, responsive and valid outcome measures.

Furthermore, in a review on “Intravenous immunoglobulin for treatment of neuromuscular disease”, Ruzhansky and Brannagan (2013) stated that “Clinical trials in amyotrophic lateral sclerosis, inclusion body myositis, and anti–myelin-associated glycoprotein neuropathy have been negative”.

Drulovic et al (2011) noted that Hashimoto's encephalopathy (HE) is a rare autoimmune syndrome characterized by various neuropsychiatric manifestations, responsive to steroid treatment and associated with Hashimoto's thyroiditis. There are only a few reports suggesting that IVIG might represent an effective treatment modality for the severe steroid-resistant HE cases. These investigators presented a patient with HE who developed a complete recovery after the IVIG therapy followed by a long-lasting remission. After detailed examinations, the diagnosis of HE was established. Two years later, in June 2001, new manifestations (unsteadiness in gait, personality changes, seizures, and persistent headache) gradually developed during a 6-month period. Response to steroids was unsatisfactory and partial, since headaches and personality changes had continuously worsened. In January 2002, the patient received IVIG (0.4 g/kg body weight daily for 5 days). Gradual improvement was noticed and a complete recovery
developed over the following weeks. Up to March 2009, during a 7-year follow-up period, remission persisted. The authors concluded that to their best knowledge, this was the first report of a long-lasting remission of HE after IVIG therapy. Therefore, this case further supported administration of IVIG, as a potentially beneficial treatment modality, in severe cases of HE that are completely or partially resistant to steroids.

Olmez et al (2013) shared their experience on clinical presentation and management of patients diagnosed with HE. These researchers identified 13 patients who met the criteria for the diagnosis of HE. The median age was 49 years (range of 2 to 66) and all except 1 were women. Encephalopathy in the form of altered mental status, stroke-like symptoms or seizures, with prompt resolution of symptoms upon receiving steroids, was the commonest presentation, seen in 7 patients. The second commonest presentation was subacute progressive decrease in cognitive function, which reversed within days to weeks after steroid therapy, seen in 4 patients. Electroencephalogram (EEG) was available in 12 patients and was abnormal in 8, showing non-specific cerebral dysfunction in all 8 and epileptiform activity in 3. Treatment consisted of steroids in the acute phase for 12 of 13 patients with rapid improvement in symptoms. Maintenance therapy was rituximab in 7 patients, IVIG in 7, azathioprine in 4, mycophenolate mofetil in 3, and methotrexate in 1 (some patients received sequential therapy with different agents). There was complete or near complete resolution of symptoms in 12 of the 13 patients. The authors concluded that they presented a cohort of patients in whom central nervous system dysfunction was associated with elevated anti-thyroid antibodies and reversal of disease followed immunomodulatory therapies. This was a small study and the findings were confounded by sequential therapies with different agents.

He and colleagues (2013) reported the findings of a case of a 61-year old man presented with unconsciousness, spasms and a previous misdiagnosis as viral encephalitis. Response to anti-viral and steroid therapy was unsatisfactory, but treatment with immunoglobulin combined with corticosteroid therapy achieved rapid and complete recovery. The authors concluded that any patient presenting with acute or subacute unexplained encephalopathy should be considered HE, even if the thyroid function is normal. Thyroid antibody testing should be performed because this may be the most important clue to diagnosis. As soon as the diagnosis is made, steroid therapy is the first choice. If the steroid therapy does not lead to immediate improvement, IVIG is an effective alternative treatment.

An UpToDate review on “Hashimoto’s encephalopathy” (Rubin, 2013) stated that “Clinical improvement with intravenous immunoglobulin, and plasmapheresis has been reported in individual cases”. However, IVIG is not mentioned in the “Summary and Recommendations” of this review.

Since available evidence is based on single-case studies as well as small case-series studies, the role of IVIG for the treatment for autoimmune encephalopathy has yet to be established.

In a Cochrane review, Wong et al (2013) assessed the safety and effectiveness of the use of IVIG antenatally to women with severe fetal red blood cell alloimmunization. These investigators searched the Cochrane Pregnancy and Childbirth Group trials register (December 19, 2012), and reference lists of articles. Randomized trials assessing the antenatal use of IVIG administered at any dose, frequency or duration with a control group (using any other, or no treatment) in the management of fetal red blood cell alloimmunization were selected for analysis. Two review authors independently assessed the available evidence. There were no included studies. The authors concluded that no information is available from randomized trials to indicate whether the antenatal use of IVIG is effective in the management of fetal red blood cell alloimmunization. Several case series suggested a beneficial role in delaying the onset of fetal anemia requiring invasive intrauterine transfusion.

An UpToDate review on “Epidemiology, pathogenesis, treatment, and prevention of enterovirus and parechovirus infections” (Modlin, 2013) stated that “The therapeutic options for more serious infections are limited and none has been subjected to adequate evaluation by clinical trials. Intravenous immune globulin (IVIG) has been administered to B-cell deficient patients with persistent meningoencephalitis, on a case by case basis, with mixed results”.

Joao (2007) stated that human B cell immune deficiencies are associated with increased susceptibility to viral and fungi infections, which are T cell immunity related infections. Also, some viral infections occurring in immune depressed patients such as cytomegalovirus (CMV) infections are recommended to be treated with IVIG in combination with anti-viral therapy. This fact has no clear biological explanation but it has been shown to be successful. Recently, B cells and immunoglobulin were identified as essential elements driving T cell receptor (TCR) diversity generation. Idiotype peptides of B cell
immunoglobulin may be the driving force for the antigen presenting function of B cells and other antigen presenting cells to influence the T cell repertoire. This seems to be another relevance of Jerne’s idiotypic network and another function of immunoglobulin. Since T cells function depends on the diversity of the TCR repertoire, means to increase the diversity of the T cell repertoire may improve T cell function in situations characterized by a contracted TCR repertoire (e.g., AIDS, primary immunodeficiency, cancer, autoimmunity and following chemotherapy and hematopoietic precursors transplantation). The clinical hypothesis put forth by this researcher is that B cells and/or immunoglobulin may be used therapeutically aiming to increase and potentially to restore T cell repertoire diversity improving T cell function in situations implicating a contracted T cell repertoire. The fact that immunoglobulin influences the composition of T cell repertoire by increasing its diversity allows a much wider application of this molecule in the clinical practice. The author presented a novel reasoning for the use of IVIG in humans, which should be explored. All the situations where immune reconstitution occurs are potentially a target for this therapeutically mechanism, aiming to improve the diversity of the reconstituted immune repertoires. This new role of Ig molecule may help to explain several effects that IVIG have in the T cell compartment, such as modulation of the activation and function of effectors T cells. The idea that immunoglobulin is essential in the generation and maintenance of a diverse compartment of T cells, affecting T cell function via that mechanism suggests a promising approach to medical conditions involving immune reconstitution. Furthermore, it represents a new paradigm of understanding the immune system as a complex, interdependent web of cells/cell products that inter- affect each other generation, function and survival.

Schmidt-Hieber et al (2009) developed a novel algorithm to define the need for high-dose prophylactic IVIG in periods of high-risk for CMV to patients after allo-SCT. Intravenous immunoglobulins were administered only if at least one of the following, monthly-assessed, criteria was fulfilled: (i) IgG concentration less than 4 g/L, (ii) NK (natural killer) cell count less than 100/microl, (iii) CD4(+) cell count less than 100/microl, and (iv) acute or chronic GVHD. The primary end-point was to determine the cumulative incidence of CMV infection in patients who received prophylactic IVIG according to the algorithm (intervention group) and compare it with that of a sequentially assessed control group, to which prophylactic IVIG were not administered. The study included 79 patients (44 in the intervention and 35 in the control group). The estimated cumulative incidence of CMV infection in the intervention and control group did not differ significantly (44 and 36 %; \( p = 0.31 \)). Additionally, prophylactic IVIG did not reduce the frequency of CMV infection episodes. Cytomegalovirus disease was rare in both cohorts (5 % and 9 %; \( p = 0.65 \)). The authors concluded that prophylactic IVIG should not be administered after allo-SCT, even if administered selectively in a high-dose to patients with delayed immune reconstitution or GVHD.

Also, an UpToDate review on “Immune reconstitution inflammatory syndrome” (Sexton and Pien, 2013) noted that many synonyms exist for IRIS [immune reconstitution inflammatory syndrome]:

- Immune recovery disease
- Immune reconstitution disease
- Immune reconstitution syndrome
- Immune restoration disease
- Immune rebound illness
- Steroid-withdrawal disease
- Immunorestitution disease
- Immune response reactions

There is no mentioning of IVIG as a therapeutic option for IRIS in this UpToDate review.

Gavhed et al (2011) stated that there is currently no well-accepted therapy for central nervous system Langerhans cell histiocytosis (CNS-LCH), a neuroinflammatory disease clinically characterized by often progressive, neurological symptoms including ataxia, dysarthria, dysphagia, hyper-tonicity, intellectual impairment and behavioral abnormalities. These investigators applied immunomodulative/anti-inflamatory treatment on a patient with progressive CNS-LCH disease – IVIG was administered monthly for 15 years to a patient with severe, image-verified neurodegenerative CNS-LCH. During the IVIG treatment, the neurological deterioration initially appeared to be halted, but over time there was still some deterioration. The authors concluded that IVIG may be beneficial in partly haltering CNS-LCH neurodegeneration, but further studies are needed.

Edeer-Karaca et al (2010) stated that common variable immunodeficiency (CVID) is an immunodeficiency syndrome characterized by generalized defective antibody production and recurrent
sino-pulmonary bacterial infections. Autoimmune disease is common in CVID, occurring in approximately 20% of patients, with a slight female predominance. Familial inheritance of CVID is very rare, and these investigators reported 2 siblings with CVID presenting remarkable autoimmune manifestations such as relapsing polychondritis, juvenile idiopathic arthritis and chronic inflammatory bowel disease. Autoimmune and inflammatory complications showed minimal improvement under regular IVIG replacement therapy, prophylactic antibiotics and immunosuppressives in these patients.

Also, an UpToDate review on “Treatment of relapsing polychondritis” (Michet, 2013) did not mention IVIG as a therapeutic option.

Hughes et al (2009) noted that idiopathic solar urticaria (SU) is a rare, debilitating photodermatosis, which may be difficult to treat. First-line treatment with anti-histamines is effective in mild cases, but remission after phototherapeutic induction of tolerance is often short-lived. Other treatment options include PE, photopheresis and cyclosporine. These researchers presented 2 cases of severe, idiopathic SU, which were resistant to conventional treatment. Both patients achieved remission after administration of IVIG and have remained in remission at 13 months and 4 years, respectively. There were only 2 case reports of successful treatment of solar urticaria with IVIG. The authors concluded that in their experience IVIG given at a total dose of 2 g/kg over several 5-day courses about a month apart is an effective treatment option for severe idiopathic SU. It is also generally safe, even if certainly subject to significant theoretical risks, such as induction of viral infection or anaphylaxis.

Llamas-Velasco et al (2011) stated that the treatment of SU can be difficult. Only a few cases of SU have been treated with IVIG (as monotherapy or combined with phototherapy), with reported fastest and durable increase of solar exposure tolerance. In this study, a 61-year old female with severe UVB- and UVA-induced SU and a 62-year old female with severe UVA and visible light-induced SU were both treated with a single course of IVIG (total dose of 2 g/kg), infused over 3 days. Photo-test, performed 3 months after the treatment, showed only a slight minimal urticating dose improvement, and both patients reported just a moderate and “transient” subjective improvement. The authors concluded that their patients’ poorer response, compared with previous reports, may be due to differences in IVIG treatment schedules.

Adamski et al (2011) reported on the effectiveness of IVIG in severe SU. These researchers performed a retrospective multi-centric study via the mailing of a questionnaire to the French photodermatology units to analyze all cases of patients with SU who were treated with IVIG. A total of 7 patients (5 women) with a mean age of 40 years (range of 32 to 55 years) and a mean disease duration of 5 years (range of 2 to 10 years) received IVIG. The administration schedule differed from one patient to another: 1.4 to 2.5 g/kg were infused over 2 to 5 days. Five of 7 patients obtained a complete remission. The number of courses necessary to obtain clinical remission varied from 1 to 3 courses. Complete remission was maintained during 4 to more than 12 months but anti-histamines were still required. In 1 case, PUVA photochemotherapy was administered. The authors concluded that the findings of this case series suggested a beneficial effect of IVIG in severe SU; but additional prospective trials including a larger number of patients are needed to demonstrate the effectiveness of IVIG and to specify the optimal modalities of their administration in this disease. Drawbacks of this study included its retrospective study design, limited number of patients, and variations in the IVIG administration schedule.

Also, an UpToDate review on “Photosensitivity disorders (photodermatoses): Clinical manifestations, diagnosis, and treatment” (Elmets, 2013) does not mention the use of IVIG as a therapeutic option.

In a Cochrane review, Ohlsson and Lacy (2013) examined the effects of IVIG on mortality/morbidity caused by suspected or proven infection at study entry in neonates. These researchers also assessed in a subgroup analysis the effects of IgM-enriched IVIG on mortality from suspected infection. MEDLINE, EMBASE, The Cochrane Library, CINAHL, trial registries, Web of Science, reference lists of identified studies, meta-analyses and personal files were searched in 2013. No language restrictions were applied. Randomized or quasi-randomized controlled trials; newborn infants (less than 28 days old); IVIG for treatment of suspected or proven bacterial/fungal infection compared with placebo or no intervention; one of the following outcomes was reported: mortality, length of hospital stay or psychomotor development at follow-up. Statistical analyses included typical risk ratio (RR), risk difference (RD), weighted mean difference (WMD), number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) (all with 95% CIs and the I-squared (I2) statistic to examine for statistical heterogeneity). The updated search identified 1 published study and 1 ongoing study. A total of 8 studies evaluating 3,871 infants were included in this review. Mortality during
hospital stay in infants with clinically suspected infection at trial entry was not significantly different after IVIG treatment (8 studies (n = 2,425); typical RR 0.94, 95 % CI: 0.80 to 1.12; typical RD -0.01, 95 % CI: -0.04 to 0.02 (I^2) = 28 % for RR and 32 % for RD). Death or major disability at 2 years corrected age was not significantly different in infants with suspected infection after IVIG treatment (1 study (n = 1,985); RR 0.98, 95 % CI: 0.88 to 1.09 RD -0.01, 95 % CI: -0.05 to 0.03). Mortality during hospital stay was not significantly different after IVIG treatment in infants with suspected infection at trial entry (RR 0.95, 95 % CI: 0.74 to 1.21 RD -0.01, 95 % CI: -0.04 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with proven infection at trial entry (RR 1.03, 95 % CI: 0.91 to 1.18; RR 0.91, 95 % CI: -0.01 to 0.06). Mortality during hospital stay in infants with clinically suspected or proven infection at trial entry was not significantly different after IVIG treatment (1 study (n = 3,493); RR 1.00, 95 % CI: 0.86 to 1.16; RR 0.00, 95 % CI: -0.02 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with suspected or proven infection at trial entry (1 study (n = 3,493); RR 1.00, 95 % CI: 0.92 to 1.09; RD -0.00, 95 % CI: -0.03 to 0.03). Length of hospital stay was not reduced for infants with suspected/proven infection at trial entry (1 study (n = 3,493); mean difference (MD) 0.00 days, 95 % CI: -0.61 to 0.61). No significant difference in mortality during hospital stay after IgM-enriched IVIG treatment for suspected infection was reported at trial entry (3 studies (n = 164); typical RR 0.57, 95 % CI: 0.31 to 1.04; RD -0.12, 95 % CI: -0.24 to 0.00; p = 0.06; (I^2) = 2 % for RR and 0 % for RD). The authors concluded that in previous reviews, they encouraged researchers to undertake well-designed trials to confirm or refute the effectiveness of IVIG in reducing adverse outcomes in neonates with suspected infection. Such a trial has been undertaken. Results of the INIS trial, which enrolled 3,493 infants, carried a heavy weight in the current update of this review, and the undisputed results showed no reduction in death or major disability at 2 years of age. They stated that routine administration of IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended.

Noguchi et al (2003) reported on the case of a 62-year-old woman who was admitted to the authors’ hospital because of muscle weakness and sensory disturbance in extremities. She showed weakness, muscle atrophy and sensory abnormality in 4 limbs with patchy distribution, suggesting involvement of multiple peripheral nerve trunks. Serum titers of anti-SS-A, SS-B, and antinuclear antibody were elevated. Sural nerve biopsy showed recanalization and lymphocytic infiltration in the epineural small vessels, suggesting the presence of vasculitis. She was diagnosed as having vasculitic neuropathy complicated with Sjogren's syndrome. Methylprednisolone pulse therapy followed by oral prednisolone was started and these symptoms gradually improved in 1 month. At age 63, she felt dysesthesia in the right lower limb and this sensory abnormality spread to upper limbs. Two years later, she was admitted again due to clumsiness of hands and gait disturbance. Neurological examination showed decreased vibration and position sense of lower limbs and limb ataxia in addition to dysesthesia. Electrophysiological studies demonstrated significant decrease in amplitude of sensory nerve action potentials and delayed somatosensory evoked potentials after N13, indicating impairment of dorsal root ganglions. She was treated with IVIG (400 mg/kg, total 15 g/day) for 5 days. One week later, sensory ataxia was improved. It has been known that Sjogren's syndrome is often complicate with various types of neuropathies including vasculitic neuropathy and sensory neuropathy. This patient developed these 2 different types of neuropathies, which were dramatically improved after 2 different therapeutic regimens; indicating the importance to select a suitable treatment regimen in accordance with the mechanism of neuropathy associated with Sjogren's syndrome.

De Toni Franceschini et al (2011) reported on the case of a 64-year-old woman, with asthma and sinusal polyposis in her medical history, who suddenly developed a painful polyneuropathy with diplopia. Nerve conduction studies, performed at the very onset of the neuropathy, could not definitely rule out a Guillain-Barre syndrome (GBS) and high-dose IVIG was administered. Clinical and laboratory findings subsequently supported the diagnosis of Churg-Strauss syndrome; corticosteroid therapy was started and clinical stabilization of neuropathy was apparently achieved. No indicators of unfavorable outcome were present at that time. Nevertheless, 30 days after the onset the patient acutely worsened with severe polyneuropathy relapse and fatal systemic diffusion to heart, kidney and mesenteric district, which a single cyclophosphamide pulse failed to control. The authors stated that this case highlighted the possibility that a GBS-like onset of Churg-Strauss syndrome neuropathy should be regarded as a part of multi-organ, severe or even life-threatening vasculitic involvement, requiring the most aggressive treatments, regardless of the presence of recognized factors of poor outcome.

Moreover, an UpToDate review on “Diagnosis and treatment of vasculitic neuropathy” (Brass and Helfgott, 2013) did not mention the use of IVIG as a therapeutic option.
Thus, there is insufficient evidence to support the use of IVIG for the treatment of vasculitic polyneuropathy.

An UpToDate review on “Treatment and prognosis of Waldenstrom macroglobulinemia” (Rajkumar, 2013) does not mention IVIG as a therapeutic option.

The Australian National IVIg Criteria Review Working Group (NICRWG)'s guideline on "Criteria for the clinical use of intravenous immunoglobulin" (2012) concluded that the evidence for IVIG for autonomic ganglionopathy is insufficient (level 4a evidence -- small case studies only) and should be used only in exceptional circumstances -- such as in urgent or life-threatening circumstances, or in circumstances in which significant morbidity would be expected and other clinically appropriate standard therapies have been either exhausted or are contraindicated.

Furthermore, a multi-center clinical trial of IVIG for autoimmune autonomic neuropathy is ongoing. https://clinicaltrials.gov/ct2/show/NCT01522235.

Simon et al (2013) evaluated the likelihood of response to IVIG by studying consecutive patients presenting with progressive, asymmetric, pure lower motor neuron (LMN) limb weakness, and determined the clinical phenotype of those who respond. A total of 31 consecutive patients with progressive, focal-onset LMN limb weakness, without evidence of clinical upper motor neuron signs; sensory, respiratory, or bulbar involvement; or evidence of motor nerve conduction block on electrodiagnostic studies, were prospectively included in this study. Each patient underwent treatment with IVIG (2 g/kg body weight) for a minimum of 3 months. Electrodiagnostic studies, a neuromuscular symptom score, and expanded Medical Research Council sum score were documented before and after IVIG treatment. The final diagnosis was determined after prolonged clinical follow-up. Only 3 of 31 patients (10 %) responded to IVIG. All responders demonstrated distal upper limb-onset weakness, EMG abnormalities confined to the clinically weak muscles, and a normal creatine kinase. This set of features was also identified in 31 % of non-responders presenting with distal upper limb weakness. Sex, age at onset, number of involved limb regions, and the duration of symptoms before treatment were not significantly different between groups. The authors concluded that the findings of this study do not support uniform use of IVIG in patients presenting with progressive asymmetric LMN limb weakness. It is suggested that IVIG treatment be limited to patients who demonstrate clinical and laboratory features suggestive of multifocal motor neuropathy. This study provided Class IV evidence that IVIG will not improve muscle function in 90 % of patients with progressive, asymmetric, pure LMN weakness.

McMahan et al (2014) highlighted novel therapies that are being used in SSc. Therapeutic interventions in SSc generally target at least 1 of 3 ongoing biological processes characteristic of the disease: vasculopathy, autoimmunity and tissue fibrosis. Treatment decisions in SSc are determined by the level of disease activity and the degree of specific organ involvement. Traditional therapy has primarily focused on organ-specific management without clear evidence of overall disease modification. The authors provided a review of a variety of agents, which are already used for other autoimmune diseases, that are now being used to treat active SSc skin or lung disease, including rituximab, tocilizumab and IVIG. Several agents studied in-vitro and in animal models of fibrosis have shown promise, including bortezomib, LPA-1 antagonists, anti-CCN2 therapy, anti-IL-13 and thrombin antagonists. The authors also provided details on targeting intracellular molecular pathways and matricellular proteins, which is another novel area of investigation. The authors concluded that combination therapy may be necessary to control the complex biological network active in SSc. They noted that most of the current evidence that suggest benefit of these agents is based on small population studies; ultimately well-designed clinical trials are needed to define the role of these agents in treating SSc.

An UpToDate review on “Overview of the treatment of acute lymphoblastic leukemia in children and adolescents” (Horton and Steuber, 2014) does not mention IVIG as a management tool. Furthermore, the National Comprehensive Cancer Network’s clinical practice guideline on “Acute Lymphoblastic Leukemia” (Version 1.2014) does not mention IVIG as a management toll.

Toledano et al (2014) evaluated a trial of immunotherapy (IT) as an aid to diagnosis in suspected autoimmune epilepsy. These investigators reviewed the charts of 110 patients seen at the authors’ autoimmune neurology clinic with seizures as a chief complaint. A total of 29 patients met the following inclusion criteria: (i) autoimmune epilepsy suspected based on the presence of greater than or equal to 1 neural autoantibody (n = 23), personal or family history or physical stigmata of autoimmunity, and frequent or medically intractable seizures; and (ii) initiated a 6- to 12-week trial of IV methylprednisolone
In an editorial that accompanied the afore-mentioned study, Ruegg and Panzer (2014) stated that “These results lay the foundation for a randomized controlled trial of IT in presumed autoimmune epilepsy, which would compare standardized treatment groups, thereby eliminating biases with regards to treatment choice and disease severity. This study should also pave the way for additional prospective studies regarding the natural history of autoimmune PRE [pharmaco-resistant epilepsy] and serves to raise awareness of the role of IT in the treatment of refractory epilepsies”.

Rogosnitzky and colleagues (2012) stated that Crohn's disease (CD) is a debilitating condition that still requires improvement in its management. There is a need for alternatives to anti-tumor necrosis factor (TNF) drugs that are costly and beneficial in less than 50% of patients. Intravenous immunoglobulin (IVIG) has been used in the management of aminosalicylate- and steroid-resistant CD for more than 20 years, although the published literature available is limited. A literature search identified 17 relevant publications since 1969, including 5 case reports of single patients, 2 abstracts, 3 conference papers, 1 review paper and 6 book or journal articles. No randomized controlled trials (RCTs) of IVIG in CD have been published. A review of the evidence identified indicated that IVIG can induce a rapid and significant improvement in aminosalicylate- and steroid-resistant CD, often within days of the initial administration. Data from longer-term studies showed that maintenance of remission over the medium-term is also possible. The authors concluded that these encouraging findings provided a rationale for the initiation of larger RCTs of IVIG in CD with the aim of providing further treatment options for this difficult-to-manage condition.

Furthermore, UpToDate reviews on “Overview of the medical management of mild to moderate Crohn disease in adults” (Farrell and Peppercorn, 2014a), “Overview of the medical management of severe or refractory Crohn disease in adults” (Farrell and Peppercorn, 2014b) and “Immunomodulator therapy in Crohn disease” (MacDermott, 2014) do not mention the use of IVIG/intravenous immunoglobulin as a therapeutic option.

An UpToDate review on “Approach to the patient with colonic polyps” (Ahnen and Macrae, 2014) states that “Cronkhite-Canada syndrome is a rare, nonfamilial disorder of unknown etiology associated with alopecia, cutaneous hyperpigmentation, gastrointestinal polyposis, onychodystrophy, diarrhea, weight loss, and abdominal pain. The polyps are hamartomas and do not appear neoplastic pathologically. Characteristic features include myxoid expansion of the lamina propria and increased eosinophils in the polyps. There is some evidence that the disorder may be immune-mediated, since it may respond to immunosuppressive therapy and, in some patients, immunostaining of the polyps for IgG4 is positive. Five-year mortality rates as high as 55 percent have been reported with most deaths due to gastrointestinal bleeding, sepsis, and congestive heart failure. Treatment has included nutritional support, glucocorticoids, azathioprine, acid suppression, and antibiotics, but no specific treatment has proven to be consistently effective”. This review does not mention IVIG as a therapeutic option.

Louis et al (2014) stated that IVIG is used in neonates with isoimmune hemolytic disease to prevent exchange transfusion (ET). However, studies supporting IVIG had methodological issues. These researchers updated the systematic review of safety and effectiveness of IVIG in neonates with isoimmune hemolytic disease. MEDLINE, Embase databases and Cochrane Central Register of Controlled Trials (Cochrane Library) were searched (from inception to May 2013) for randomized or
quasi-randomized controlled trials comparing IVIG with placebo/controls in neonates with isoimmune hemolytic disease without any language restriction. Three investigators assessed methodological quality of included trials. Meta-analyses were performed using random effect model and risk ratio (RR)/risk difference (RD) and mean difference with 95 % CI calculated. A total of 12 studies were included; 10 trials (n = 463) of Rh isoimmunization and 5 trials (n = 350) of ABO isoimmunization (3 studies had both population). Significant variations in risk of bias precluded an overall meta-analysis of Rh isoimmunization. Studies with high risk of bias showed that IVIG reduced the rate of ET in Rh isoimmunization (RR 0.23, 95 % CI: 0.13 to 0.40), whereas studies with low risk of bias that also used prophylactic phototherapy did not show statistically significant difference (RR 0.82, 95 % CI: 0.53 to 1.26). For ABO isoimmunization, only studies with high risk of bias were available and meta-analysis revealed efficacy of IVIG in reducing ET (RR 0.31, 95 % CI: 0.18 to 0.55). The authors concluded that the effectiveness of IVIG is not conclusive in Rh hemolytic disease of newborn with studies with low risk of bias indicating no benefit and studies with high risk of bias suggesting benefit. They stated that the role of IVIG in ABO disease is not clear as studies that showed a benefit had high risk of bias.

Beken et al (2014) noted that there is still no consensus on the use of IVIG in ABO hemolytic disease of the newborn routinely. These investigators examined if administration of IVIG to newborns with ABO incompatibility is necessary. A total of 117 patients with ABO hemolytic disease and positive Coombs test were enrolled into the study. The subjects were healthy except jaundice. Infants were divided into 2 groups: Group I (n = 71) received 1 dose of IVIG (1 g/kg) and LED phototherapy; and Group II (n = 46) received only LED phototherapy. One patient received erythrocyte transfusion in Group I, no exchange transfusion was performed in both groups. Mean duration of phototherapy was 3.1 ± 1.3 days in Group I and 2.27 ± 0.7 days in Group II (p < 0.05). Mean duration of hospital stay was 5.34 ± 2.2 days in Group I and 3.53 ± 1.3 days in Group II (p < 0.05). Mean duration of phototherapy was 4.0 ± 1.5 days and 2.73 ± 1.1 days in double and single doses of IVIG, respectively, and this was statistically significant (p < 0.05). The authors concluded that IVIG therapy didn’t decrease neither phototherapy nor hospitalization duration in infants with ABO hemolytic disease. They stated that meticulous follow-up of infants with ABO hemolytic disease and LED phototherapy decreased morbidity; IVIG failed to show preventing hemolysis in ABO hemolytic disease.

An UpToDate review on “Brachial plexus syndromes” (Bromberg, 2014) does not mention the use of IVIG as a therapeutic option.

UpToDate reviews on “Diagnosis and management of solitary extramedullary plasmacytoma” (Rajkumar, 2014a) and “Diagnosis and management of solitary plasmacytoma of bone” (Rajkumar, 2014b) do not mention IVIG as a therapeutic option.

An UpToDate review on “Postural tachycardia syndrome” (Freeman and Kaufman, 2014) does not mention the use of IVIG as a therapeutic option for POTS.

Parambil and colleagues (2011) noted that small fiber neuropathy (SFN) is commonly associated with sarcoidosis and can cause significant morbidity to afflicted patients. The appropriate treatment of this condition, when associated with sarcoidosis, is not well-established. These investigators presented the findings of case series of 3 patients with sarcoidosis and SFN. The presenting clinical features, skin biopsy results, autonomic reflex screen and quantitative sudomotor axon reflex testing (QSART) findings, and response to therapy are delineated. They described 3 patients with biopsy-proven sarcoidosis who developed intractable neuropathic pain and/or symptoms related to associated autonomic dysfunction despite treatment with various immunosuppressive medications and narcotic analgesics. QSART showed evidence of a post-ganglionic sudomotor abnormality in 1 patient and was normal in the other 2. Skin biopsy findings were abnormal, demonstrating a non-length-dependent sensory SFN in all 3 patients. Painful neuropathic symptoms, as well as symptoms related to dysautonomia from SFN responded significantly to treatment with intravenous immunoglobulin (IVIG). The authors concluded that IVIG appears to be effective in relieving symptoms from SFN associated with sarcoidosis, suggesting an underlying immune mechanism. Moreover, they stated that larger prospective, controlled studies would be needed to confirm this response to IVIG and to further elucidate the underlying pathobiology behind this association with sarcoidosis.

Tzekou and Fehlings (2014) stated that neuroinflammation plays an important role in the secondary pathophysiological mechanisms of spinal cord injury (SCI) and can exacerbate the primary trauma and thus worsen recovery. Although some aspects of the immune response are beneficial, it is thought that leukocyte recruitment and activation in the acute phase of injury results in the production of cytotoxic
substances that are harmful to the nervous tissue. Therefore, suppression of excessive inflammation in the spinal cord could serve as a therapeutic strategy to attenuate tissue damage. The immunosuppressant methylprednisolone has been used in the setting of SCI, but there are complications which have attenuated the initial enthusiasm. Hence, there is interest in other immunomodulatory approaches, such as IVIG. Importantly, IVIG is used clinically for the treatment of several auto-immune neuropathies, such as GBS, CIDP and Kawasaki disease, with a good safety profile. Thus, it is a promising treatment candidate for SCI. Indeed, IVIG has been shown by these researchers to attenuate the immune response and result in improved neurobehavioral recovery following cervical SCI in rats through a mechanism that involves the attenuation of neutrophil recruitment and reduction in the levels of cytokines and cytotoxic enzymes. The authors reviewed published data in the context of relevant mechanisms of action that have been proposed for IVIG in other conditions. They hoped that this discussion will trigger future research to provide supporting evidence for the efficiency and detailed mechanisms of action of this promising drug in the treatment of SCI, and to facilitate its clinical translation.

Xie and colleagues (2015) noted that Clarkson disease (systemic capillary leak syndrome) is a highly rare disorder of unknown etiology. The disease is characterized by episodes of transient vascular collapse, which leads to hypotensive shock and anasarca. Previous treatment of this potentially devastating condition has been largely ineffective. In a longitudinal follow-up study, these researchers evaluated IVIG prophylactic therapy in a cohort of 29 patients with Clarkson disease. All patients received treatments at the discretion of their primary providers and retrospectively via questionnaire recorded symptoms beginning with their first documented episode of the disease until May 31, 2014. Twenty-two out of 29 patients (76 %) responded to the questionnaire, and 18 out of the 22 respondents received monthly prophylaxis with IVIG during the study period for a median interval of 32 months. The median annual attack frequency was 2.6/patient prior to IVIG therapy and 0/patient following initiation of IVIG prophylaxis (p = 0.001); 15 out of 18 subjects with a history of 1 or more acute Clarkson disease episodes experienced no further symptoms while on IVIG therapy. The authors concluded that IVIG prophylaxis is associated with a dramatic reduction in the occurrence of systemic capillary leak syndrome attacks in most patients, with minimal side effects. They stated that a prospective, randomized trial is needed to fully evaluate the benefits of IVIG for Clarkson disease and to determine optimal dosage and duration of therapy.

Appendix

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<th>Condition</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>IVIG may be considered medically necessary in persons with acute disseminated encephalomyelitis who have an insufficient response to intravenous corticosteroid treatment.</td>
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<tr>
<td>Autoimmune hemolytic anemia, refractory</td>
<td>IVIG may be considered medically necessary in persons with warm-type autoimmune hemolytic anemia that does not respond to corticosteroids or splenectomy, or those for whom the latter two treatments are contraindicated.</td>
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<tr>
<td>Bacterial infection in HIV-infected children</td>
<td>Consistent with recommendations of the Working Group on Antiretroviral Therapy of the National Pediatric HIV Resource Center IVIG is considered medically necessary in children with HIV-infection who meet any of the following criteria:</td>
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<td></td>
<td>I. Those with recurrent serious bacterial infections, i.e., defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1-year period;</td>
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<td>II. Those who fail to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine;</td>
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<td></td>
<td>III. Those living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live;</td>
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<tr>
<td><strong>Birdshot (vitiligenous) retinochoroidopathy</strong></td>
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<tr>
<td>IVIG is considered medically necessary for birdshot (vitiligenous) retinochoroidopathy that is not responsive to immunosuppressives (e.g., corticosteroids, cyclosporine).</td>
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<thead>
<tr>
<th><strong>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), also known as Chronic Relapsing Polyneuropathy</strong>, including diabetes mellitus-CIDP and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric or focal neurologic deficits with slowly progressive or relapsing course over 2 months or longer (with neurophysiological abnormalities).</td>
</tr>
<tr>
<td><strong>Note:</strong> A meta-analysis comparing the efficacy if IVIG, plasma exchange, and oral glucocorticoids found equivalence between all three, at least within the first 6 weeks of therapy (Van Schaik et al, 2002). IVIG is considered under accepted guidelines as the preferred treatment, particularly in children, when there is difficulty with venous access for plasmapheresis, and those susceptible to the complications of long-term corticosteroid therapy (Orange et al, 2006).</td>
</tr>
<tr>
<td>Persons typically respond to IVIG or plasma exchange within the first several weeks of treatment and may demonstrate sustained improvement for many weeks or months. Relapses may require periodic isolated treatments with a single dose of IVIG or single plasma exchange. If a person responds successfully to infrequent booster treatments of either IVIG or plasma exchange, it is considered medically necessary to prescribe maintenance therapy with IVIG to prevent relapse, rather than adding corticosteroids or other immunosuppressants.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Chronic Lymphocytic Leukemia (CLL) in patients with hypogamma-globulinemia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG level less than 600 mg/dL; and:</td>
</tr>
</tbody>
</table>

| I. 1 severe bacterial infection within preceding 6 months or 2 or more bacterial infections in 1 year; or |

| II. Evidence of specific antibody deficiency. |

<table>
<thead>
<tr>
<th><strong>Dermatomyositis, Polymyositis(includes Juvenile)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Members presenting at least one item from the 1st criterion and four items from the 2nd through 9th criteria are said to have dermatomyositis. Patients presenting no items from the 1st criterion and at least four items from the 2nd through 9th criteria are said to have polymyositis.</td>
</tr>
</tbody>
</table>

| A. Skin lesions |

| 1. Heliotrope rash (red purple edematous erythema on the upper palpebra) |

| 2. Gottron's sign (red purple keratotic, atrophic erythema, or macules on the extensor surface of finger joints) |

| 3. Erythema on the extensor surface of extremity joints: slightly raised red purple erythema over elbows or knees |

<p>| B. Proximal muscle weakness (upper or lower extremity and trunk) |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. Elevated serum CK (creatine kinase) or aldolase level</td>
<td></td>
</tr>
<tr>
<td>D. Muscle pain on grasping or spontaneous pain</td>
<td></td>
</tr>
<tr>
<td>E. Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)</td>
<td></td>
</tr>
<tr>
<td>F. Positive anti-Jo-1 (histadyl tRNA synthetase) antibody</td>
<td></td>
</tr>
<tr>
<td>G. Non-destructive arthritis or arthralgias</td>
<td></td>
</tr>
<tr>
<td>H. 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)</td>
<td></td>
</tr>
<tr>
<td>I. Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen)</td>
<td></td>
</tr>
</tbody>
</table>

AND

II. Member has severe active illness; and

III. Member is intolerant or refractory to 1st and 2nd line therapies:

A. 1st line therapy - Corticosteroids (e.g., prednisone);
B. 2nd line therapy - Immuno-suppressants (e.g., methotrexate, azathioprine, cyclophosphamide, and cyclosporine).

**Enteroviral meningoencephalitis**

IVIG is considered medically necessary in severe cases of enteroviral meningoencephalitis lacking other therapeutic options.

**Fetal Alloimmune Thrombocytopenia (FAIT)**

Maternal and paternal platelet typing reveals the father has a platelet antigen that the mother lacks and the mother has detectable antibodies to this antigen (to HPA 1a are the most common cause of FAIT); and

I. At 20 weeks or later, cordocentesis reveals fetal platelets less than 20 x 1000/mL(3); or
II. Previous pregnancy affected by FAIT.

**Guillain Barre Syndrome (GBS)**
a.k.a. acute infective polyneuritis (includes GBS variants: Miller-Fisher syndrome [MFS], pan autonomic polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN))

I. Severe GBS with significant weakness such as inability to stand or walk without aid, respiratory or bulbar weakness, or Miller-Fisher syndrome (MFS); and
II. The disorder has been diagnosed during the first 2 weeks of the illness; and
III. IVIG is initiated within one month of symptom onset. **Note:** Based on the 2003 AAN guidelines, IVIG should usually be initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms.

**Hematopoietic Stem Cell Transplant (HSCT) or Bone Marrow Transplant (BMT)**

IVIG is considered medically necessary for prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for treatment of recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL), who
<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| HIV-associated Thrombocytopenia - Adult       | I. Significant bleeding in thrombocytopenic patients or platelet count less than 20,000/ul; and  
II. Failure of RhIG in Rh-positive patients.                                                                                                                                                           |
| HIV-associated Thrombocytopenia - Pediatric   | Infants and children less than 13 years of age whose and  
I. Child has received 2 doses of measles vaccine and lives in a region with a high prevalence of measles; or  
II. Member has HIV-associated thrombocytopenia despite anti-retroviral therapy; or  
III. Member has chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy; or  
IV. T4 cell count is greater than or equal to 200/mm3.                                                                                                                                              |
| Hemolytic Disease of the Newborn              | Not responding to phototherapy to decrease the need for exchange transfusion. Physician discretion important in deciding.                                                                                                                                           |
| Hyperimmunoglobulin E Syndrome (Job Syndrome; Hyper IgE syndrome) | Recurrent staphylococcal abscesses and markedly elevated serum IgE with normal IgG, IgA, and IgM concentrations.                                                                                           |
| Idiopathic Thrombocytopenic Purpura (ITP) - Adult | I. Other causes of thrombocytopenia have been ruled out by history and peripheral smear; and  
Unresponsive to corticosteroid therapy; and  
Management of acute bleeding due to severe thrombocytopenia (platelet counts less than 30,000/ul); or  
II. To increase platelet counts prior to invasive major surgical procedures (e.g., splenectomy), or  
III. To defer or avoid splenectomy; or  
IV. In members with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage. |
| Idiopathic Thrombocytopenic Purpura (ITP) - Pediatric | Acute ITP:  
I. IVIG as initial therapy if platelet count less than 20,000/ul, especially when member has emergency bleeding or is at risk for severe life-threatening bleeding; or  
II. Persons with severe thrombo-cytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage. |
**Note:** IVIG not indicated if only mild manifestations of bleeding.

**Chronic ITP:**
In high-risk persons when platelet count low or person symptomatic; and

1. Failure of other therapies, or
2. Member is a high risk for post-splenectomy sepsis.

### Idiopathic Thrombocytopenic Purpura (ITP), Chronic Refractory

1. Age of 10 years or older; and
2. Duration of illness of greater than 6 months; and
3. No concurrent illness/disease explaining thrombocytopenia; and
4. Prior treatment with corticosteroids and splenectomy has failed or member is at high-risk for post-splenectomy sepsis.

### Immune Thrombocytopenic Purpura (ITP) in Pregnancy

1. Refractory to steroids with platelet counts less than 10,000/ul in the 3rd trimester; or
2. Platelet counts less than 30,000/ul associated with bleeding before vaginal delivery or C-section; or
3. Pregnant women who have previously delivered infants with autoimmune thrombocytopenia; or
4. Pregnant women who have platelet counts less than 50,000/ul during the current pregnancy; or
5. Pregnant women with past history of splenectomy.

### Immunosuppressed Patients
To prevent or modify recurrent bacterial or viral infections (e.g., CMV) in members with iatrogenically induced, or disease associated immunosuppression (IgG less than 400 mg/dL) with one of the following:

1. Solid organ transplants or extensive surgery with immunosuppression (Note: In particular, IVIG may be medically necessary in persons undergoing multiple courses of plasmapheresis as a treatment for allograft rejection or for other indications; these persons may receive IVIG at the completion of therapy if their IgG level is less than 400 mg/dL); or
2. Hematological malignancy; or
3. Extensive burns; or

### Kawasaki disease (Mucocutaneous Lymph Node Syndrome [MCLS])
Diagnosis must be established -- no specific lab test -- diagnosis is established by meeting the following criteria:

1. Fever present for at least 5 days; and
2. 4 of the following 5 conditions are met:
   - A. Mucous membrane changes such as a red tongue and dry fissured lips;
   - B. Swelling of the hands and feet;
   - C. Enlarged lymph nodes in the neck;
   - D. Diffuse red rash covering most of the body;
<table>
<thead>
<tr>
<th>E. Redness of the eyes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lambert-Eaton Myasthenic Syndrome (LEMS)</strong></td>
</tr>
<tr>
<td>No response to anti-cholinesterases and dalfampridine (Amypra); and</td>
</tr>
<tr>
<td>I. Used as an alternative to plasma exchange if weakness is severe; or</td>
</tr>
<tr>
<td>II. When there is difficulty with venous access for plasmapheresis.</td>
</tr>
<tr>
<td><strong>Myasthenia Gravis</strong></td>
</tr>
<tr>
<td>Treatment of acute myasthenic crisis with decompensation (respiratory failure, or disabling weakness requiring hospital admission); and other treatments have been unsuccessful or are contraindicated (e.g., azathioprine, cyclosporine, and cyclophosphamid).</td>
</tr>
<tr>
<td><strong>Note:</strong> For management of myasthenic crises, IVIG is administered over 2 to 5 days. Use of IVIG as maintenance therapy is considered experimental and investigational.</td>
</tr>
<tr>
<td><strong>Moersch-Woltmann (Stiff-man) Syndrome</strong></td>
</tr>
<tr>
<td>I. Presence of anti-GAD antibody; and</td>
</tr>
<tr>
<td>II. Benzodiazepines (e.g., Valium) and/or baclofen, phenytoin, clonidine, tizanidine have failed.</td>
</tr>
<tr>
<td><strong>Multifocal Motor Neuropathy with Conduction Block</strong></td>
</tr>
<tr>
<td>Progressive, symptomatic multifocal motor neuropathy that has been diagnosed on the basis of electrophysiologic findings that rule out other possible conditions that may not respond to IVIG treatment.</td>
</tr>
<tr>
<td><strong>Multiple Myeloma (MM)</strong></td>
</tr>
<tr>
<td>I. &quot;Plateau Phase&quot; MM (greater than 3 months since diagnosis); and</td>
</tr>
<tr>
<td>II. IgG level less than 600 mg/dL; and</td>
</tr>
<tr>
<td>III. 2 or more significant infections in last year or a single life threatening infection; or</td>
</tr>
<tr>
<td>Evidence of specific antibody deficiency.</td>
</tr>
<tr>
<td><strong>Multiple Sclerosis (MS) - Relapsing-remitting (not primary or secondary progressive MS)</strong></td>
</tr>
<tr>
<td>I. Severe manifestations of relapsing-remitting MS (not primary or secondary progressive MS); and</td>
</tr>
<tr>
<td>II. Standard approaches (i.e., interferons – Betaseron, Avonex, Rebif) have failed, become intolerable, or are contraindicated.</td>
</tr>
<tr>
<td><strong>Neonatal Hemochromatosis</strong></td>
</tr>
<tr>
<td>Treatment of pregnant women who have a history of pregnancy ended in documented neonatal hemochromatosis. (<strong>Note:</strong> Dosage should be 1g/kg body weight weekly from the 18th week until the end of gestation).</td>
</tr>
<tr>
<td><strong>Neuroblastoma associated paraneoplastic opsoclonus-myoclonus-ataxia syndrome</strong></td>
</tr>
<tr>
<td>Treatment of opsoclonus-myoclonus-ataxia associated with neuroblastoma.</td>
</tr>
<tr>
<td><strong>Opsoclonus-myoclonus</strong></td>
</tr>
<tr>
<td>Medically necessary as last-resort treatment for refractory opsoclonus-myoclonus.</td>
</tr>
<tr>
<td>Erythrovirus (formerly parvovirus) B19 Infection, Chronic, with Severe Anemia (Pure Red Cell Aplasia)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Post-transfusion purpura (PTP)</td>
</tr>
<tr>
<td>Primary Humoral Immunodeficiencies</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
1.0 mcg/mL); or

III. Selective IgG subclass deficiencies (see criteria in section of selective IgG subclass deficiency below); or

IV. Normal total IgG levels with severe polysaccharide non-responsiveness and evidence of recurrent severe difficult-to-treat infections (e.g., recurrent otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, multiple antibiotic hypersensitivities, chronic or recurrent sinusitis) (see table below) with a documented requirement for antibiotic therapy:

A. Member has unexplained recurrent or persistent severe bacterial infections despite adequate treatment, including all of the following:

1. Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis);
2. Prophylactic antibiotics;
3. Increased vigilance and appropriate antibiotic therapy for infections; and
4. Immunization with conjugate vaccines in patients who have not responded to polysaccharide vaccines.

B. Serum antibody titers to pneumococcus must be measured prior to immunization and 4 to 6 weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax); at least 14 polysaccharide antigens must be tested.

C. Polysaccharide non-responsiveness is defined as lack of protective antibody titer (specific IgG antibody titer less than 1.3 mcg/ml) in greater than 70% of antigens tested (more than 50% in children aged 2 to 5 years).

D. Further evidence of infection, including sinus and lung imaging, complete blood counts, C-reactive protein measurement, and erythrocyte sedimentation rate determination, may be required to support the need for IVIG supplementation.

E. For children 12 years of age or younger with normal total IgG levels and severe polysaccharide nonresponsiveness, IVIG must be discontinued and the medical necessity of IVIG re-evaluated 1 year after initiating therapy and every 2 years thereafter by reassessing immune response to protein and polysaccharide antigens. Immune response must be re-evaluated at least 3 months after discontinuation of IVIG. IVIG must also be discontinued at that time if the number and/or severity of infections have not been reduced, as not all persons with polysaccharide nonresponsiveness benefit from IVIG.

The use of IVIG may not be medically necessary in certain secondary immunodeficiency states; correction of the underlying condition is the preferred approach.
<table>
<thead>
<tr>
<th>Rasmussen Encephalitis</th>
<th>For children whose symptoms do not improve with anti-epileptic drugs and corticosteroids.</th>
</tr>
</thead>
</table>
| **Selective IgG Subclass Deficiency** | I. Deficiency of one or more IgG subclasses to levels less than 2 standard deviations below the age-specific mean (see table below). These levels must be assessed on at least two occasions while the patient is free of infections; and  
II. Member has unexplained recurrent or persistent severe bacterial infections despite adequate treatment, including all of the following:  
   A. Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (e.g., asthma, allergic rhinitis);  
   B. Prophylactic antibiotics;  
   C. Increased vigilance and appropriate antibiotic therapy for infections; and  
   D. Immunization with conjugate vaccines in patients who have not responded to polysaccharide vaccines; and  
III. Member has demonstrated an inability to mount an adequate response to protein and polysaccharide antigens, as determined by the following criteria:  
   A. Member has documented inability to mount an antibody response to protein antigens: Serum antibody titers to tetanus and/or diphtheria must be obtained prior to immunization with diphtheria and/or tetanus vaccine and 3 to 4 weeks after immunization. An inadequate response is defined as a postvaccination titer less than 0.1 international units/mL for diphtheria, and 0.1 international units/mL or less for tetanus; and  
   B. Member has documented inability to mount an adequate antibody response to polysaccharide antigens. Serum antibody titres to at least 14 pneumococcus serotypes must be measured prior to immunization and 4 to 6 weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax). An inadequate response is defined as lack of protective antibody titer (i.e., specific IgG concentration less than 1.3 mcg/mL) in at least 70% of serotypes tested (in at least 50% of serotypes tested in children aged 2 to 5 years); and  

**Note:** Response to polysaccharide antigens is not reliable in children less than 2 years of age.  
IV. In children 12 years of age or younger, IVIG must be discontinued and the medical necessity of IVIG must be re-evaluated 1 year after initiating therapy and every 2 years thereafter by re-assessing immune response to protein and polysaccharide antigens. Immune response must be re-evaluated at least 3 months after discontinuation of IVIG. IVIG must also be discontinued at that time if the number |
and/or severity of infections have not been reduced, as not all persons with selective IgG subclass deficiencies benefit from IVIG.

<table>
<thead>
<tr>
<th>Indications</th>
<th>2 to 5 years</th>
<th>6+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections (URIs) treated with antibiotics in last 12 months</td>
<td>≥ 4</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Otitis treated with antibiotics (per year)</td>
<td>≥ 3</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Sinusitis episodes (per year)</td>
<td>≥ 2</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Chronic, treatment-resistant sinusitis (&gt;1 mo)</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Pneumonias (per year)</td>
<td>≥ 2</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Invasive infections (sepsis, meningitis, osteomyelitis)</td>
<td>≥ 2</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Severe invasive infections</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td><strong>Gastrointestinal Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic diarrhea due to rotavirus, other</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Chronic/recurrent Giardia lamblia infection</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td><strong>Antibiotic Use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for preventive antibiotic use</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Chronic antibiotic use without effect</td>
<td>&gt; 2 months</td>
<td>&gt; 2 months</td>
</tr>
<tr>
<td>Allergy to antibiotics</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Need for IV antibiotics to clear infection</td>
<td>≥ 1</td>
<td>≥ 1</td>
</tr>
</tbody>
</table>

The laboratory's own reference ranges should be used, where available. If the laboratory's reference ranges are not submitted with the immunoglobulin level results, the following standard reference ranges may be applied.

<table>
<thead>
<tr>
<th>Normal Immunoglobulin Levels (mg/dl)</th>
<th>Normal IgG Subclass Levels (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>IgA</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>1 - 2 mo</td>
<td>1 - 53</td>
</tr>
<tr>
<td>2 - 3 mo</td>
<td>3 - 47</td>
</tr>
<tr>
<td>3 - 4 mo</td>
<td>4 - 73</td>
</tr>
<tr>
<td>4 - 5 mo</td>
<td>8 - 84</td>
</tr>
<tr>
<td>5 - 6 mo</td>
<td>8 - 68</td>
</tr>
<tr>
<td>6 - 8 mo</td>
<td>11 - 90</td>
</tr>
<tr>
<td>8 mo - 1 yr</td>
<td>16 - 84</td>
</tr>
<tr>
<td>1 - 2 yr</td>
<td>14 - 106</td>
</tr>
<tr>
<td>2 - 3 yr</td>
<td>14 - 123</td>
</tr>
<tr>
<td>3 - 4 yr</td>
<td>22 - 159</td>
</tr>
<tr>
<td>6 - 9 yr</td>
<td>33 - 202</td>
</tr>
<tr>
<td>9 - 11 yr</td>
<td>45 - 236</td>
</tr>
<tr>
<td>11 yr &amp; up</td>
<td>70 - 312</td>
</tr>
</tbody>
</table>

Aetna considers IVIG therapy experimental and investigational for any of the following conditions (in alphabetical order):

- Acquired factor VIII inhibitors
- Acquired von Willebrand's disease
- Acute lymphocytic leukemia
- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Acute optic neuritis
- Adrenoleukodystrophy
- Alzheimer’s disease
- Amyotrophic lateral sclerosis
- Angioidema
- Anti-myelin-associated glycoprotein neuropathy
- Antiphospholipid syndrome
- Aplastic anemia
- Asthma
- Attention deficit hyperactivity disorder
- Autism
- Autoimmune autonomic ganglionopathy
- Epilepsy
- Fahn's disease
- Fetal red blood cell alloimmunization
- Gastric enterovirus
- Gastroenteropathy
- Goodpasture’s syndrome
- Hashimoto’s encephalopathy
- Hemolytic transfusion reaction
- Hemolytic-uremic syndrome
- Hemophagocytic syndrome (e.g., hemophagocytic lymphohistiocytosis)
- Henoch-Schonlein purpura
- HTLV-1 associated myelopathy
- Hunter syndrome (mucopolysaccharidosis type II)
- Idiopathic environmental illness and multiple chemical sensitivity syndrome
- Idiopathic lumbosacral plexopathy
- Idiopathic pulmonary fibrosis
- Immune-mediated neutropenia
- Paraneoplastic syndromes other than neuroblastoma
- Paraproteinemic neuropathy (IgM variant)
- Parkinson's disease
- Parsonage-Turner syndrome (brachial neuritis)
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)
- Pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND)
- Plasmacytoma, postural tachycardia syndrome (POTS)
- POEMS syndrome **
- Polyarteritis nodosa
- Polyneuritis cranialis
- Pre-thymectomy progressive lumbosacral plexopathy
- Pyoderma gangrenosum
<table>
<thead>
<tr>
<th>Autoimmune autonomic neuropathy</th>
<th>Immune reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune bullous skin diseases</td>
<td>Inclusion body myositis</td>
</tr>
<tr>
<td>Autoimmune chronic urticaria</td>
<td>Infertility</td>
</tr>
<tr>
<td>Autoimmune encephalopathy</td>
<td>Intractable seizures</td>
</tr>
<tr>
<td>Autoimmune epilepsy</td>
<td>Isaacs syndrome</td>
</tr>
<tr>
<td>Autoimmune inner ear disease</td>
<td>Isoimmune hemolytic disease</td>
</tr>
<tr>
<td>Autoimmune liver disease</td>
<td>Landau-Kleffner syndrome</td>
</tr>
<tr>
<td>Behçet's syndrome</td>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>Leukemia, acute lymphoblastic</td>
</tr>
<tr>
<td>Cardiomyopathy, acute</td>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>Lipidosis</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>Lower motor neuron syndrome</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>Malignancy, non-hematologic</td>
</tr>
<tr>
<td>Clarkson disease (systemic capillary leak syndrome)</td>
<td>Mannose-binding lectin deficiency</td>
</tr>
<tr>
<td>Clostridium difficile colitis</td>
<td>Maternal autoantibody-mediated cardiomyopathy</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
<td>Mitochondrial encephalopathy</td>
</tr>
<tr>
<td>Congenital factor VII deficiency</td>
<td>Multiple sclerosis - primary progressive or secondary types</td>
</tr>
<tr>
<td>Congenital heart block</td>
<td>Myalgia, myositis, unspecified</td>
</tr>
<tr>
<td>Convulsive syndromes</td>
<td>Myalgic encephalomyelitis</td>
</tr>
<tr>
<td>Critical illness polyneuropathy</td>
<td>Myelopathy, HTLV-I associated</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Necrotizing enterococcalis</td>
</tr>
<tr>
<td>Cronkhite-Canada syndrome</td>
<td>Neonatal lupus syndromes</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Neonatal sepsis (treatment)</td>
</tr>
<tr>
<td>Degas disease</td>
<td>Neonatal sepsis (prophylaxis)</td>
</tr>
<tr>
<td>Depression</td>
<td>Nephritic syndrome</td>
</tr>
<tr>
<td>Dermatosis, autoimmune blistering</td>
<td>Nephropathy, membranous</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Diabetic amyotrophy</td>
<td>Neuromyelitis optica (Devic’s disease)</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>Neurosarcoidosis</td>
</tr>
<tr>
<td>Dravet's syndrome</td>
<td>Nodular (follicular) lymphoma</td>
</tr>
<tr>
<td>Diamond-Blackfan anemia</td>
<td>Obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Dysautonomia, acute idiopathic</td>
<td>Ophthalmopathy, euthyroid</td>
</tr>
<tr>
<td>Eczema</td>
<td>Oral use of IVIG for any indication</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Orthostatic tachycardia syndrome</td>
</tr>
<tr>
<td>Endotoxemia</td>
<td>Otitis media, recurrent</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic cerebellar degeneration</td>
</tr>
</tbody>
</table>

** The term "POEMS" is actually an acronym for the most common symptoms and signs of the syndrome: "P" - peripheral neuropathy (numbness, tingling, and weakness of the feet and hands); "O" - organomegaly (large organs, like the liver, lymph nodes and spleen); "E" - endocrinopathy (abnormal hormone levels including sex hormones, thyroid hormones, etc.); "M" - monoclonal plasma-proliferative disorder (a collection of abnormal bone marrow cells, called plasma cells); most patients will have at least on abnormal bone x-ray associated with these plasma cells; "S" - skin changes (increased skin pigment, increased body hair, thickening of the skin, etc.).
## Table: Brands of Immune Globulins and FDA-Approved Indications:

<table>
<thead>
<tr>
<th>Brand of Immune Globulin</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivigam</td>
<td>Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>Carimune NF</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>Flebogamma</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Gammagard</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Gammaked</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td>Gammaplex</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Gammar-P I.V.</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Gamunex</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy</td>
</tr>
<tr>
<td>Hizentra (subcutaneous)</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>HyQvia</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Iveegam EN</td>
<td>Primary immunodeficiencies, Kawasaki syndrome</td>
</tr>
<tr>
<td>Octagam</td>
<td>Primary immunodeficiencies</td>
</tr>
<tr>
<td>Panglobin</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>Polygam S/D</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura, Kawasaki syndrome, B-cell chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Privigen</td>
<td>Primary immunodeficiencies, immune thrombocytopenic purpura</td>
</tr>
</tbody>
</table>


* Primary immunodeficiencies includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

** An intra-muscular formulation of immune globulin, GamaSTAN S/D, has been approved for the following indications: prophylaxis of hepatitis A; prevention or modification of measles (rubeola) in persons exposed fewer than 6 days previously; passive immunization against varicella in immunosuppressed patients; prophylaxis of rubella in pregnancy when therapeutic abortion is not an option; and prevention of serious infection in patients with IgG deficiencies.

## Table: Exception Criteria for Coverage of Parenteral Immunoglobulin Products Other than Least-Cost Medically Necessary Brand:

If medical necessity criteria are met, only the least-cost medically necessary IVIG product is covered. All other IVIG products are not covered unless any of the following exception criteria is met:

I. Documented IgA deficiency with need to be on an ultra-low IgA product, eg. Flebogamma or Gammagard S/D; or
II. Documented objective intolerance to the least-cost medically necessary IVIG product, Gammaplex, following 1-2 infusions; or
III. Non responders who had failed another IVIG product previously and are currently stable on the existing product; or
IV. Documented risk factors for volume overload (for example, congestive heart failure, end stage renal disease and renal dysfunction) and physician’s order of fluid volume restriction; or
V. For emergent administration, eg. platelets less than 30K with bleeding. For this use, a one-time exception will be allowed; or
VI. For request of subcutaneous immunoglobulin due to inability to continue receiving IVIG (e.g. infusion reactions not controlled by infusion rate adjustments or access site issues that are ongoing and unresolved by traditional means, etc.).

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

90281  Immune globulin (Ig), human, for intramuscular use
90283  Immune globulin (IgIV), human, for intravenous use
90284  Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

Other CPT codes related to the CPB:

20200 - 20206  Biopsy, muscle, superficial, or deep, or biopsy, muscle, percutaneous needle
33930 - 33945  Heart/lung or heart transplantation
36430 - 36455  Transfusion, blood or blood components
38221  Bone marrow; biopsy, needle or trocar
38230  Bone marrow harvesting for transplantation; allogenic
38232  autologous
38240  Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241  autologous transplantation
50300 - 50380  Renal transplantation
62270  Spinal puncture, lumbar, diagnostic
78630 - 78650  Cerebrospinal fluid flow, imaging (not including introduction of material); cisternography, ventriculography, shunt evaluation, tomographic (SPECT), or cerebrospinal fluid leakage detection and localization
86325  Immunelectrophoresis; other fluids (e.g., urine, cerebrospinal fluid) with concentration
86975 - 86978  Pretreatment of serum for use in RBC antibody identification; incubation with drugs, each, or by dilution, or incubation with inhibitors, each, or by differential red cell absorption using patient RBCs or RBCs of known phenotype, each absorption
95860 - 95887  Electromyography and nerve conduction tests
95907 - 95913  Nerve conduction studies
95937  Neuromuscular junction testing (repetitive stimulation, paired stimuli), each nerve, any 1 method
96360  Intravenous infusion, hydration; initial, 31 minutes to 1 hour
+96361  each additional hour (List separately in addition to code for primary procedure)
96365  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
+96366 each additional hour (List separately in addition to code for primary procedure)
+96367 additional sequential infusion of a new drug/substance, up to 1 hour (list separately in addition to code for primary procedure)
+96368 concurrent infusion (List separately in addition to code for primary procedure)
96369 Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
+96370 each additional hour (List separately in addition to code for primary procedure)
+96371 additional pump set-up with establishment of new subcutaneous infusion site (s) (List separately in addition to code for primary procedure)

HCPCS codes covered if selection criteria are met:

J1459 Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1556 Injection, immune globulin (bivigam), 500 mg
J1557 Injection, immune globulin, (gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1559 Injection, immune globulin (hizentra), 100 mg
J1561 Injection, immune globulin, (Gamunex/Gamunex-C/Gammaked), nonlyophilized (e.g., liquid), 500 mg
J1566 Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568 Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1569 Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g., liquid), 500 mg
J1572 Injection, immune globulin, (Flebogamma / Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg
J1599 Injection, immune globulin, intravenous, non-lyophilized (eg, liquid), not otherwise specified, 500 mg

Other HCPCS codes related to the CPB:

J1830 Injection interferon beta-1b, 0.25 mg
J9212 - J9216 Injection, interferon alfacon-1, recombinant, 1 mcg, interferon alfa-2a, recombinant, 3 million units, interferon alfa-2b, recombinant, 1 million units, interferon alfa-N3, (human leukocyte derived), 250,000 IU, or interferon gamma-1b, 3 million units
Q3027 Injection, interferon beta-1a, 1 mcg for intramuscular use
S9338 Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-9 codes covered if selection criteria are met:

040.82 Toxic shock syndrome
041.01 Infection streptococcus, group A
042  Human immunodeficiency virus [HIV] disease [bacteria control or prevention]
055.0 - 055.9  Measles [modification] [intramuscular use only]
079.83  Parvovirus B19
203.00 - 203.02  Multiple myeloma
203.10 - 203.12  Plasma cell leukemia
203.80 - 203.82  Other immunoproliferative neoplasms
204.10 - 204.12  Lymphoid leukemia, chronic [B-cell] [with hypogammaglobulinemia and recurrent infections or specific antibody deficiency]
279.00  Hypogammaglobulinemia, unspecified
279.04  Congenital hypogammaglobulinemia
279.05  Immunodeficiency with increased IgM
279.06  Common variable immunodeficiency [Good syndrome]
279.11  DiGeorge's syndrome
279.12  Wiskott-Aldrich syndrome
279.2  Combined immunity deficiency
279.50  Graft-versus-host disease, unspecified
279.51  Acute graft-versus-host disease
279.52  Chronic graft-versus-host disease
279.53  Acute on chronic graft-versus-host disease
283.0  Autoimmune hemolytic anemias [warm-type, refractory]
284.81  Red cell aplasia (acquired) (adult) (with thymoma)
286.0  Congenital factor VIII disorder
286.1  Congenital factor IX disorder
287.31  Immune thrombocytopenic purpura [when a rapid rise in platelet count is required, such as prior to surgery, to control excessive bleeding, or to avoid splenectomy]
287.4  Secondary thrombocytopenia [HIV associated, pediatric or adult, when criteria are met] [post-transfusion purpura]
287.5  Thrombocytopenia, unspecified
288.1  Functional disorders of polymorphonuclear neutrophils [Job's syndrome]
289.81 - 289.9  Other and unspecified diseases of blood and blood-forming organs
323.61  Infectious acute disseminated encephalomyelitis (ADEM) [refractory]
333.91  Stiff-man syndrome [unresponsive to other therapies]
340  Multiple sclerosis [relapsing-remitting when standard approaches have failed, become intolerable, or are contraindicated] [not covered for reducing the risk of post-partum exacerbation]
357.0  Acute infective polyneuritis [so severely affected that they at least require aid to walk, that the disorder is diagnosed during the first 2 weeks of the illness, and that there are no contraindications] [Miller-Fisher syndrome (MFS)]

357.81  Chronic inflammatory demyelinating polyneuritis

357.89  Other inflammatory and toxic neuropathy

358.00 - 358.01  Myasthenia gravis [treatment of acute crisis with decompensation] [other treatments unsuccessful or contraindicated]

446.1  Acute febrile mucocutaneous lymph node syndrome [MCLS] [Kawasaki disease]

694.4 - 694.8  Pemphigus, pemphigoid, or benign mucous membrane pemphigoid, and other specified bullous dermatoses [if failed has contraindications to conventional therapy or rapidly progressive disease in which clinical response could not be affected quickly enough using conventional agents] [not covered for autoimmune bullous skin diseases]

695.13  Stevens-Johnson syndrome

695.14  Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome

695.15  Toxic epidermal necrolysis

710.0  Systemic lupus erythematosus [severe for whom other interventions have been unsuccessful, have become intolerable, or are contraindicated]

710.3  Dermatomyositis

710.4  Polymyositis [in persons who are resistant to first and second line therapies]

728.86  Necrotizing fasciitis [toxic, due to group A streptococcus]

773.0 - 773.2  Hemolytic disease of fetus or newborn, due to isoimmunization [not responding to phototherapy, to decrease need for exchange transfusion][excludes fetal red blood cell alloimmunization]

776.1  Transient neonatal thrombocytopenia

996.81  Complications of transplanted kidney

996.82  Complications of transplanted liver

996.83  Complications of transplanted heart

996.84  Complications of transplanted lung

996.85  Complication of transplanted bone marrow [prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for recipients who are markedly hypogammaglobulinemic (IgG level less than 400 mg/dL), or who have CMV, EBV or RSV infection]

996.86  Complications of transplanted pancreas

996.87  Complications of transplanted intestine

V01.4  Contact with or exposure to rubella [intramuscular use only]

V01.71  Contact with or exposure to varicella [passive immunization in immunosuppressed patients] [intramuscular use only]

V07.2  Prophylactic immunotherapy

V42.0  Organ or tissue replaced by transplant, kidney
V42.1     Organ or tissue replaced by transplant, heart
V42.6     Organ or tissue replaced by transplant, lung
V42.7     Organ or tissue replaced by transplant, liver
V42.81    Organ or tissue replaced by transplant, bone marrow [prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for recipients who are markedly hypogammaglobinemic (IgG level less than 400 mg/dL), or who have CMV, EBV or RSV infection]
V42.82    Organ or tissue replaced by transplant, peripheral stem cells replaced by transplant [prophylaxis in allogeneic or syngeneic transplant recipients within the first 100 days post-transplant; after 100 days post-transplant IVIG is indicated for recipients who are markedly hypogammaglobinemic (IgG level less than 400 mg/dL), or who have CMV, EBV or RSV infection]
V42.83    Pancreas replaced by transplant
V42.84    Intestines replaced by transplant
V49.83    Awaiting organ transplant status

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

008.45    Clostridium difficile intestinal infection
011.20 - 011.26 Tuberculosis of lung with cavitation
032.82    Diphtheritic myocarditis
036.43    Meningococcal myocarditis
074.23    Coxsackie myocarditis
078.89    Other specified diseases due to viruses [gastric enterovirus]
088.81    Lyme disease
093.82    Syphilitic myocarditis
099.3     Reiter's disease
130.3     Myocarditis due to toxoplasmosis
135       Sarcoidosis
136.9     Unspecified infectious and parasitic diseases
140.0 - 199.2 Malignant neoplasm (except hematologic)
200.20 - 200.28 Burkitt's tumor or lymphoma
202.00 - 202.08 Nodular (follicular) lymphoma
202.50 - 202.58 Letterer-Siwe disease [Langerhans cell histiocytosis]
204.00 - 204.02 Lymphoid leukemia, acute
205.00 - 205.02 Acute myeloid leukemia
205.10 - 205.12 Chronic myelogenous leukemia
209.00 - 209.30 Malignant carcinoid tumor
249.00 - 249.91 Secondary diabetes mellitus
250.00 - 250.93  Diabetes mellitus

272.7  Lipidoses

273.1 - 273.3, 273.9  Monoclonal paraproteinemia, other paraproteinemias, macroglobulinemia, or unspecified disorder of plasma protein metabolism [Waldenstrom]

277.00 - 277.09  Cystic fibrosis

277.2  Other disorders of purine and pyrimidine metabolism

277.5  Mucopolysaccharidoses (Hunter's syndrome)

277.6  Other deficiencies of circulating enzymes

279.49  Autoimmune disease, not elsewhere classified [autoimmune encephalopathy]

283.11  Hemolytic-uremic syndrome

284.01 - 284.9  Aplastic anemia

286.3  Congenital deficiency of other clotting factors [congenital factor VII deficiency]

286.4  von Willebrand's disease

287.0  Allergic purpura (Henoch-Schonlein)

288.00 - 288.09  Neutropenia

288.4  Hemophagocytic syndromes [hemophagocytic lymphohistiocytosis]

296.20 - 296.36  Major depression

299.00 - 299.01  Autistic disorder

300.3  Obsessive-compulsive disorder

307.20 - 307.23  Tics

311  Depression

314.01  Attention deficit disorder with hyperactivity

320.0 - 322.9  Meningitis [infection in neonates]

323.0 - 323.9  Encephalitis/myelitis and encephalomyelitis [limbic]

330.0  Leukodystrophy

331.0  Alzheimer's disease

332.0 - 332.1  Parkinson's disease

333.4  Huntington's chorea

335.20  Amyotrophic lateral sclerosis

337.1  Peripheral autonomic neuropathy in disorders classified elsewhere [vasculitic polyneuropathy]

337.20 - 337.29  Reflex sympathetic dystrophy [complex regional pain syndrome]

337.9  Unspecified disorder of autonomic nervous system [autoimmune autonomic neuropathy]

341.0  Neuromyelitis optica [Devic's syndrome]

345.00 - 345.91  Epilepsy and recurrent seizures
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>348.30 - 348.39</td>
<td>Encephalopathy, not elsewhere classified [mitochondrial encephalopathy] [autoimmune encephalopathy]</td>
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<tr>
<td>352.6</td>
<td>Multiple cranial nerve palsies</td>
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<tr>
<td>353.5</td>
<td>Neuralgic amyotrophy [diabetic] [Parsonage-Turner syndrome]</td>
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<tr>
<td>356.8 - 356.9</td>
<td>Other specified idiopathic peripheral neuropathy [anti-myelin associated</td>
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<td>glycoprotein neuropathy]</td>
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<td>357.4</td>
<td>Polyneuropathy in other diseases classified elsewhere [small fiber neuropathy]</td>
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<tr>
<td>358.8</td>
<td>Other specified myoneural disorders [Isaacs syndrome]</td>
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<tr>
<td>364.00 - 364.3</td>
<td>Acute and subacute iridocyclitis, chronic iridocyclitis, certain types</td>
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<tr>
<td></td>
<td>of iridocyclitis, and unspecified iridocyclitis</td>
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<tr>
<td>377.30 - 377.32</td>
<td>Optic neuritis</td>
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<tr>
<td>390</td>
<td>Rheumatic fever without mention of heart involvement</td>
</tr>
<tr>
<td>391.0 - 391.9</td>
<td>Rheumatic fever with heart involvement</td>
</tr>
<tr>
<td>392.9</td>
<td>Rheumatic chorea without mention of heart involvement [Sydenham's chorea]</td>
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<tr>
<td>422.0</td>
<td>Acute myocarditis in diseases classified elsewhere</td>
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<tr>
<td>425.4</td>
<td>Other primary cardiomyopathies</td>
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<tr>
<td>446.0</td>
<td>Polyarteritis nodosa</td>
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<td>446.21</td>
<td>Goodpasture's syndrome</td>
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<td>446.4</td>
<td>Wegener's granulomatosis</td>
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<td>446.6</td>
<td>Thrombotic microangiopathy</td>
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<td>447.8</td>
<td>Other specified disorders of arteries and arterioles [Degas disease]</td>
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<tr>
<td>473.0 - 473.9</td>
<td>Chronic sinusitis</td>
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<tr>
<td>480.0 - 486</td>
<td>Pneumonia [not related to RSV]</td>
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<tr>
<td>493.00 - 493.92</td>
<td>Asthma</td>
</tr>
<tr>
<td>516.3</td>
<td>Idiopathic fibrosing alveolitis [idiopathic pulmonary fibrosis]</td>
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<tr>
<td>516.5</td>
<td>Adult pulmonary Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>531.00 - 538</td>
<td>Diseases of stomach and duodenum</td>
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<tr>
<td>555.0 - 558.9</td>
<td>Non-infectious enteritis and colitis</td>
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<tr>
<td>560.0 - 564.9</td>
<td>Other diseases of intestines</td>
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<tr>
<td>557.0</td>
<td>Acute vascular insufficiency of intestine</td>
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<tr>
<td>580.0 - 581.9</td>
<td>Nephritis and nephrotic syndrome</td>
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<td>582.2</td>
<td>Chronic glomerulonephritis, with lesion of membranoproliferative</td>
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<td></td>
<td>glomerulonephritis</td>
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<tr>
<td>583.1</td>
<td>Nephritis and nephropathy, not specified as acute or chronic, with lesion</td>
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<td>of membranous glomerulonephritis</td>
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<tr>
<td>584.5 - 584.9</td>
<td>Acute renal failure</td>
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<tr>
<td>628.0 - 628.9</td>
<td>Infertility, female</td>
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</tbody>
</table>
686.01  Pyoderma gangrenosum
692.72  Acute dermatitis due to solar radiation [solar urticarial]
692.9  Eczema
694.4 - 694.8  Bullous dermatoses
708.8  Other specified urticaria
710.1  Systemic sclerosis
710.2  Sicca syndrome [Sjogren's syndrome]
714.0 - 714.9  Rheumatoid arthritis
729.1  Myalgia and myositis, unspecified
733.99  Other disorders of bone and cartilage [relapsing polychondritis]
746.86  Congenital heart block
771.81 - 771.89  Other infections specific to the perinatal period
780.39  Other convulsions
780.71  Chronic fatigue syndrome
785.0  Tachycardia, unspecified [orthostatic tachycardia syndrome]
785.59  Other shock without mention of trauma
786.30  Hemoptysis, unspecified [diffuse alveolar hemorrhage]
795.79  Other and unspecified nonspecific immunological findings
995.1  Angioneurotic edema
995.90  Systemic inflammatory response syndrome (SIRS), unspecified, NOS [immune reconstitution]
V13.29  Other genital system and obstetric disorders

Other ICD-9 codes related to the CPB:

075  Infectious mononucleosis [Epstein Barr virus]
078.5  Cytomegaloviral disease
079.6  Respiratory syncytial virus (RSV)
466.11  Acute bronchiolitis due to RSV
480.1  Pneumonia due to RSV
771.1  Congenital Cytomegalovirus Infection
200.00 - 202.98  Lymphosarcoma and reticulosarcoma
204.20 - 208.91  Subacute, other, and unspecified lymphoid leukemia, myeloid leukemia, monocytic leukemia, other specified leukemia, and leukemia of unspecified cell type
323.81  Other causes of encephalitis and encephalomyelitis [noninfectious acute disseminated encephalomyelitis (ADEM)] [Rasmussen's encephalitis or syndrome]
333.2  Myoclonus
336.3 Myelopathy in other diseases classified elsewhere
336.8 Other myelopathy
357.82 Critical illness polyneuropathy [acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN)]
358.1 Myasthenic syndromes in diseases classified elsewhere [Eaton-Lambert syndrome]
379.59 Other irregularities of eye movement
446.20 - 446.29 Hypersensitivity angiitis
728.85 Spasm of muscle
728.87 Muscle weakness (generalized)
780.66 Febrile nonhemolytic transfusion reaction
781.3 Lack of coordination
999.89 Other transfusion reaction
V42.82 Peripheral stem cells replaced by transplant

The above policy is based on the following references:


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