This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Drug:** Immune Globulins (IVIG)

**Class:** Biologics

**Formulary Medication:** N/A

**Effective Date:** August 2014

**Clinical Policy:**

**FDA Approved Indications for IVIG products (CBER)**

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<tr>
<th>Brand</th>
<th>PID</th>
<th>CLL</th>
<th>ITP</th>
<th>Kawasaki Syndrome</th>
<th>CIDP</th>
<th>Multifocal Motor Neuropathy</th>
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PID = primary immune deficiency, CLL = chronic lymphocytic leukemia, ITP = idiopathic thrombocytopenic purpura, CIDP = chronic inflammatory demyelinating polyneuropathy

1. Due to the various dosage forms and adverse events profile IVIG products will be covered based on approved indications after failure of first line treatment options (For detailed criteria please see section: **Clinical Criteria**)
   a. Approvable non-FDA approved indications or “off-label” indications where anecdotal evidence has shown efficacy and where clinical trials may not be appropriate due to rarity of the disease or ethics: Guillain-Barre syndrome, dermatomyositis, bone marrow transplantation, and Lambert-Eaton Syndrome.
   b. Other non-FDA approved indications (“off-label” condition) will be reviewed and considered based on evidence for efficacy. Use for the non-FDA approved indication must be found in at least one pharmaceutical compendium: United States Pharmacopeia Drug Information (USPDI), Drug Information for Healthcare Professional, American...
Hospital Formulary Service (AHFS) Drug Information, or Micromedex DrugDex. The Clinical Review process will also consider information submitted by the prescriber supporting the intended off-label use in the form of two supporting journal articles from nationally recognized peer reviewed journals (e.g. New England Journal of Medicine).

2. Lab Tests/Monitoring Parameters:
   a. Baseline renal (BUN & Creatinine Clearance)
   b. Platelets and Hgb levels
   c. Immunoglobulin levels (Ig)
   d. IgA deficiency or IgA antibodies

Clinical Criteria:

1) Primary Immunodeficiency Syndrome (PID)
   a) For patients with a primary immunodeficiency syndrome. These include, but are not limited to:
      i) Congenital agammaglobulinemia (X-linked agammaglobulinemia)
      ii) Hypogammaglobulinemia
      iii) Common variable immunodeficiency
      iv) X-linked immunodeficiency with hyperimmunoglobulin M
      v) Severe combined immunodeficiency
      vi) Wiskott-Aldrich syndrome
   b) Duration of Prior Authorization: Re-evaluate every 3 months

2) Idiopathic Thrombocytopenic Purpura (ITP)
   a) For patients with idiopathic thrombocytopenic purpura (ITP) who require a rapid, temporary increase in platelet count or to control excessive bleeding.
      i) Documented platelet count in one of the following range:
         (1) Less than 30 x 10^9 / L
         (2) Less than 50 x 10^9 / L with symptoms of active bleeding
   b) Duration of Prior Authorization: Re-evaluate every month

3) Kawasaki Disease (KD)
   a) Confirmed diagnosis of Kawasaki Disease
   b) Duration of Prior Authorization: Re-evaluate every month

4) B-cell Chronic Lymphocytic Leukemia (CLL)
   a) Confirmed diagnosis of Chronic Lymphocytic Leukemia
   b) One of the following:
      i) Documented hypogammaglobulinemia (IgG < 600 mg/dL)
      ii) History of bacterial infection(s) associated with B-cell CLL
   c) Duration of Prior Authorization: Re-evaluate every 3 months

5) Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
   a) Confirmed diagnosis of chronic inflammatory demyelinating polyneuropathy
   b) Duration of Prior Authorization: Re-evaluate every 3 months

6) Bone Marrow Transplantation
   a) For patients 20 years and older
b) Confirmed allogeneic bone marrow transplant

c) Documented severe hypogammaglobulinemia (IgG < 400 mg/dL)

d) Duration of Prior Authorization: Re-evaluate every month

7) Dermatomyositis and Polymyositis
   a) Confirmed diagnosis of dermatomyositis or polymyositis.
   b) Failure or intolerance to one of the following: corticosteroid therapy, methotrexate, azathioprine, or cyclophosphamide
   c) Duration of Prior Authorization: Re-evaluate every 3 months

8) Multifocal Motor Neuropathy
   a) Confirmed diagnosis of multifocal motor neuropathy
   b) Duration of Prior Authorization: Re-evaluate every 3 months

9) Guillain-Barre Syndrome
   a) Confirmed diagnosis of Guillain-Barre Syndrome
   b) Severe disease - requiring aid to walk
   c) Onset of neuropathic symptoms within the last four weeks
   d) Duration of Prior Authorization: Re-evaluate every 3 months

10) Lambert-Eaton Myasthenic Syndrome
    a) Documented diagnosis of Lambert-Eaton Myasthenic Syndrome
    b) Duration of Prior Authorization: Re-evaluate every 3 months

11) Acute Myasthenia Gravis Exacerbation
    a) Confirmed diagnosis of myasthenia gravis with myasthenic exacerbation, defined by one of the following symptoms in the last month:
       i) Difficulty swallowing
       ii) Acute respiratory failure
       iii) Major functional disability responsible for the discontinuation of physical activity
    b) Prescribed by a neurologist
    c) IVIG will not be approved for chronic maintenance therapy
    d) Duration of Prior Authorization: Re-evaluate every 3 months

12) Hizentra (SCIG) will be approved based on all of the following criteria:
    a) For patients with a primary humoral immunodeficiency disease. This includes but is not limited to the following: (ICD-9 codes 279.04, 279.05, 279.06, 279.12, and 279.2)
       i) Congenital agammaglobulinemia (X-linked agammaglobulinemia)
       ii) Hypogammaglobulinemia
       iii) Common variable immunodeficiency
       iv) X-linked immunodeficiency with hyperimmunoglobulin M
       v) Severe combined immunodeficiency
       vi) Wiskott-Aldrich syndrome
    b) One of the following:
       i) Failure, contraindications, or intolerance to IVIG
       ii) Poor venous access

**Dosing Range** (dosing will vary between products, please refer to FDA approved label):

1) Primary Immunodeficiency Syndrome
a) Carimune NF: 400 - 800 mg/kg IV every 3 to 4 weeks
b) Flebogamma, Gammagard Liquid, Gammagard S/D, Gamunex-C, Gammaked, or Octagam: 300 – 600 mg/kg IV every 3 to 4 weeks
c) Privigen: 200 - 800 mg/kg IV every 3 to 4 weeks
d) Gammalex or Bivigam: 300 – 800 mg/kg IV every 3 to 4 weeks

2) Idiopathic Thrombocytopenic Purpura
a) Carimune NF: 0.4 g/kg IV daily for 2–5 consecutive days
   i) In acute ITP of childhood, if an initial platelet count reaches 30-50,000/μL after the first two doses, therapy may be discontinued after the second day of the 5 day course
   ii) In adults and children, if after induction therapy the platelet count falls to less than 30,000/μL and/or the patient manifests clinically significant bleeding, 0.4 g/kg may be given as a single infusion. If an adequate response does not result, the dose can be increased to 0.8-1 g/kg given as a single infusion.
b) Gammagard S/D: 1 g/kg IV; up to three separate doses may be given on alternate days if required
c) Gamunex-C or Gammaked: 1 g/kg/day IV for two consecutive days, or 0.4 g/kg/day IV for five consecutive days
   i) If after administration of the first 1 g/kg dose, an adequate increase in the platelet count is observed at 24 hours, the second dose may be withheld
d) Privigen or Gammalex: 1 g/kg IV daily for 2 consecutive days

3) Chronic Inflammatory Demyelinating Polyneuropathy
a) Gamunex-C or Gammaked:
   i) Initial dose: 2 g/kg IV in divided doses over two to four consecutive days
   ii) Maintenance: 1 g/kg IV over 1 day or 0.5 g/kg/day IV given on two consecutive days, every 3 weeks

4) Kawasaki Disease
a) Gammagard S/D: One dose of 1 g/kg IV, or 400 mg/kg/day for four days beginning within 7 days of fever onset

5) Chronic Lymphocytic Leukemia
a) Gammagard S/D: 400 mg/kg IV every 3 to 4 weeks

6) Bone Marrow Transplant*
a) Prevention of bacterial infections during the first 100 days after HCT with severe hypogammaglobulinemia (IgG < 400mg/dL) 500 mg/kg/week
b) Prevention of bacterial infections beyond 100 days post HCT with severe hypogammaglobulinemia (IgG < 400mg/dL)
   i) 500mg/kg every 3-4 weeks

7) Dermatomyositis*
a) 2 g/kg IV divided over two to five days, every month for three months

8) Multifocal Motor Neuropathy*
a) Gammagard Liquid: 0.5-2.4 g/kg/month IV

9) Guillain-Barre Syndrome*
a) 400 mg/kg/day IV for 5 days
10) Lambert-Eaton Myasthenic Syndrome*
   a) 2 g/kg IV divided over two consecutive days

11) Myasthenia Gravis Exacerbation*
   a) 400 mg/kg/day IV for 5 days

* Suggested dosing for off-label indications is based on clinical trial data.

Clinical Evidence:

A. Clinical Trials

Idiopathic Thrombocytopenic Purpura (ITP)
The use of IVIG therapy has been shown to be associated with a significant increase in platelet levels in adults and children with ITP. Among children with chronic ITP, the initial response has been reported to be more marked in splenectomized patients than in non-splenectomized patients. A randomized trial comparing IVIG to oral corticosteroids in children with untreated acute ITP (n=108) showed similar results for rapid responders in both treatment arms. When administered to 29 patients with previously untreated or steroid-resistant acute ITP, IVIG treatment (1 gm/kg/day) resulted in a mean platelet increase greater than 50,000/μL in 24 hours; the average peak platelet count was 194,000/microliter. Randomized studies have shown no difference in efficacy between IVIG dosing of 0.4 g/kg/day for 5 days or 1 g/kg/day as a single infusion. A prospective randomized trial involving 30 adult patients with chronic ITP (comparing IVIG, prednisolone or combination of the two) with a minimum follow-up of 2 years showed that the response rates, duration of response and requirement for splenectomy were the same in all arms.

Kawasaki Disease (KD)
The efficacy of IVIG 2 g/kg/day was compared to IVIG 400 mg/kg/day, each given for 4 days, in 549 children. Both groups received standard dosages of aspirin. Children receiving the 2 g/kg doses had lower temperatures and shorter durations of fever. A combination of IVIG and aspirin was reported to be more effective than aspirin alone in reducing the incidence of coronary artery abnormalities (CAA) in Kawasaki syndrome (n=168). Patients received IVIG 400 mg/kg/day (given on four consecutive days) plus aspirin or aspirin alone. Fewer patients receiving IVIG had observed coronary artery abnormalities at 2 weeks (8% vs. 23%) and at 7 weeks (4% vs.18%). A meta-analysis of 6 trials (n= 1629) showed that the prevalence of CAA at 30 days was significantly lower in patients receiving IVIG 2 g/kg compared to patients taking various IVIG doses of less than 2 g/kg (p<0.05). At 60 days, the prevalence of CAA was significantly lower in patients receiving IVIG 2 g/kg compared to those receiving less than 1.2 g/kg (p < 0.01). The prevalence of CAA was inversely related to the dose of IVIG.

Chronic Lymphocytic Leukemia (CLL)
In a double-blind study, 84 patients with CLL who were judged to be at increased risk of bacterial infection were randomized to receive IVIG (400 mg/kg) or a placebo every three weeks for one year.24 Eligible patients had hypogammaglobulinemia, a history of infection, or both. The patients receiving IVIG had significantly fewer bacterial infections during the study period than those receiving placebo (23 vs. 42; P = 0.01). This reduction was most striking in the patients who completed a full year of treatment (14 vs. 36; P = 0.001). The period from study entry to the first serious bacterial infection was significantly longer in the patients receiving immunoglobulin (P = 0.026). Forty-two CLL patients with hypogammaglobulinemia (IgG < 600 mg/dL) and/or a history of at least one episode of severe infection in the 6 months preceding inclusion in the study were randomly allocated to receive either an infusion of
300 mg/kg IVIG every 4 weeks for 6 months or no treatment. Patients then switched to observation or IVIG for another 12 months; finally, they received IVIG or no therapy for 6 more months. A significantly lower incidence of infectious episodes was observed during IVIG prophylaxis in 30 patients who completed the 6-month period of either observation or IVIG therapy. The same applied to the 17 patients who completed 12 months of either observation or IVIG prophylaxis.

**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

A multicenter, randomized, double-blind, cross-over trial (n=32) comparing IVIG treatment (2g/kg over one to two days) to oral prednisone (tapered from 60 mg to 10 mg daily) showed comparable results with IVIG and prednisolone. Both treatments produced significant improvements in an 11-point disability scale compared to baseline at two weeks after randomization. The authors concluded that IVIG and oral steroids are efficacious in the treatment of CIDP in the short-term. A randomized, double-blind, multicenter study (n=33) compared IVIG (1 g/kg) given on days 1, 2, and 21 vs. placebo in patients with untreated CIDP. The primary outcome measure was the change in muscle strength from baseline to day 42 using the average muscle score (AMS). Mean AMS was significantly improved on day 42 with IVIG treatment vs. placebo treatment (0.62 vs. -0.1, p=0.006). The authors concluded that the data supports the use of IVIG as the initial treatment for CIDP. A cross-over study (n=20) comparing plasma exchange (twice a week for 3 weeks, then once weekly) and IVIG (0.4g/kg once a week for 3 weeks, then 0.2 g/kg once a week) for a total of 6 weeks found no significant differences in neuropathic end points between the two treatments. End points included: neurological disability score; muscle weakness of the neurological disability score; summated compound muscle action potentials of ulnar, median, and peroneal nerves; summated sensory nerve action potentials of ulnar and sural nerves; and vibratory detection threshold of the great toe. The authors concluded that both treatments were efficacious.

**Bone Marrow Transplant**

In a randomized trial of 382 patients, transplant recipients given IVIG (500 mg /kg to day 90, then monthly to day 360 after transplantation) were compared with controls not given IVIG. Neither survival nor the risk of relapse was altered by immunoglobulin.36 However, among patients greater than or equal to 20 years old, there was a reduction in the incidence of acute graft versus host disease (GVHD) (34% vs. 51%; p = 0.0051) and a decrease in deaths due to transplant-related causes after transplantation of HLA-identical marrow (30% vs. 46%; p = 0.023). The authors concluded that passive immunotherapy with intravenous immunoglobulin decreases the risk of acute GVHD, associated interstitial pneumonia, and infections after bone marrow transplantation. A multicenter, randomized, double-blind study compared different doses of IVIG for prevention of graft-versus-host disease (GVHD) and infection after allogeneic bone marrow transplantation. Patients were given 100mg/kg, 250mg/kg, or 500mg/kg doses of IVIG weekly for 90 days and then monthly until 1 year after transplant. A total of 618 patients were randomized and results show no significant difference in the cases of GVHD in any group. The range of patients incurring GVHD was between 35% and 42% for the 3 groups. The authors conclude that a smaller amount of IVIG can be used to achieve the same effect. A randomized, double-blind, placebo-controlled trial (n=200) evaluated IVIG in the prophylaxis of complications after allogeneic stem-cell transplantation. Patients from 19 centers were enrolled and IVIG at doses of 50mg/kg, 250mg/kg, or 500mg/kg were given from day –7 to day 100 after transplant or placebo. IVIG was found not to have a significant effect compared to placebo. The authors conclude that IVIG is not beneficial in infection prevention for allogeneic stem-cell transplantation.

**Dermatomyositis**

A double-blind, placebo-controlled study of patients (n=15) with biopsy-proved, treatment-resistant dermatomyositis evaluated therapy with IVIG at a dose of 2g/kg every month for three months. All patients also received prednisone (mean daily dose: 25 mg). The eight patients assigned to IVIG had a
significant improvement in scores of muscle strength (p<0.018) and neuromuscular symptoms (p<0.035), whereas the seven patients assigned to placebo did not. With crossovers, a total of 12 patients received immune globulin. Of these, nine with severe disabilities had a major improvement to nearly normal function. Several other small, open-label studies have also suggested that treatment with IVIG can increase proximal muscle strength and improve cutaneous disease. In an open study with 20 adult patients diagnosed with refractory polymyositis and dermatomyositis, significant clinical improvement was noted in 15 of the 20 patients receiving IVIG. Patients had previously failed traditional treatments (i.e., immunosuppressants, plasmapheresis).

Multifocal Motor Neuropathy (MMN)
A Cochrane systemic review of four randomized controlled trials of patients with MMN (n= 34) showed that strength improved in 78% of patients treated with IVIG, compared to only 4% of placebo-treated patients (RR 11.00; 95% CI 2.86 to 42.25).44 Disability improved in 39% of patients after IVIG treatment and in 11% after placebo (not significant). Mild, transient side effects were reported in 71% of intravenous immunoglobulin treated patients. Serious side effects were not encountered. A double-blind, placebo-controlled, cross-over study (n=13) was used to determine the effect of IVIG on neurologic function in patients with MMN. Patients with lower motor neuron syndromes associated with partial motor conduction block were assigned to either IVIG (2g/kg total dose) or placebo. Results indicate increased grip strength and neurologic disability scores in the IVIG treatment group.

Guillain Barre Syndrome (GBS)
A multicenter, randomized trial of adult patients with GBS (n=383) compared plasma exchange (PE), IVIG (0.4 g/kg daily for 5 days), or PE plus IVIG. Four weeks after randomization, the mean improvement on a seven-point disability grade scale was 0.9 (SD 1.3) in the PE-group patients, 0.8 (1.3) in the IVIG-group, and 1.1 (1.4) in the patients who received both treatments (intention-to-treat analysis). None of the differences between the groups for this major outcome criterion was significant. Secondary outcomes were also not significant. A randomized, controlled trial compared either five plasma exchanges (each of 200 to 250 ml per kilogram of body weight) or five doses IVIG (0.4 g /kg/d). The predefined outcome measure was improvement at four weeks by at least one grade on a seven-point scale of motor function. After 150 patients had been treated, strength had improved by one grade or more in 34 percent of those treated with plasma exchange, as compared with 53 percent of those treated with immune globulin (difference, 19 %; 95 percent confidence interval, 3% to 34%; p= 0.024). The median time to improvement by one grade was 41 days with plasma exchange and 27 days with immune globulin therapy (p=0.05).

Lambert-Eaton Myasthenic Syndrome
A randomized, double-blind, placebo-controlled crossover trial, compared serial indices of limb, respiratory, and bulbar muscle strength and the serum titer of calcium-channel antibodies in nine patients over an 8-week period, following infusion on two consecutive days of immunoglobulin at 1 g/kg/day or placebo. IVIG was followed by significant improvements in the three strength measures (p = 0.017 to 0.038) associated with a significant decline in serum calcium-channel antibody titers (p = 0.028).

Myasthenia Gravis
The use of IVIG to treat acute exacerbations of myasthenia is justified (ABN [Association of British Neurologists], 2005). It is more convenient and possibly safer than plasma exchange. Evidence is lacking to support IVIG use in stable asthenia or as a long term therapy.44 A review of five randomized controlled trials, all of which investigated short-term benefit of IVIG in myasthenia gravis was conducted.62 The first study of 87 participants with exacerbation found no statistically significant
difference between immunoglobulin and plasma exchange after two weeks. The second study of 12 participants with moderate or severe myasthenia gravis treated in a crossover design trial found no statistically significant difference in the efficacy of immunoglobulin and plasma exchange after four weeks. The third study with 15 participants with mild or moderate myasthenia gravis found no statistically significant difference in efficacy of IVIG and placebo after six weeks. The fourth study terminated early. It included 33 participants with moderate exacerbations of myasthenia gravis and showed no statistically significant difference in the efficacy of IVIG and methylprednisolone. The fifth trial including 173 people with myasthenia gravis exacerbations, showed no superiority of IVIG 1 g/kg on two consecutive days over IVIG 1 g/kg on a single day. The authors concluded that in severe exacerbations of myasthenia gravis, one randomized controlled trial did not show a significant difference between IVIG and plasma exchange. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIG. A further trial showed no significant difference between IVIG and oral methylprednisolone. In chronic myasthenia gravis, there is insufficient evidence from randomized trials to determine whether IVIG is efficacious. More research is needed to determine whether IVIG reduces the need for steroids as suggested by two case series.

B. National Guidelines


IVIG should be offered for treating Guillain-Barre syndrome (GBS) in adults (Level A) and 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 nonresponsive 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 postpolio 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. Most studies concluded IVIG-related serious adverse effects were rare. Given the variable nature of these diseases, individualized treatments depending on patient need and physician judgment are important.


Despite high-dose IVIG is widely being used in the treatment of a number of immune-mediated neurological diseases, the consensus on its optimal use is insufficient. The efficacy of IVIG has been proven in Guillain-Barre syndrome (level A), chronic inflammatory demyelinating polyradiculoneuropathy (level A), multifocal mononeuropathy (level A), acute exacerbations of myasthenia gravis (MG) and short term treatment of severe MG (level A recommendation), and some paraneoplastic neuropathies (level B). IVIG is recommended as a second-line treatment in combination with prednisone in dermatomyositis (level B) and treatment option in polymyositis (level C). IVIG should be considered as a second or third-line therapy in relapsing–remitting multiple sclerosis, if conventional immunomodulatory therapies are not tolerated (level B), and in relapses during pregnancy or post-partum period (good clinical practice point). IVIG seems to have a favorable effect also in paraneoplastic
neurological diseases (level A), stiff-person syndrome (level A), some acute-demyelinating diseases and childhood refractory epilepsy (good practice point).

Rating of Recommendations:

- **Level A rating** (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.
- **Level B rating** (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.
- **Level C rating** (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.
- **Good Practice Points** - Where there was a lack of evidence but consensus was clear, the Task Force has stated their opinion as good practice points.

**Idiopathic Thrombocytopenic Purpura:**

- **American Society of Hematology (2011)** — The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count. The decision to treat should involve a discussion with the patient and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects, and health-related quality of life.
  - **Initial Management**
    - First-line treatment includes observation, corticosteroids, IVIG or anti-D immunoglobulin. Anti-D should be used with caution given recent FDA warnings of severe hemolysis. It is therefore not advised in patients with bleeding causing a decline in hemoglobin, or those with evidence of autoimmune hemolysis.
    - Consider treatment for patients with a platelet count < 30 x 10^9/L
    - Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIG
  - **Subsequent Management**
    - Adults who have a platelet count > 30 x 10^9/L and are asymptomatic following splenectomy do not require further therapy. If previous treatment with corticosteroids, IVIG or anti-D has been successful, these options may be used as needed to prevent bleeding. If previous treatment with IVIG or anti-D has been unsuccessful, subsequent treatment may include splenectomy, rituximab, thrombopoietin receptor agonists or more potent immunosuppression.

**Chronic Lymphocytic Leukemia:**

- **British Committee for Standards in Haematology (2011)** – IVIG replacement therapy should be considered as a means of reducing the incidence of bacterial infections in patients with a low serum IgG level who have experienced a previous major or recurrent minor bacterial infection despite optimal and bacterial prophylaxis. The goal should be to reduce the incidence of infection and the immunoglobulin dose should be adjusted accordingly. Patients should be reviewed regularly to evaluate the effectiveness of immunoglobulin replacement therapy and whether there is a continuing need for treatment. Patients who develop serious and/or recurrent infections despite antimicrobial prophylaxis and immunoglobulin replacement should be managed in conjunction with a microbiologist, infectious diseases specialist and/or immunologist.
- **National Comprehensive Cancer Network (2009)** - Patients with chronic lymphocytic leukemia with recurrent infections, particularly those patients with encapsulated organisms and
hypogammaglobulinemia, may benefit from intravenous gamma globulin. Three forms of autoimmune cytopenia occur in CLL/SLL and may require targeted therapy. Initial therapy for autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) is steroidal. Intravenous immunoglobulin may be used in the treatment of refractory disease.

Bone Marrow Transplantation

- **American Society for Blood and Marrow Transplantation (2009)**
  - Preventing Early Disease
    - Although IVIG has been recommended for use in producing immune system modulation for GVHD Prevention, IVIG should not be routinely administered to HCT recipients for prophylaxis of bacterial infection within the first 100 days after transplantation. For patients with severe hypogammaglobulinemia (ie, IgG < 400mg/dL), IVIG prophylaxis may be considered. Dosage should be individualized to maintain trough serum IgG concentrations >400 mg/dL.
  - Preventing Late Disease
    - In the absence of severe hypogammaglobulinemia (ie, IgG levels < 400 mg/dL, which might be associated with bacteremia or recurrent pulmonary infections), routine monthly IVIG administration to HCT recipients > 100 days after allogeneic or autologous HCT is not recommended.
    - IVIG is not recommended for CMV disease prophylaxis among HCT recipients.

Guillain Barre Syndrome

**American Academy of Neurology (2012)** – IVIG should be offered to treat GBS in adults (Level A). IVIG combined with plasmapheresis should not be considered for treating GBS (Level B). Evidence is insufficient to recommend methylprednisolone in combination with IVIG (Level U).

Kawasaki Disease

- **American Heart Association (2004)** - Patients should be treated with IVIG, 2 g/kg in a single infusion (evidence level A: multiple randomized clinical trials), together with aspirin. This therapy should be instituted within the first 10 days of illness and, if possible, within 7 days of illness. Treatment of Kawasaki disease before day 5 of illness appears no more likely to prevent cardiac sequelae than treatment on days 5 to 7, but it may be associated with an increased need for IVIG retreatment. IVIG also should be administered to children presenting after the 10th day of illness (i.e., children in whom the diagnosis was missed earlier) if they have either persistent fever without other explanation or aneurysms and ongoing systemic inflammation, as manifested by elevated ESR or CRP (evidence level C: primarily expert consensus). Approximately >10% of patients with Kawasaki disease fail to defervesce with initial IVIG therapy. Failure to respond usually is defined as persistent or recrudescent fever >36 hours after completion of the initial IVIG infusion. Most experts recommend retreatment with IVIG, 2 g/kg (evidence level C: primarily expert consensus). The putative dose-response effect of IVIG forms the theoretical basis for this approach.

Myasthenia Gravis:

- **American Academy of Neurology (2012)**—IVIG should be considered in the treatment of Myasthenia Gravis (Level B). This recommendation was based on studies involving primarily moderately or severely affected patients. The benefits and risks of this medication should be
weighed carefully in patients with mild MG. Further studies of IVIg efficacy in MG are warranted due to the few randomized trials and small study size to date.

Multifocal Motor Neuropathy:
- **American Academy of Neurology (2012)**—IVIG should be considered for the treatment of multifocal motor neuropathy (Level B). Multifocal motor neuropathy is a chronic disease requiring ongoing treatment. No data are available to address optimal treatment dosing, interval and duration.

Dermatomyositis:
- **American Academy of Neurology (2012)**—IVIG may be considered for the treatment of nonresponsive dermatomyositis in adults (Level C).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
- **American Academy of Neurology (2012)**—IVIG should be offered for the long-term treatment of CIDP (Level A). Dosing, frequency and duration of IVIG for CIDP may vary depending on the clinical assessment. Data are insufficient to address the comparative efficacy of other CIDP treatments (e.g. steroids, plasmapheresis, immunosuppressants). Experts have identified that there may be overuse of IVIG in long-term care of CIDP. AAN was unable to evaluate this question using available randomized trial data at the time.

References:
2. Clinical Pharmacology: Immune Globulin
7. Facts and Comparision: Immune Globulin
8. Facts and Comparison: Vivaglobin

15. National Heart Lung and Blood institute: Idiopathic Thrombocytopenic Purpura October 27, 2009

16. National Institute of Neurological Disorders and Stroke: NINDS Chronic Inflammatory Demyelinating Polyneuropathy

