Immune globulin intravenous (IVIG) Prior Approval Criteria
April 2017

- Bivigam® (immune globulin intravenous – Biotest Pharmaceuticals Corporation);
- Carimune® NF Nanofiltered (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG]);
- Flebogamma® DIF (immune globulin intravenous – Grifols Biologicals Inc [manufactured by Instituto Grifols, SA]);
- Gammagard Liquid, Gammagard® S/D (immune globulin intravenous – Baxter Healthcare Corporation);
- Gammaked™ (immune globulin intravenous caprylate/chromatography purified – Kedrion Biopharma [manufactured by Talecris Biotherapeutics {Grifols Therapeutics Inc}]);
- Gammmaplex® (immune globulin intravenous – BPL Inc [manufactured by Bio Products Laboratory]);
- Gamunex®-C (immune globulin intravenous caprylate/ chromatography purified – Grifols [manufactured by Grifols Therapeutics Inc]);
- Octagam® (immune globulin intravenous – Octapharma USA Inc [manufactured by Octapharma Pharmazeutika Produktionsges.m.b.H.]);
- Privigen® Liquid (immune globulin intravenous – CSL Behring LLC [manufactured by CSL Behring AG])

Immune globulin intravenous (IVIG) products are of concentrated human immunoglobulins, primarily immunoglobulin G (IgG), that are prepared from pooled plasma collected from a large number of human donors. The donors in a typical pool of plasma have a wide range of antibodies against infectious agents. These products have IgG subclasses similar to that found in normal humans.

All of the US licensed products (except Octagam 10%) are Food and Drug Administration (FDA)-approved for replacement therapy in patients with primary immune deficiencies due to defects in humoral immunity. Individual products are indicated for use in other conditions. The following indications are FDA-approved:

1. Replacement therapy for primary humoral immune deficiency (PID), including but not limited to the humoral immune defect in the following conditions: common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA) [congenital agammaglobulinemia], Wiskott-Aldrich Syndrome, and severe combined immunodeficiencies (SCID). Gammagard Liquid 10%, Gammaked, and Gamunex-C may be administered via intravenous (IV) or subcutaneous (SC) infusion for primary immunodeficiency. IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure. IVIG is also indicated for measles prophylaxis in individuals with PID who have been exposed to measles or who are at high risk of measles exposure.

2. B-cell chronic lymphocytic leukemia (CLL) for prevention of bacterial infections in patients with hypogammaaglobulinemia and/or recurrent bacterial infections.

3. Chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

4. Idiopathic (immune) thrombocytopenic purpura (ITP), acute and chronic, when a rapid rise in platelet count is needed to prevent and/or control bleeding or to allow a patient with ITP to undergo surgery.

6. Multifocal motor neuropathy (MMN) in adults as maintenance therapy to improve muscle strength and disability.\(^3\)

IVIG also is used for many off-label indications. Most evidence for clinical effectiveness of IVIG is anecdotal (i.e., case reports, open series, or cohort studies). Some conditions, however, have been studied in controlled trials. Usually IVIG is indicated only if standard approaches have failed, become intolerable, or are contraindicated.

**POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of IVIG products. Because of the specialized skills required for evaluation and diagnosis of patients treated with IVIG as well as the monitoring required for adverse events and long-term efficacy, approval requires IVIG products to be prescribed by or in consultation with a physician who specializes in the condition being treated. **All approvals are provided for 12 months unless otherwise noted below.**

**Automation:** None.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of IVIG products is recommended in patients who meet one of the following criteria.

**Food and Drug Administration (FDA)-Approved Indications**

1. Immunodeficiency, Primary Humoral (Treatment). Approve for 1 year in patients who meet the following criteria (A and B):
   A) IVIG is prescribed by or in consultation with one of the following physician specialists: an allergist/immunologist, immunologist, otolaryngologist (ear nose and throat [ENT] physician), pulmonologist, or an infectious diseases physician who treats patients with primary immune deficiencies; AND
   B) The patient has one of the following primary humoral or combined immune deficiencies (i, ii, iii, iv, v, vi, or vii):
      i. Common variable immunodeficiency (CVID)\(^14\)\(^\text{-}\)\(^17\) AND the patient meets the following criteria (a, b, c, and d):
         a) Patient has a documented history of significant recurrent or persistent, severe bacterial infections (such as recurrent pneumonias, frequent episodes of bacterial infections such as sinusitis, otitis, bronchitis, skin structure infections, or infections of the gastrointestinal tract)\(^14\)\(^\text{-}\)\(^18\)\(^\text{-}\)\(^19\) according to the prescribing physician; AND
         b) Infections are responding inadequately to treatment with antibiotics\(^14\)\(^\text{-}\)\(^19\) and/or appropriate prophylaxis with antibiotics OR the patient has multiple antibiotic hypersensitivities that interfere with treatment\(^18\) according to the prescribing physician; AND
         c) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\(^14\) according to the prescribing physician; AND
         d) The patient has at least ONE of the following according to the prescribing physician:
            1. Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory); OR
            2. Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory; OR
      Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\(^19\)
      (3) Markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) can be used instead of a protein if the patient already has antibodies to tetanus and diphtheria.\(^14\)\(^\text{-}\)\(^19\)\(^\text{,}\)\(^21\)\(^\text{-}\)\(^22\) OR
   ii. X-linked agammaglobulinemia (XLA) [Bruton’s agammaglobulinemia, congenital agammaglobulinemia],\(^14\)\(^\text{-}\)\(^23\) OR
iii. Severe combined immunodeficiencies (SCID);\textsuperscript{14,24} OR
iv. Wiskott-Aldrich syndrome,\textsuperscript{14,18,25-26} OR
v. Hyper-Immunoglobulin M (IgM) syndromes, X-linked or autosomal recessive;\textsuperscript{18,27-29} OR
vi. Other combined immunodeficiencies with significant hypogammaglobulinemia or antibody production defect\textsuperscript{14} (e.g., ataxia-telangiectasis,\textsuperscript{14,30} DiGeorge syndrome,\textsuperscript{14,27} nuclear factor κB essential modifier [NEMO] deficiency\textsuperscript{14}) AND the patient has frequent and severe infections according to the prescribing physician; OR
vii. Unspecified hypogammaglobulinemia AND the patient meets the following criteria (a, b, c, and d):
   a) Patient has a documented history of significant recurrent or persistent, severe bacterial infections (such as recurrent pneumonias, frequent episodes of bacterial infections such as sinusitis, otitis, bronchitis, skin structure infections, or infections of the gastrointestinal tract)\textsuperscript{14,18-19} according to the prescribing physician; AND
   b) Infections are responding inadequately to treatment with antibiotics\textsuperscript{14,20} and/or appropriate prophylaxis with antibiotics or the patient has multiple antibiotic hypersensitivities that interfere with treatment\textsuperscript{18} according to the prescribing physician; AND
   c) Other disorders that may increase susceptibility to infection such as allergy or anatomic defects, have been sought out and treated aggressively if present\textsuperscript{14} according to the prescribing physician; AND
   d) The patient has at least ONE of the following according to the prescribing physician:
      (1) Reduced total serum IgG level (age-adjusted and according to the normal reference range for the reporting laboratory); OR
      (2) Reduced IgG1 and IgG3 subclass levels or reduced IgG1 alone according to the normal reference range for the reporting laboratory; OR
         Note: Patients with low levels of IgG1 and/or IgG2 will almost always have reduced levels of total IgG.\textsuperscript{19}
      (3) Markedly impaired antibody response to protein (e.g., tetanus, diphtheria) antigen OR antibody testing with a polysaccharide antigen (pneumococcus) can be used instead of a protein if the patient already has antibodies to tetanus and diphtheria.\textsuperscript{14,19,21-22}
2. B-Cell Chronic Lymphocytic Leukemia (CLL) for Prevention of Bacterial Infections. Approve in patients who meet the following criteria (a, b, and c):
   a) The patient has an IgG level < 500 mg/dL (5.0 g/L);\textsuperscript{31} AND
   b) The patient has a history of a serious bacterial infection that required IV antibiotic therapy or hospitalization;\textsuperscript{31} AND
   c) IVIG is prescribed by or in consultation with an oncologist, hematologist, or infectious diseases physician.

IVIG is indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell CLL.\textsuperscript{4,31-32} The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on non-Hodgkin’s lymphomas (version 1.2015) recommends evaluation of serum IgG if < 500 mg/dL in patients with CLL who have recurrent sinopulmonary infections requiring antibiotics or hospitalization.\textsuperscript{31} IVIG has been associated with a significant decrease in infections, but no improvement in survival. According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins.\textsuperscript{32} IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but there was no consensus on specific criteria to use for duration of treatment with IVIG.

3. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) or Polyradiculoneuropathy. Approve if IVIG is prescribed by or in consultation with a neurologist.

IVIG is indicated to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse in patients with CIDP.\textsuperscript{5,7,33-34} IVIG is recommended as an equivalent alternative to plasma exchange in children and adults with CIDP.\textsuperscript{35-37} IVIG has been effective at improving certain motor functions for up to 48 weeks after initial therapy.\textsuperscript{35,38} In short-term, controlled trials, IVIG improved disability more than prednisolone and the quality of life was better with IVIG because adverse effects were less.\textsuperscript{36} The goal is to prevent or decrease the frequency of relapses and stabilize the disease.\textsuperscript{33}

4. Idiopathic (Immune) Thrombocytopenic Purpura (ITP) or Immune Thrombocytopenia (IT), Acute and Chronic. Approve if the patient meets the following criteria (a, b, or c):
   a) Adults and adolescents (> 17 years of age) with ITP/IT. Approve for ONE of the following (i, ii, or iii):
      i. Acute bleeding in a patient who is newly diagnosed or requiring therapy for the first time OR in patients with persistent or chronic ITP. Approve IVIG for 1 month if the patient meets the following criteria (1, 2 and 3):
         (1) IVIG is prescribed by or in consultation with a hematologist; AND
         (2) One of the following applies:
             • The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT;\textsuperscript{39} OR
             • There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid;\textsuperscript{40} OR
             • A corticosteroid is contraindicated according to the prescribing physician; AND
         (3) The platelet count is < 30,000 per mm\textsuperscript{3} (microliter).
      ii. To increase platelet counts before surgical procedures (e.g., splenectomy) or dental procedures, approve IVIG for 1 month if the patient meets the following criteria (1 and 2):
         (1) IVIG is prescribed by or in consultation with a hematologist; AND
The platelet count is $< 50,000$ per mm$^3$ OR if the patient is undergoing major surgery (e.g., central nervous system or cardiac surgery) and the platelet count is $< 75,000$ per mm$^3$.

iii. The patient has **persistent** (3 to 12 months duration) or **chronic** ($\geq 12$ months duration) ITP/IT. Approve IVIG if the patient meets the following criteria (1, 2 and 3):

(1) IVIG is prescribed by or in consultation with a hematologist; AND

(2) One of the following applies:
   - The patient has tried a systemic corticosteroid (e.g., prednisone) for ITP/IT; OR
   - There is an urgent need to increase the platelet count quickly AND IVIG will be started with a systemic corticosteroid; OR
   - A corticosteroid is contraindicated according to the prescribing physician; AND

(3) IVIG is required to prevent bleeding.

b) Children and adolescents ($\leq 17$ years of age) with ITP/IT. Approve for one of the following (i, ii, iii, or iv):

i. Acute bleeding in a patient who is newly diagnosed or requiring therapy for the first time OR in patients with persistent or chronic ITP. Approve for one month if the patient meets the following criteria (1 and 2):

(1) IVIG is prescribed by or in consultation with a hematologist; AND

(2) There is significant acute mucous membrane bleeding or other noncutaneous bleeding.

ii. The patient has **persistent** (3 to 12 months) or **chronic** ($\geq 12$ months) ITP/IT. Approve if the patient meets the following criteria (1 and 2):

(1) IVIG is prescribed by or in consultation with a hematologist; AND

(2) IVIG is required to prevent bleeding;

iii. Inaccessibility (such as travel, distance from hospital), activity level of the patient, or noncompliance is a concern with the prescribing physician. Approve if the patient meets the following criteria (1 and 2):

(1) IVIG is prescribed by or in consultation with a hematologist; AND

(2) Child/adolescent is at risk of bleeding;

iv. To increase the platelet count before major surgery such as splenectomy, or before other surgery, dental extraction(s), or other procedures likely to cause blood loss. Approve for 1 month if IVIG is prescribed by or in consultation with a hematologist.

c) Pregnant woman with ITP/IT. Approve for one of the following (i or ii):

i. Before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia. Approve for 2 weeks if IVIG is prescribed by or in consultation with a hematologist;

ii. Pregnant woman in any trimester. Approve for 3 months if IVIG is prescribed by or in consultation with a hematologist. (This does not include before normal vaginal delivery, cesarean section, or spinal or epidural anesthesia.)

IVIG is indicated for the treatment of patients with ITP to increase platelet counts to prevent bleeding or to allow the patient with ITP to undergo surgery. See Appendix A for more information.

5. **Kawasaki Disease.** Approve IVIG for 1 day in patients who meet the following criteria (a and b):

a) IVIG is prescribed by or in consultation with a pediatric cardiologist or a pediatric infectious diseases physician; AND

b) The patient has persistent or recrudescent (recurring) fever or signs of inflammation 24 to 48 hours after completing the initial IVIG infusion(s).

Note: These criteria assume that the first dose was given in a hospital within 7 to 10 days of onset.
IVIG is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients. The efficacy of IVIG in reducing the prevalence of coronary artery abnormalities is well-established when given in conjunction with aspirin in the acute phase of Kawasaki disease. Treatment with IVIG during the acute phase reduces the risk of coronary artery aneurysms from 17% to 4%. Patients should receive a single dose of IVIG together with aspirin within the first 10 days of illness, and if possible, within 7 days of illness. IVIG can also be given in children presenting after the 10th day of illness (i.e., the diagnosis was missed earlier) if they have persistent fever without other explanation or aneurysms and ongoing systemic inflammation. Patients with persistent or recrudescent fever that is present 36 hours after the end of the first IVIG infusion can be retreated with IVIG one time.

6. Multifocal Motor Neuropathy (MMN) (Treatment). Approve if IVIG is prescribed by or in consultation with a neurologist.

IVIG is indicated as maintenance therapy to improve muscle strength and disability in adults with MMN. In several placebo-controlled trials, IVIG improved muscle strength and neurological disability scores. IVIG is the only proven effective treatment and is considered first-line treatment. Plasma exchange and corticosteroids are not effective. IVIG is beneficial in maintenance treatment but the disease continues to progress over many years.

Other Uses with Supportive Evidence

7. Autoimmune Mucocutaneous Blistering Diseases (Pemphigus Vulgaris, Pemphigus Foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid [Cicatricial Pemphigoid], and Epidermolysis Bullosa Acquisita). Approve in children or adults who meet the following criteria (a and b):

a) IVIG is prescribed by or in consultation with a dermatologist; AND
b) The patient meets ONE of the following criteria (i, ii, or iii):  
   i. The patient has tried a systemic corticosteroid OR a corticosteroid is contraindicated according to the prescribing physician AND the patient has tried an immunosuppressive agent (e.g., azathioprine, cyclophosphamide, dapsone, methotrexate [MTX], ciclosporine, mycophenolate mofetil, tacrolimus) OR an immunosuppressive agent is contraindicated according to the prescribing physician;
   ii. The patient has rapid, debilitating, progressive disease, that cannot be controlled with a systemic corticosteroid and an immunosuppressive agent;
   iii. The disease is so serious that there is inadequate time for therapy with a systemic corticosteroid and an immunosuppressive agent to have a rapid enough effect.

Conventional therapy (a systemic corticosteroid and an immunosuppressive agent) is started at the same time or before IVIG. Many case reports and uncontrolled case series suggest benefit of IVIG in patients with recalcitrant disease or in those with contraindications to conventional therapy. The total duration of treatment with IVIG can be at least 2 years or longer. The interval between infusions is increased gradually and prolonged clinical remission has been reported with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, and mucous membrane pemphigoid (cicatricial pemphigoid).

8. Cytomegalovirus (CMV) Interstitial Pneumonia in Patients with Hematopoietic Cell Transplantation (HCT). Approve for 2 months when IVIG is prescribed by or in consultation with an oncologist, hematologist, or an infectious diseases physician.

For CMV pneumonia, therapy consists of ganciclovir IV injection (or foscarnet IV injection if CMV is ganciclovir-resistant) and IVIG in combination. Whether adding IVIG adds efficacy is controversial, and there are no data to support adding IVIG for the treatment of any manifestation of CMV disease other than pneumonia. CytoGam® (CMV immune globulin IV injection) may be
preferred instead of IVIG for interstitial pneumonia. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) recommends the combination of ganciclovir and IVIG for the therapy of CMV pneumonia.\(^{51}\) For other types of CMV disease, the EBMT recommends ganciclovir or foscarnet without IVIG. These recommendations are consistent with the NCCN guidelines (version 2.2014) for prevention and treatment of cancer-related infections.\(^{50}\) IVIG is not indicated for CMV prophylaxis and preemptive therapy. (See Exclusions.)

9. **Dermatomyositis or Polymyositis.** Approve in patients who meet the following criteria (a, b and c):
   a) IVIG is prescribed by or in consultation with a neurologist or a rheumatologist; AND
   b) The patient has tried a systemic corticosteroid\(^{35,37,54-55}\) OR a corticosteroid is contraindicated according to the prescribing physician; AND
   c) The patient has tried an immunosuppressive agent (e.g., azathioprine, MTX, cyclosporine, cyclophosphamide, mycophenolate mofetil)\(^{35,54-55}\) OR an immunosuppressive agent is contraindicated according to the prescribing physician.

IVIG may be used in patients with dermatomyositis with severe active illness for whom other interventions have been unsuccessful or intolerable.\(^{54-55}\) In one double-blind, placebo-controlled crossover trial, patients with treatment resistant dermatomyositis who received IVIG for 3 months had significant improvement in muscle strength, neuromuscular symptoms, and rash.\(^{56}\) IVIG has been used to maintain response in dermatomyositis.

IVIG may be considered amongst the treatment options for patients with polymyositis not responding to first line immunosuppressive treatment.\(^{37,54}\) In uncontrolled series, IVIG has been effective in polymyositis.

10. **Desensitization Therapy Prior to and Immediately after Solid Organ (Kidney, Heart, Lung, Liver, Intestinal) Transplantation.** Approve IVIG if prescribed by or in consultation with a physician affiliated with a transplant center.

Patients with preexisting anti-human leukocyte antigen (HLA) antibodies (sensitized patients) are more likely to have a positive cross match with possible donors and have a lower likelihood of receiving a solid organ transplant with longer wait times. Most of the information on use of IVIG for desensitization is in patients with kidney transplantation but many of the same principles apply to transplantation of other organs and tissues.\(^{57-58}\)

**Kidney.** IVIG has been used in highly sensitized patients to reduce allosensitization, ischemia-reperfusion injuries, and acute rejections episodes in renal allograft recipients.\(^{57,59-62}\) IVIG has been used alone or after plasmapheresis. IVIG is also used in combination with Rituxan\textsuperscript{®} (rituximab injection for IV infusion). In one Phase III double-blind trial in patients with end stage renal disease (ESRD), IVIG was better than placebo in reducing anti-HLA antibody levels and improving transplantation rates in highly sensitized patients.\(^{59}\)

**Heart.** IVIG has been used as a desensitization agent in patients undergoing cardiac transplantation.\(^{61-62}\) Randomized trials are not available and many of the studies have not defined response. The studies have not shown that IVIG alone reduced antibody and results concerning survival after transplant are conflicting. In one study in sensitized patients with a left ventricular assist device who were awaiting cardiac transplant, treatment with IVIG reduced serum reactivity to HLA class I antigens, decreased the risk of positive cross-match reactions, and shortened the waiting time for cardiac transplantation.\(^{63}\) In another study, in 35 sensitized patients who had orthotopic heart transplantation, IVIG was used with plasmapheresis pre-transplant to allow successful cardiac transplantation and to improve survival.\(^{64}\)

**Lung or Liver.** The role of IVIG or any other desensitization therapy in patients prior to lung transplantation who are sensitized to HLA is not known.\(^{61}\) There is insufficient evidence to
recommend for or against use of IVIG in these patients for desensitization or for treatment of rejection.\textsuperscript{61-62} Regarding liver transplantation, antibody mediated rejection after transplantation is rare and patients are not routinely evaluated for HLA antibody formation.\textsuperscript{61} According to guidelines from the Canadian Blood Services and the National Advisory Committee on Blood and Blood Products of Canada\textsuperscript{61} there is insufficient evidence to make a recommendation for or against routine use of IVIG in preparation for liver transplantation or for treatment of rejection/ABO-incompatible liver transplantation. Use of IVIG in combination with other therapies in patients undergoing lung or liver transplantation requires further study.

Small intestine. Limited published information is available in sensitized recipients of small intestine transplants.\textsuperscript{65-66} In a pilot study, highly sensitized patients (n = 6) with intestinal failure (short gut syndrome) who were awaiting isolated small bowel transplant received IVIG and immunosuppressive therapy pre-transplant.\textsuperscript{65} Four of the six patients had reduction in high panel peak reactive antibody (PRA) and received intestinal transplantation. Patients continued on IVIG post-transplant at Days 1, 7 and 21. The waiting time for transplant and mortality was similar to non-sensitized patients.

IVIG is also used post transplant to treat acute antibody-mediated rejection and steroid-resistant acute cellular rejection.\textsuperscript{61} These patients are hospitalized.

11. Guillain-Barré Syndrome (GBS). Approve for 1 month in patients who meet the following criteria (a and b):
   a) IVIG is prescribed by or in consultation with a neurologist or a specialist with experience in diagnosing and treating patients with GBS; AND
   b) The patient meets one of the following criteria (i or ii):
      i. IVIG is initiated within 2 weeks and no longer than 4 weeks of onset of neuropathic symptoms (weakness, inability to stand or walk without assistance, respiratory or bulbar weakness);
      ii. The patient has had a relapse, but had an initial response to IVIG.

IVIG is recommended as an equivalent alternative to plasma exchange in children and adults with GBS.\textsuperscript{33,35,67} IVIG is the treatment of choice, since plasmapheresis is not always readily available.\textsuperscript{68} In controlled trials, IVIG was as effective or more effective than plasmapheresis in improving strength, time to unaided walking, or discontinuation of ventilation.\textsuperscript{35} The effects of IVIG and plasma exchange are equivalent in hastening recovery, and multiple complications are less frequent with IVIG than with plasma exchange.\textsuperscript{67} The American Academy of Neurology (AAN) recommends IVIG in patients who require aid to walk within 2 or 4 weeks from the onset of neuropathic symptoms.\textsuperscript{68} Treatment with IVIG after 4 weeks from onset is indicated since some patients may relapse and the relapse may be severe enough to warrant a repeat course of IVIG.\textsuperscript{35-36} The first course of IVIG therapy may have been given in a hospital.

Patients who receive IVIG for GBS are usually hospitalized. Patients with severe GBS, that is, patients with bulbar or respiratory weakness, muscle weakness, inability to stand or walk and whose symptoms are progressing over 7 to 10 days or who have symptoms that interfere with eating or breathing are hospitalized for treatment with IVIG or plasma exchange. In children symptoms are different and usually are leg or back pain and with progression being more rapid than in adults.\textsuperscript{73} Many patients with GBS recover fully without therapy. The effect of IVIG in GBS has only been investigated in randomized controlled trials in patients who are unable to walk at nadir (i.e., severely affected patients), not in mildly affected patients who are able to walk unaided at nadir.\textsuperscript{69} IVIG is not indicated or proven to be effective in mildly affected GBS patients.\textsuperscript{54,69}

The European Federation of Neurological Societies (EFNS) task force on the use of IVIG in the treatment of neurological diseases states that no recommendation can be made as to whether patients with Miller Fisher syndrome (a variant of GBS) should be treated with IVIG, because this has not been well studied.\textsuperscript{54} In a retrospective review of 92 patients with Miller Fisher syndrome, the authors
concluded that IVIG and plasmapheresis did not seem to have influenced patients’ outcomes. The American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) consensus statement on the use of IVIG in neuromuscular conditions notes, on the basis of a single retrospective analysis and case reports, it is difficult to clearly define the role of IVIG in treating Miller Fischer syndrome. Further, the literature suggests that best medical management may suffice for many patients.

12. Hematopoietic Cell Transplantation (HCT) to Prevent Bacterial Infection. Approve IVIG for 6 months in patients who meet the following criteria (a, b, c, and d):

a) IVIG is prescribed by or in consultation with a hematologist, oncologist or infectious diseases physician; AND
b) The patient has had a HCT within the previous year; AND
c) The patient has an IgG level < 500 mg/dL OR the patient has multiple myeloma or malignant macroglobulinemia (In the professional opinion of a specialist physician, we have adopted this criterion for IgG level < 500 mg/dL); AND
d) According to the prescribing physician the patient has a significant risk of having frequent and/or severe bacterial infections despite antibiotic therapy.

HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (i.e., allogeneic or autologous) or cell source (i.e., bone marrow, peripheral blood, or umbilical cord blood). With regard to IVIG, guidelines recommend the following for prevention or preemptive treatment of specific infections in HCT recipients. In adult or adolescent HCT recipients (allogeneic or autologous), IVIG is indicated to prevent bacterial infections in those with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL) during the first 100 days after HCT. In pediatric patients, IVIG is indicated in those with an allogeneic HCT if hypogammaglobulinemia is severe during the first 100 days after HCT. For prevention of bacterial infections beyond 100 days post HCT (allogeneic or autologous), IVIG is recommended in recipients with severe hypogammaglobulinemia (i.e., serum IgG < 400 mg/dL).

Although IVIG has been recommended for use in producing immune system modulation for the prevention of graft-versus-host disease (GVHD), routine administration of IVIG to HCT recipients for prophylaxis of bacterial infection within the first 100 days after transplantation is not recommended. Some centers check total IgG levels in high-risk HCT recipients (e.g., those with unrelated marrow grafts). For patients with severe hypogammaglobulinemia (i.e., IgG < 400 mg/dL) IVIG prophylaxis may be considered to maintain a trough serum IgG concentration > 400 mg/dL. Also, in preventing late disease (> 100 days after HCT), routine use of IVIG monthly is not recommended unless the IgG level is < 400 mg/dL to prevent bacterial infections. These reduced levels may be associated with bacteremia or recurrent sinopulmonary infections.

In a randomized trial where IVIG or no IVIG prophylaxis were given from Day 90 to Day 360 post bone marrow transplant (with patients receiving MTX plus cyclosporine for GVHD prophylaxis), the incidence of bacteremia, sepsis, localized infection, survival, obliterative bronchiolitis, or the incidence or mortality of chronic GVHD were not reduced with IVIG. Patients with severe demonstrable hypogammaglobulinemia (e.g., IgG levels < 400 mg/dL) can continue receiving IVIG. IVIG supplementation is often used in patients with severe infections and IgG levels < 400 mg/dL to maintain levels until infections resolve.

Gamimune® N, a brand of IVIG that has been discontinued, was FDA-approved for the treatment of bone marrow transplant patients ≥ 20 years of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic etiologies, and acute GVHD in the first 100 days posttransplant. Currently marketed IVIG products do not carry this indication.

13. Human Immunodeficiency Virus (HIV)-Associated Thrombocytopenia. Approve for 1 month in patients who meet the following criteria (a and b):
a) IVIG is prescribed by or in consultation with an infectious diseases specialist or a physician who specializes in the treatment of HIV infection; AND

b) The patient meets ONE of the following criteria (i or ii):
   i. The patient is receiving combination antiretroviral therapy (cART) for their HIV infection;
   ii. The patient has clinically significant bleeding complications according to the prescribing physician.

Secondary ITP can occur in patients with HIV infection. Effective viral suppression using antiretroviral therapy improves HIV-associated cytopenias, including thrombocytopenia. Treatment of secondary ITP (HIV-associated) with short-term corticosteroid therapy increases the platelet count in a similar manner as in non-HIV infected persons and does not appear to be associated with adverse effects. IVIG and Rh(D) immune globulin (IV or intramuscular [IM] injection) [Rhophylac®/WinRho® SDF] have been reported to increase the platelet count. Splenectomy is an effective option for patients who fail to respond to corticosteroid or IVIG therapy.

Evidence for IVIG use in HIV-associated thrombocytopenia is mostly based on case reports and cohort studies and most studies predate the current standard practices for treatment of HIV. Rh(D) immune globulin is FDA-approved in non-splenectomized, Rh(D) positive patients for the treatment of childhood acute or chronic ITP, chronic ITP in adults, and ITP secondary to HIV infection (adults and children). The safety and efficacy of Rh(D) immune globulin have not been evaluated in patients who are splenectomized or in patients who are Rh(D) negative. The American Society of Hematology (ASH) guidelines for immune thrombocytopenia recommend initial treatment with corticosteroids, IVIG, or Rh(D) immune globulin for patients with secondary ITP due to HIV (no preference for initial therapy is expressed). In symptomatic patients who fail one of these therapies, splenectomy is recommended. No platelet count cut-offs are addressed in this patient population. A Canadian expert panel of hematologists recommends IVIG as a treatment option when there is active bleeding or when platelet counts are < 10,000/mm³. Their recommendations do not discuss use of Rh(D) immune globulin.

14. Human Immunodeficiency Virus (HIV)-Infected Infants and Children to Prevent Recurrent Bacterial Infections. Approve in patients who meet the following criteria (a, b, c, and d):

a) IVIG is prescribed by or in consultation with an infectious diseases specialist or an immunologist; AND

b) The patient is < 13 years of age; AND

c) The patient is receiving combination antiretroviral therapy (cART); AND

d) The patient has ONE of the following (i, ii or iii):
   i. Hypogammaglobulinemia (IgG < 400 mg/dL);
   ii. Functional antibody deficiency is demonstrated by poor specific antibody titers (that is, the patient does not develop specific antibody responses against protein and polysaccharide antigens);
   iii. Functional antibody deficiency is demonstrated by the patient having recurrent (two or more per year), serious bacterial infections (e.g., bacteremia, meningitis, pneumonia) despite administration of cART and appropriate antimicrobial prophylaxis.

IVIG is no longer recommended for primary prevention of serious bacterial infections in HIV-infected children unless hypogammaglobulinemia is present or functional antibody deficiency is demonstrated by recurrent bacterial infections. Usually neither IVIG nor antimicrobial prophylaxis is necessary in patients receiving effective antiretroviral therapy. In rare situations where cART and antibiotic prophylaxis are not effective in preventing frequent recurrent serious bacterial infections, secondary prophylaxis with IVIG can be considered. In children with greater than two serious bacterial infections in a one-year period and who cannot tolerate cART, secondary prophylaxis is indicated. The first choice of therapy for secondary prophylaxis is trimethoprim-sulfamethoxazole and IVIG every 2 to 4 weeks is an alternative.
Gamimune N, a brand of IVIG that has been discontinued, was FDA-approved for pediatric HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization and to increase the time free of serious bacterial infection. Currently marketed IVIG products do not carry this indication.

15. Lambert-Eaton Myasthenic Syndrome (LEMS), Treatment. Approve in patients who meet the following criteria (a and b):
   a) IVIG is prescribed by or in consultation with a neurologist; AND
   b) The patient meets ONE of the following conditions (i or ii):
      i. The patient has non-paraneoplastic LEMS;
      ii. The patient has paraneoplastic LEMS AND meets ONE of the following criteria (1 or 2):
         (1) The patient has tried at least one of the following: a systemic corticosteroid OR azathioprine OR another immunosuppressive agent (e.g., cyclosporine, mycophenolate mofetil);
         (2) The patient has a contraindication to BOTH a corticosteroid AND azathioprine and other immunosuppressive agents according to the prescribing physician.

In one placebo-controlled crossover trial, a single dose of IVIG produced significant improvement in muscle strength and reduced serum calcium channel antibody titers in patients with LEMS. There have been only five randomized controlled trials of treatment for LEMS: four with 3,4-diaminopyridine (amifampridine tablets) [available in the US through a compassionate use program] and one with IVIG. Plasma exchange, steroids, and immunosuppressive agents have not been studied in randomized controlled trials. IVIG may be useful as adjunctive therapy in difficult to treat patients.

16. Multiple Myeloma. Approve in patients who meet the following criteria (a, b and c):
   a) The patient has stable (plateau phase) disease (> 3 months from diagnosis); AND
   b) The patient has severe recurrent bacterial infections according to the prescribing physician; AND
   c) IVIG is prescribed by or in consultation with a hematologist, oncologist, or infectious diseases specialist.

Patients with multiple myeloma are often functionally hypogammaglobulinemic with total immunoglobulin production being elevated but the repertoire of antibody production restricted. The NCCN clinical practice guidelines on multiple myeloma (version 2.2015) recommend that IVIG prophylaxis be considered in the setting of recurrent, life-threatening infections. Prophylactic IVIG replacement therapy has reduced infection rates in patients in the plateau phase, but no effect has been demonstrated in newly diagnosed patients. In one randomized placebo-controlled trial, prophylactic use of IVIG reduced serious and life-threatening infections in immunosuppressed patients with multiple myeloma. According to a Canadian expert panel of hematologists, IVIG is recommended for infection prophylaxis in these adults who have either a recent episode of a life-threatening infection thought to be caused by low levels of polyclonal immunoglobulins or recurrent episodes of clinically significant infections (e.g., pneumonia) that are caused by low levels of polyclonal immunoglobulins. IVIG is an option for acute life-threatening infections in these patients. This panel of hematologists recommended re-evaluation every 4 to 6 months when used for prophylaxis but there was no consensus on specific criteria to use for duration of treatment with IVIG. In another guideline from the British Committee for Standards in Haematology and UK Myeloma Forum, therapy for up to 6 months was recommended.

17. Multiple Sclerosis (MS), Acute Severe Exacerbation. Approve for 5 days in patients who meet the following criteria (a and b):
   a) IVIG is prescribed by or in consultation with, a neurologist or a physician who specializes in the treatment of MS; AND
   b) The patient meets ONE of the following criteria (i or ii):


i. The patient has either not responded to or has had a significant adverse reaction AND is continuing to deteriorate despite therapy with ONE of the following (1, 2 or 3):
(1) Oral or IV corticosteroids (e.g., methylprednisolone sodium succinate injection);
(2) Plasma exchange;
(3) Acthar® H.P. gel (Acthar) [repository corticotropin injection; adrenocorticotropic hormone {ACTH}];

ii. A systemic corticosteroid or Acthar is contraindicated AND the patient is not a candidate for plasma exchange according to the prescribing physician. (In the professional opinion of a specialist physician, we have adopted this criterion.)

High dose corticosteroids, usually methylprednisolone, are first-line treatment of MS relapses, if needed. 85 Acthar is an option in patients who cannot tolerate the adverse effects of high-dose corticosteroids, have been treated unsuccessfully with corticosteroids, or who cannot use IV therapy. In patients who are unresponsive to corticosteroids or Acthar, second-line therapy with plasmapheresis (plasma exchange) is an alternative. Two studies showed that IVIG had no effect on recovery from acute relapse when given either concomitantly with, or immediately before therapy with IV methylprednisolone. 35,54 According to an expert panel of neurologists guidelines, IVIG is only recommended for acute exacerbations of MS in patients with severe refractory optic neuritis who have had no recovery of vision after 3 months of standard steroid therapy or in patients who have a contraindication to corticosteroid therapy. 35 For other MS uses (relapsing remitting MS [RRMS]), this panel has recommended either a single 1 g/kg dose or 0.4 g/kg daily for 5 days.

18. Multiple Sclerosis (MS), Post-Partum to Prevent Relapses. Approve IVIG for 6 months in women who meet the following criteria (a and b):

a) IVIG is prescribed by or in consultation with, a neurologist or a physician who specializes in the treatment of MS; AND

b) The patient is not currently receiving disease modifying therapy (DMT) for MS (e.g., Avonex® [interferon beta-1a injection, IM], Plegridy™ [peginterferon beta-1a SC injection], Rebif® [interferon beta-1a injection, SC], Betaseron®/Extavia® [interferon beta-1b injection], Copaxone® [glatiramer acetate injection], Gilenya® [fingolimod capsules], Aubagio® [teriflunomide tablets], Tecfidera® [dimethyl fumarate capsules], Tysabri® [natalizumab injection], Novantrone® [mitoxantrone injection]) to prevent relapses.

None of the DMTs have been approved for use in women who are nursing. IVIG is the treatment of choice for post partum mothers with MS who are nursing. 86

There is an increase in relapse rates in women with MS during the initial 3 months after birth which may continue for up to 6 months (in patients not receiving therapy). 87-89 In one randomized, confirmatory, multicenter, double-blinded-placebo-period (Days 1 through 3 post-partum) trial, women with clinically confirmed RRMS and at least one relapse within the 2 years prior to pregnancy received treatment with one of the following IVIG regimens: IVIG 150 mg/kg Day 1 post-partum followed by placebo injections on Days 2 and 3 (Group I), or IVIG 900 mg/kg over a 3 day period (Group II). 89 Initial IVIG treatment was followed by an open phase in which both groups received five doses of IVIG 150 mg/kg at monthly (every 4 weeks) intervals. Prior to pregnancy the number of relapses per women per year in the 2 years prior to pregnancy was 1.0 ± 0.7 and 1.0 ± 0.6 in Group I and Group II, respectively. In Groups I and II, 75.6% and 81.5% of patients respectively, remained relapse-free during the 3-month post-partum period (primary efficacy endpoint). The difference between the groups (6%) at 3 months was not statistically significant (P = 0.2353). Numerically more patients in Group II remained relapse-free compared with Group I between Months 4 to 6 (82.3% vs. 70.9%) and within the total observation period of 6 months (69.1% vs. 57.5%); none of these differences reached statistical significance between groups.

Steroids may be used to treat acute relapses during pregnancy and in the post-partum period in nursing women (see Multiple Sclerosis, Acute Severe Exacerbation).
IVIG is **not** recommended for maintenance treatment to prevent relapses. (See Exclusions.)

### 19. Myasthenia Gravis

Approve IVIG for 5 days in patients who meet the following criteria (a and b).

- **a)** IVIG is prescribed by or in consultation with a neurologist; AND
- **b)** The patient meets ONE of the following criteria (i, ii, iii, or iv):
  1. The patient has an exacerbation of myasthenia gravis;\(^\text{35}\)
  2. The patient requires stabilization of myasthenia gravis before surgery;\(^\text{35}\)
  3. The patient has been started on an immunosuppressive drug (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil)\(^\text{90}\) and is waiting for full effect;
  4. The patient has responded to a previous course of IVIG therapy, but weakens (relapses) and has no response to other medications. (In the professional opinion of a specialist physician reviewing the data, we have adopted this criterion.)

**Note:** Patients with myasthenia gravis **crisis** are hospitalized. Crisis is defined by respiratory failure resulting from myasthenic weakness and necessitating assisted ventilation.

IVIG is used for severe exacerbations and as a short-term measure. Some patients may require additional courses of therapy, but IVIG is **not** appropriate for maintenance therapy in myasthenia gravis.\(^\text{35,91}\) Mild to moderate myasthenia gravis can be successfully managed with symptomatic and immunosuppressive medications. IVIG should be reserved for the treatment of severe exacerbations or myasthenia crises.

IVIG is used in clinical practice as short-term therapy until more effective long-term immunosuppression can be achieved for patients with severe myasthenic exacerbations or in preparation for surgery.\(^\text{35}\) In one randomized study, IVIG 0.4 g/kg for either 3 or 5 days was similar in efficacy to plasma exchange in patients with severe exacerbations of myasthenia gravis.\(^\text{92}\) Therapy with IVIG is an alternative to plasma exchange, especially in children, patients with poor vascular access, or when plasma exchange is not readily available.\(^\text{93}\) IVIG may be considered in patients with severe myasthenia gravis to treat acute severe decompensation when other treatments have been unsuccessful or are contraindicated.\(^\text{35}\) In one randomized, double-blind, placebo-controlled trial in 51 patients (not hospitalized) with myasthenia gravis and worsening weakness, IVIG-treated patients had a clinically meaningful improvement in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity at Day 14 and Day 28.\(^\text{94}\) The greatest improvement occurred in patients with more severe disease (QMG Score for Disease Severity > 10.5). There is insufficient evidence from randomized controlled trials to determine whether IVIG is effective in chronic (moderate or severe but stable) myasthenia gravis.\(^\text{91}\)

### 20. Passive Immunization for Measles (Post-Exposure Prophylaxis)

Approve 1 day of IVIG for patients who meet the following criteria (a or b):

- **a)** The patient is a pregnant woman and meets the following criteria (i and ii); OR
  1. The patient has been exposed to measles and IVIG will be given within 6 days of exposure;
  2. The patient does not have evidence of immunity to measles (i.e., the patient does not have a history of the disease or age-appropriate vaccination).
- **b)** The patient is severely immunocompromised (e.g., patients with a bone marrow transplant, GVHD, acute lymphoblastic leukemia (ALL), AIDS, HIV-infected patients) according to the prescribing physician, AND the patient has been exposed to measles and IVIG will be given within 6 days of exposure.

**Note:** For patients with primary immune deficiency, see criteria for Immunodeficiency, Primary Humoral.

When administered within 6 days of exposure, immune globulin (IG) can prevent or modify measles in patients who are nonimmune.\(^\text{12}\) IG therapy is not indicated in persons who have received one dose
of measles-containing vaccine at age ≥ 12 months, unless they are severely immunocompromised. IG therapy should not be used to control measles outbreaks, but is used to reduce the risk of infection and complications in the person receiving it. IG therapy has not been shown to prevent rubella or mumps infection after exposure and is not recommended for that purpose.

The ACIP recommends the use of IG therapy for post-exposure prophylaxis of measles in the following patients who are at risk for severe disease and complications from measles: infants < 12 months of age; pregnant women without evidence of measles immunity; and severely immunocompromised persons. IM IG can be given to other persons who do not have evidence of measles immunity, but priority is given to persons exposed in settings with intense, prolonged, close contact. For patients exposed without evidence of measles immunity, a rapid IgG antibody test can be used to inform immune status, if administration of IG is not delayed. For infants aged < 12 months IM IG is used; infants aged 6 through 11 months can receive measles, mumps, and rubella (MMR) vaccine instead of IG if given within 72 hours of exposure. Pregnant women without evidence of measles immunity who are exposed to measles should receive IVIG. Severely Immunosuppressed patients who are exposed to measles should receive IVIG prophylaxis regardless of immunologic or vaccination status because they may not be protected by the vaccine. Severely immune compromised patients include patients with severe primary immunodeficiency; patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment or longer in patients with GVHD; patients on treatment for ALL within and until at least 6 months after completion of immunosuppressive chemotherapy; and patients with AIDS or HIV-infected persons with severe immunosuppression (defined as CD4 percent < 15% [all ages] or CD4 count < 200 lymphocytes/mm³ [aged > 5 years]) and those who have not received MMR vaccine since receiving effective antiretroviral therapy. Some experts include HIV-infected persons who lack recent confirmation of immunologic status or measles immunity.

21. Passive Immunization for Varicella (Chickenpox) [Post-Exposure Prophylaxis]. Approve 1 day of IVIG for patients who meet the following criteria (a or b):

a) The patient is an HIV-infected infant or child and meets the following criteria (i, ii, iii, and iv):
   i. IVIG is prescribed by or in consultation with an infectious diseases specialist or an immunologist;
   ii. The patient is < 13 years of age;
   iii. VariZIG® (varicella zoster immune globulin IM injection) is not available;
   iv. The patient does not have evidence of immunity to varicella (i.e., patient does not have a history of the disease or age-appropriate vaccination); OR

b) The patient is not an HIV-infected infant or child and meets the following criteria (i, ii, iii, and iv):
   i. IVIG is prescribed by or in consultation with an infectious diseases specialist or immunologist;
   ii. VariZIG is not available;
   iii. The patient does not have evidence of immunity to varicella (i.e., patient does not have a history of the disease or age-appropriate vaccination);
   iv. The patient meets ONE of the following criteria (1 or 2):
      (1) The patient is immune compromised;
      (2) The patient is pregnant.

HIV-infected children without a history of previous chickenpox or children who have not received two doses of varicella vaccine should receive VarizIG or, if not available, IVIG within 10 days (ideally within 4 days) after close contact with a person who has chickenpox or shingles. Post-exposure prophylaxis with VarizIG, or if VarizIG is not available, IVIG should be considered for HIV-infected children with moderate-to-severe immune compromise even if they have been immunized with varicella vaccine. Children who have received IVIG within 2 or 3 weeks of exposure do not require additional passive immunization.
VariZIG is indicated for post-exposure prophylaxis in certain patients without immunity to varicella and is given as soon as possible after exposure, preferably within 4 days, and as late as 10 days after exposure. Whether to administer VariZIG depends on three factors: 1) whether the patient lacks evidence of immunity to varicella; 2) whether the exposure is likely to result in infection; and 3) whether the patient is at greater risk for varicella complications than the general population. Patients without evidence of immunity to varicella who are at high risk for severe varicella and complications, who have been exposed to varicella or herpes zoster, and for whom varicella vaccine is contraindicated should receive VariZIG. The following patient groups are recommended by the Centers for Disease Control and Prevention (CDC) to receive VariZIG: 1) immunocompromised patients without evidence of immunity; 2) newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after) [these babies are probably hospitalized]; 3) hospitalized premature infants born at ≥ 28 weeks of gestation whose mothers do not have evidence of immunity to varicella; 4) hospitalized premature infants born at < 28 weeks gestation or who weigh ≤ 1,000 g at birth, regardless of their mothers’ evidence of immunity to varicella; and 5) pregnant women without evidence of immunity. In situations where administration of VariZIG does not appear possible within 10 days of exposure, IVIG is considered an alternative and should be given within 10 days of exposure (and ideally within 96 hours after exposure). The dose is 400 mg/kg given once. Patients who have received IVIG 400 mg/kg within the prior 3 weeks should be protected. For pregnant women who cannot receive VariZIG, clinicians can choose either IVIG or closely monitor the women for signs or symptoms of varicella and institute acyclovir therapy if illness occurs.

22. Pure Red Blood Cell Aplasia (PRCA) Secondary to Chronic (Persistent) Parvovirus B19 Infection. Approve for 3 months in patients who meet the following criteria (a, b, and c):
   a) IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
   b) The patient has a chronic immunodeficient condition (e.g., patients with HIV infection, solid organ transplants [e.g., renal, liver], chemotherapy for hematologic malignancy); AND
   c) The patient has clinically significant anemia as determined by the prescribing physician OR the patient is transfusion dependent.

In immunosuppressed patients lacking neutralizing antibodies, IVIG has been useful for the treatment of persistent B19 infection. IVIG has been used to treat severe anemia secondary to chronic B19 infection in the context of solid-organ transplantation, HIV infection, or primary antibody deficiency. Three to five days of IVIG induces an increase in reticulocyte count with an accompanied rise in the hemoglobin level, and is often curative in that B19 is cleared from the body. Persistent B19 infection in apparently immunocompetent individuals who possess neutralizing antibodies does not respond well to IVIG. In immunocompetent children, adolescents and adults, parvovirus B19 is self-limiting and does not require treatment with IVIG. PRCA and the underlying persistent parvovirus B19 infection may be terminated rapidly by discontinuing immunosuppressive therapy or by instituting antiretroviral therapy in patients with AIDS. IVIG has been curative in patients with congenital immunodeficiency, but in patients with AIDS, parvovirus often persists at lower levels; relapses of anemia may require repeated administration of immunoglobulin. Maintenance therapy has been used in patients who relapse.

23. Pure Red Blood Cell Aplasia (PRCA), Immunologic Subtype. Approve for 2 months in patients who meet the following criteria (a, b, and c):
   a) IVIG is prescribed by or in consultation with an infectious diseases specialist, immunologist, hematologist, or transplant specialist; AND
   b) The patient has tried a systemic corticosteroid (e.g., prednisone); AND
   c) The patient has tried either cyclophosphamide OR cyclosporine.

The Canadian expert panel of hematologists recommends prednisone followed by cyclophosphamide or cyclosporine as first-line therapy for immunologic type PRCA. Based on case reports about 50% of patients have an initial benefit with IVIG therapy. This panel considers IVIG a reasonable second-line option since this is a serious condition. The immunologic subtype mechanism may be humoral
or cellular and can be caused by tumors, certain drugs (e.g., azathioprine, carbamazepine), connective tissue disorders, and incompatible bone marrow transplant.

24. **Stiff-Person Syndrome (Moersch-Woltman Syndrome).** Approve in patients who meet the following criteria (a and b):
   a) IVIG is prescribed by or in consultation with a neurologist; AND
   b) The patient meets ONE of the following criteria (i or ii):
      i. The patient has tried a benzodiazepine (e.g., diazepam) OR baclofen;
      ii. The patient has contraindications to both a benzodiazepine AND baclofen according to the prescribing physician.

In one double-blind, placebo-controlled crossover trial in 16 patients with stiff-person syndrome, IVIG 2 g/kg divided into two consecutive daily doses and given once monthly for 3 months, decreased stiffness scores significantly and decreased heightened sensitivity scores.

25. **Thrombocytopenia, Fetal Alloimmune.** Approve infusion of IVIG to a pregnant woman as antenatal therapy for 6 months if IVIG is prescribed by or in consultation with a hematologist or an obstetrician.

Antenatal therapy with IVIG administered to the mother is effective in increasing fetal platelet counts in neonatal alloimmune thrombocytopenia (NAIT). IVIG reduces the risk of intracranial hemorrhage (ICH) and increases the fetal platelet count. In one prospective, multicenter study, 73 women with alloimmune thrombocytopenia who had not delivered an infant with an ICH in a prior pregnancy were randomized to receive either IVIG 2 g/kg/week (group A) or IVIG 1 g/kg/week plus prednisone 0.5 mg/kg/day (group B), starting at about 20 weeks of gestation. Fetal blood sampling was performed at about 32 weeks of gestation and, if the fetal platelet count was < 30,000 per mm$^3$ or cordocentesis could not be done, salvage therapy was given. Salvage therapy in patients in group A was addition of prednisone 0.5 mg/kg/day and in patients in group B was increasing IVIG to 2 g/kg/week in addition to the prednisone they were already taking. One neonate in each group suffered an ICH (primary outcome variable) during the neonatal period and neither was due to treatment failure. At the time of fetal blood sampling, the average platelet counts were 121,600 per mm$^3$ in group A and 116,100 per mm$^3$ in group B. The average birth platelet counts were 169,400 per mm$^3$ in group A and 134,000 per mm$^3$ in group B. In all, 27% of patients in group A and 17% of patients in group B received salvage therapy. Randomized controlled trials comparing IVIG or steroids vs. no treatment alone have not been done because of the known risk of ICH.

According to guidelines from an expert panel of hematologists, there is no evidence to support use of IVIG in newborns with fetal/neonatal alloimmune thrombocytopenia; first-line therapy is antigen-negative compatible platelets and IVIG is adjunctive.

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**
IVIG has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Adrenoleukodystrophy.** Evidence does not support IVIG use. Only one small study (n = 12) is available; IVIG did not arrest disease progression.

2. **Alzheimer’s Disease (AD).** In one multicenter, double-blind, Phase III, placebo-controlled trial (unpublished), 390 patients with mild to moderate AD were randomized to therapy with IVIG 400
mg/kg or 200 mg/kg or to placebo given every 2 weeks for 18 months. There was no statistically significant difference in the rate of cognitive decline when compared to placebo (mean 7.4 in the 400 mg/kg group; 8.9 in the 200 mg/kg group; 8.4 in the placebo group). There was not a statistically significant change in functional ability when compared to placebo (mean of -11.4 in the 400 mg/kg group; -12.4 in the 200 mg/kg group; -11.4 in the placebo group). Large placebo-controlled trials with a longer observation period are needed to establish efficacy, determine the optimal dosing regimen, and to confirm the safety of IVIG in the general AD population.

3. **Amyotrophic Lateral Sclerosis.** There is insufficient evidence to recommend IVIG. Only case series are available; no improvement in muscle strength was observed.

4. **Anemia, Aplastic.** Evidence does not support IVIG use.

5. **Asthma.** Global Initiative for Asthma (GINA) guidelines for asthma management and prevention do not include recommendations for use of IVIG.

6. **Atopic Dermatitis.** Evidence does not support IVIG use. According to a practice parameter endorsed by the American Academy of Allergy, Asthma and Immunology (AAAAI); the American College of Allergy, Asthma and Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology, use of IVIG to treat severe refractory atopic dermatitis has produced conflicting results. Most studies are not controlled and included small numbers of patients. According to the practice parameter, although children appear to have a better response than adults, controlled studies are needed to answer the question of efficacy in a more definitive manner. In one randomized, placebo-controlled study, children with moderate to severe atopic dermatitis (n = 40) received 3 injections of IVIG 2 g/kg or placebo every month over a 12-week period. The disease severity index was significantly decreased 3 months after completing treatments compared with baseline values (P < .05), but improvement had decreased by 6 months after therapy. Guidelines from the American Academy of Dermatology state that there is insufficient data to make a recommendation for the use of IVIG in the management of atopic dermatitis.

7. **Autism.** Evidence does not support IVIG use. In case series, IVIG has not demonstrated consistent efficacy in the majority of patients. Well-controlled, double-blind trials are needed.

8. **Chronic Fatigue Syndrome.** Evidence does not support IVIG use. One randomized, placebo-controlled trial did not find benefits in quality of life measures nor the Profile of Mood States for IVIG. Although scores were improved in IVIG and placebo treatment groups, no significant between group difference was demonstrated.

9. **Complex Regional Pain Syndrome (Reflex Sympathetic Dystrophy).** There is insufficient evidence to recommend IVIG. In one single center study a single dose of 0.5 g of IVIG per kg produced a decrease in pain intensity by 50% or more compared to placebo in 3 of 12 patients. Further studies are needed.

10. **Crohn’s Disease.** There is insufficient evidence to recommend IVIG. In one single center case collection report, 19 patients with acute Crohn’s disease (Crohn’s Disease Activity Index [CDAI] 284.1 ± 149.8) who were resistant to steroids received IVIG daily for 7 to 10 days. Four weeks after completing therapy, 14 patients were in clinical remission (CDAI < 150). Spontaneous remissions cannot be excluded. Prospective, randomized, placebo-controlled trials are needed to determine if IVIG has a role in the treatment of Crohn’s disease.

11. **Cystic Fibrosis.** There is insufficient evidence to recommend IVIG. In one single-center retrospective case review of 16 children with cystic fibrosis, IVIG was reportedly effective. Well designed, controlled trials are needed.
13. **Cytomegalovirus (CMV) Disease Prophylaxis in Hematopoietic Cell Transplantation (HCT) Recipients.** IVIG is not recommended. IVIG has been used in the past for CMV prophylaxis, but CMV prophylaxis is currently based on using seronegative blood in seronegative recipients, screening for CMV antigenemia, and prophylaxis with ganciclovir in some patients. However, IVIG is recommended for other indications in these patients. See Other Uses with Supportive Evidence.

14. **Cytomegalovirus (CMV) Infection, Preemptive Therapy for CMV Infection or Treatment of CMV Disease, in Allogeneic Hematopoietic Cell Transplantation (HCT) Recipients.** IVIG is not recommended. Preemptive therapy is defined as receiving therapy when there is evidence of active, but asymptomatic, CMV infection and is based on tests that rapidly detect CMV viremia or antigenemia. Preemptive therapy is used in most cases instead of prophylaxis for CMV management. First-line preemptive therapy for CMV infection is ganciclovir or foscarnet. Although most studies using IVIG for preemptive therapy were randomized, the patient populations were heterogeneous, the IVIG dose varied, most but not all used ganciclovir, and they were not adequately controlled. IVIG monotherapy does not appear to be effective for preemptive therapy. CDC, Infectious Diseases Society of America (IDSA), and the ASBMT guidelines do not include recommendations for use of IVIG in preemptive therapy of CMV infections.

15. **Cytomegalovirus (CMV) Infections, Prophylaxis or Treatment in Solid Organ Transplantation, (e.g., Heart, Kidney) for Prophylaxis.** Antiviral therapy is currently used. Antiviral agents (ganciclovir, Valcyte™ [valganciclovir oral tablets or solution]) and Cytogam are effective in preventing and treating CMV in solid organ transplant recipients.

16. **Diabetes Mellitus, Immunotherapy.** Evidence does not support IVIG use. Antibodies against islet cell antigens are implicated in the autoimmune pathogenesis of type 1 diabetes mellitus. In one 2-year randomized controlled trial, IVIG was given every 2 months to children and adults with type 1 diabetes. No beneficial effect was shown with IVIG compared to control and the authors concluded that IVIG therapy is unlikely to be a viable option for immunotherapy.

17. **Epilepsy, Pediatric Intractable.** Only one randomized controlled trial is available in a small (n = 61) number of patients (n = 4 with Lennox Gastaut syndrome; n = 49 with partial epilepsy; and n = 8 with generalized epilepsy). In this study, there was no statistically significant difference between IVIG and placebo for the primary endpoint (a 50% or greater reduction in seizure frequency). All patients were treated with anti-epileptic drugs (not specified). Additional controlled trials are needed in well-defined populations. The Canadian expert panel of neurologists does not recommend IVIG for pediatric intractable epilepsy. The EFNS recognizes IVIG may have a favorable effect in childhood refractory epilepsy and rated it as a good practice point which indicates the lowest level of evidence. IVIG is considered a last resort effort in the treatment of intractable pediatric epilepsy.

18. **Fibromyalgia Syndrome.** There is insufficient evidence to recommend IVIG. In one open-label single center study, 15 patients with fibromyalgia syndrome and distal demyelinating polyneuropathy received IVIG 400 mg/kg given daily for 5 days. Pain, tenderness, and strength reportedly improved. These patients were not diagnosed with CIPD. Double-blind, placebo-controlled trials are needed to determine if IVIG is effective in fibromyalgia syndrome.

19. **Graft-Versus-Host Disease (GVHD), Acute (Within First 100 days After Hematopoietic Cell Transplantation [HCT]).** IVIG is not recommended unless the patient has severe hypogammaglobulinemia. Current guidelines do not include using IVIG for this indication unless the patient has severe hypogammaglobulinemia defined as IgG < 400 mg/dL. IVIG is
recommended in patients with severe hypogammaglobulinemia after transplantation to prevent bacterial infection. (See HCT above under Other Uses with Supportive Evidence.)

20. Graft-Versus-Host Disease (GVHD), chronic, Prevention in Hematopoietic Cell Transplantation (HCT) Recipient. IVIG is not recommended unless the patient has severe hypogammaglobulinemia. In one randomized trial where IVIG or no IVIG prophylaxis were given from Day 90 to Day 360 post-transplantation, the incidence or mortality of chronic GVHD was not reduced with IVIG. (See HCT above under Other Uses with Supportive Evidence.)

21. Heart Block, Congenital (Prevention). Evidence does not support IVIG use. In a multicenter, prospective, open-label clinical trial IVIG did not prevent the recurrence of congenital heart block (CHB) or reduce maternal antibody titers in 20 mothers with a prior history of a child with CHB. A similarly designed European study found no benefit of IVIG as prophylactic therapy for CHB in high-risk mothers. These studies were designed to study the use IVIG therapy to prevent autoimmune-associated CHB in the fetuses of high-risk pregnant women.

22. Heart Failure, Chronic. There is insufficient evidence to recommend IVIG. In one randomized, placebo-controlled trial, IVIG given monthly for 26 weeks improved left ventricular ejection fraction (LVEF) in patients with chronic heart failure and LVEF < 40%. In another controlled trial in patients with recent onset dilated cardiomyopathy and LVEF < 40%, IVIG, given for 2 consecutive days with no maintenance IVIG, did not improve LVEF more than placebo. Larger trials are needed in well defined populations (cause and severity) to determine if IVIG has a role in the treatment of heart failure.

23. Hematopoietic Cell Transplantation (HCT) in Allogeneic Recipients from Human Leukocyte Antigen (HLA)-Identical Sibling Donors. IVIG is not recommended. In one placebo-controlled trial, prophylactic IVIG had no benefit over placebo for prophylaxis of infection, interstitial pneumonia, GVHD, transplantation-related mortality at 6 months, or survival at 24 months. IVIG is recommended in patients with severe hypogammaglobulinemia after HCT to prevent bacterial infection and acute GVHD. (See HCT to prevent bacterial infections above under Other Uses with Supportive Evidence.)

24. Human Immunodeficiency Virus (HIV) Infection, Adults, for Prophylaxis of Infections. IVIG is not recommended; antiretroviral therapy should be used in certain circumstances after exposure to HIV infection.

25. Immune Globulin M (IgM) Paraproteinemic Demyelinating Neuropathy (or Other Paraproteinemic Demyelinating Neuropathies). The Canadian expert panel of neurologists does not recommend IVIG for IgM paraproteinemic neuropathy because the available evidence is limited to small trials with variable quality and mixed results. In one 4-week, placebo-controlled, crossover trial comparing IVIG to placebo, IVIG produced a modest but statistically significant decrease in overall disability and a significant improvement in many secondary outcome measures (e.g., time to walk 10 meters, grip strength, and sensory symptom scores). However, the short duration of follow-up makes it unclear whether this is clinically significant in a chronic condition. A EFNS/Peripheral Nerve Society guideline recommends IVIG or plasma exchange be considered for initial therapy especially in patients with rapid worsening or clinically similar course to typical CIDP, although any benefit may be only short term. This recommendation was rated as a good practice point which indicates the lowest level of evidence. Long term studies are needed.


27. Infantile Spasms (West Syndrome). There is insufficient evidence to recommend IVIG.
28. **Marburg Variant Multiple Sclerosis (MS).** The Canadian panel of expert neurologists guidelines agreed that other therapies besides IVIG have greater validity. Marburg disease is an acute and often fatal, demyelinating phenotype that is characterized by fulminant demyelination and necrosis. The expert panel said that IVIG may be considered among the treatment options considering the life-threatening nature of this condition. Studies are not available using IVIG for this condition.

29. **Multiple Sclerosis (MS), Primary Progressive.** Evidence does not support IVIG use. Clinical trials are needed. Also see studies for MS, secondary progressive below.

30. **Multiple Sclerosis (MS), Secondary Progressive.** Evidence does not support IVIG use. In one placebo-controlled trial in patients in an advanced stage of secondary progressive MS, IVIG therapy for 27 months had no beneficial effect on the primary outcome measure, time to confirmed Expanded Disability Status Scale (EDSS) progression (hazard ratio [HR]: 1.11; 95% confidence interval [CI]: 0.08, 1.53 for IVIG vs. placebo). The annual relapse rate was 0.46 for both groups. No significant differences between the treatment groups were found in any of the other clinical outcome measures or in the change of T2-lesion load over time. In another placebo-controlled trial, patients with primary progressive (n = 34) or secondary progressive [n = 197] MS were randomized to IVIG once monthly or placebo for 2 years. Mean duration of MS was 14 to 15 years and mean EDSS scores were about 5.5 at baseline. In the intent-to-treat (ITT) population [both groups combined] IVIG delayed progression by 12 weeks compared to placebo and diminished the rate of patients with sustained progression by 15%; this effect was significant in those with primary progressive disease. In all, 51% of patients withdrew from the study. The study was not powered to show differences between the primary and secondary progressive groups and the number of patients with primary progressive disease was too small to draw valid conclusions. EDSS scores were similar with IVIG and placebo. Treatment with IVIG cannot be recommended for patients with secondary or primary progressive MS.

31. **Multiple Sclerosis (MS), Relapsing Remitting for the Prevention of Relapses.** IVIG has been beneficial in controlled trials in preventing relapses in RRMS, but additional studies are needed. In one Phase II, multicenter, double-blind, placebo-controlled trial, 127 patients with RRMS were randomized to therapy with IVIG 0.2 or 0.4 g/kg or to placebo (0.1% albumin) given every 4 weeks for 48 weeks. After 1 year, there was no statistical difference in the percentage of relapse-free patients (IVIG 0.2 g/kg: 57% of patients [n = 25/44]; IVIG 0.4 g/kg: 60% of patients [n = 25/42]; placebo: 68% of patients [n = 28/41]). The P value for the treatment effect was 0.29. The studies of IVIG have usually involved small heterogeneous patient populations, have lacked complete data on clinical and magnetic resonance imaging (MRI) outcomes, or have used methods that have been questioned. In one retrospective analysis of pregnant women with RRMS, patients who received IVIG during pregnancy and postpartum or postpartum only had lower relapse rates than those who were untreated. Randomized, double-blind trials are needed to confirm these findings, to determine the optimal dose, and to compare IVIG with interferon beta products (e.g., Betaseron, Rebif), Copaxone, and other DMTs. Current evidence suggests IVIG is of little benefit in slowing disease progression.

32. **Nephropathy, Membranous.** Evidence does not support IVIG use. IVIG has been used in several types of glomerulonephritis in cases resistant to conventional therapy, but no controlled studies supporting their use exist. IVIG may increase the likelihood of remission when used at an early stage, but it does not appear to have an impact on the long-term prognosis of membranous nephropathy. The dose and length of treatment remain to be defined.

33. **Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) Syndrome.** Evidence does not support IVIG use.
35. Post-Polio Syndrome. There is insufficient evidence to recommend IVIG. Post-polio syndrome is characterized by new muscle weakness, atrophy, fatigue and pain developing several years after the acute polio. In one double-blind trial, 135 patients were randomized to either IVIG or placebo initially and then repeated 3 months later. At 6 months, median muscle strength differed by 8.3% in favor of IVIG (P = 0.029) with 15% being considered clinically significant. Quality of life measured by Short Form-36 (SF-36) questionnaire was not significantly different between therapies. Patients with significant pain (≥ 20 mm on a visual analog scale) at the start of the study had greater improvement with IVIG than with placebo (P = 0.037). This study was not large enough to identify patients who were most likely to derive the greatest benefit. A 2011 Cochrane Review included the above study as well as another randomized, double-blind, placebo-controlled trial in 20 adults with post-polio syndrome. Treatment with IVIG had no beneficial effect on activity limitations and fatigue and inconsistent effects on muscle strength with only one of the two studies finding an improvement in strength and the other not. Additional studies are needed to clarify the role of IVIG in post-polio syndrome.

36. Recurrent Spontaneous Pregnancy Loss (RSPL) [Including Antiphospholipid Antibody-Positive Women]. Evidence does not support IVIG use. In one double-blind pilot study, IVIG did not improve obstetric or neonatal outcomes beyond those achieved with a heparin and low-dose aspirin regimen. In another double-blind trial (n = 82 of whom 47 had an index pregnancy) live birth rates did not differ significantly between IVIG-treated and placebo-treated women (70% vs. 63%; P = 0.76; odds ratio [OR]: 1.37 [95% CI: 0.41, 4.61]). The American Society for Reproductive Medicine practice committee states that several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss and this treatment is not recommended.

37. Selective Immune Globulin A (IgA) Deficiency as the Sole Immunologic Abnormality. Evidence does not support use of IVIG. Selective IgA deficiency is defined as a serum IgA level less than 0.07 g/L, but normal serum IgG and IgM levels in a patient greater than 4 years of age in whom other causes of hypogammaglobulinemia have been excluded. Selective IgA deficiency may coexist in some patients with poor specific IgG antibody production, with or without IgG2 subclass deficiency. Some of these patients with a concomitant specific antibody defect might benefit therapy with IVIG.

38. Systemic Lupus Erythematosus (SLE). There is no role for IVIG as a first-line treatment in patients with SLE. Well-controlled trials are needed to determine which subsets of patients will benefit the most from IVIG. First-line therapy for active SLE is corticosteroids and antimalarial drugs (hydroxychloroquine). Second-line drugs are azathioprine, MTX, or mycophenolate mofetil.

39. Systemic Sclerosis (Scleroderma). Evidence does not support IVIG use. In one small open-label trial, IVIG reduced skin fibrosis in patients with systemic sclerosis. Randomized, double-blind, placebo-controlled trials are needed. In the natural course of the disease, skin atrophy may develop which would affect the measurement of skin involvement. Well-designed, randomized trials are not available to assess how IVIG would affect the other manifestations of systemic sclerosis (blood vessels, visceral organs, joint disease).

40. Thrombocytopenia, Heparin-Induced (HIT). IVIG is not recommended. HIT is a prothrombotic disorder; IVIG could potentially increase the risk of thrombosis and is not recommended. Appropriate management alternatives such as supportive care and judicious use of blood products and plasma exchange (where indicated) are recommended.

41. Thrombotic Thrombocytopenic Purpura (TTP)/Hemolytic Uremic Syndrome (HUS). Evidence does not support IVIG use. A Canadian expert panel of hematologists states that IVIG may be one option among adjunctive therapies when first-line therapy has failed.
42. **Uveitis, Noninfectious.** Evidence does not support use of IVIG. There are no controlled trials using IVIG to treat uveitis. For acute uveitis corticosteroids are used. For chronic uveitis, immunosuppressive therapy (e.g., MTX, cyclosporine, mycophenolate mofetil, azathioprine) is used either to reduce the adverse effects of corticosteroids or to provide better control of ocular inflammation. In case series, IVIG has been effective in treating uveitis in patients who were refractory to corticosteroids and immunosuppressive agents.

43. **Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS).** Evidence does not support IVIG use. Patients should be in a formal research protocol. In one controlled trial, 29 children with new onset or severe exacerbations of obsessive compulsive disorder (OCD) or tic disorder after streptococcal infections were randomized to IVIG, plasma exchange, or placebo. Patients who received either IVIG or plasma exchange improved compared to placebo. However, there are many limitations to this study. Additional studies are needed to determine the role of immunomodulatory therapies and antibiotic prophylaxis in PANDAS. A Phase III placebo-controlled clinical trial is underway to test the efficacy of IVIG in treating OCD symptoms related to PANDAS.

44. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. IVIG has been used in many conditions when multiple other therapies have failed or are not tolerated and for rare conditions. Many case reports and pilot studies have reported its use for various indications and data are preliminary. Well-designed studies are needed to assess safety and efficacy. For conditions that are rare more information is needed to assess IVIG’s place in therapy. Criteria will be updated as new published data are available.

### Approval Duration

*Approval = 1 year (365 days)*

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**APPENDIX A**

ITP can occur in isolation (primary) or in association with other disorders (secondary) [e.g., autoimmune diseases, viral infections such as hepatitis C and HIV, and certain drugs]. An International Working Group (IWG) consensus panel defines primary ITP as a platelet count < 100,000 per mm$^3$ in the absence of other causes or disorders associated with thrombocytopenia. ITP is also defined by time from diagnosis: newly diagnosed (diagnosis to 3 months), persistent (3 months to 12 months from diagnosis), or chronic {lasting for more than 12 months}. These definitions may not apply to patients with secondary forms of ITP.

In adults with ITP/IT who are acutely bleeding, American Society of Hematology (ASH) guidelines indicate that if the platelet count is < 30,000/mm$^3$ initial therapy is systemic corticosteroids. Longer courses of steroids over shorter courses of steroids or IVIG are preferred as first-line treatment in adults because they are associated with a longer time-to-loss of response. IVIG may be used with
corticosteroids when a more rapid increase in platelet count is required. IVIG may be added to corticosteroid therapy if thrombocytopenia persists or worsens after about 3 days of corticosteroid therapy.\textsuperscript{32,40} If there is an urgent need to increase the platelet count quickly, IVIG can be started with a corticosteroid.\textsuperscript{16}

Adults who are at risk for intracerebral bleeding will be hospitalized and treated with a high-dose corticosteroid, IVIG, and platelet transfusions or other modalities.\textsuperscript{40}

Systemic glucocorticoids have been the standard initial therapy for adults with moderate to severe thrombocytopenia and symptomatic purpura.\textsuperscript{40-41,43} Evidence for use of glucocorticoids is based on case series and on a small randomized trial that compared glucocorticoid therapy to IVIG and both in combination as initial treatment. According to the ASH guideline, there is limited evidence for basing treatment recommendations on a specific platelet count or age for all patients. Observational data of patients with ITP have suggested that bleeding risk is increased with platelet counts < 20,000 or < 30,000 per mm\textsuperscript{3}, but it is unclear whether offering treatment to all patients with ITP at these levels will result in decreased bleeding. In patients with recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids or with IVIG or Rh\textsubscript{D} immune globulin, there is no evidence to guide a sequence of treatments.

Splenectomy remains the only treatment that provides sustained remission off all treatments at 1 year and beyond.\textsuperscript{40} ASH recommends splenectomy for patients who have failed corticosteroids. Patients who do not achieve spontaneous remission or do not maintain a complete response following cessation of therapy are classified as having persistent (3 to 12 months from diagnosis) or chronic (lasting > 12 months) ITP. Patients who have failed splenectomy or relapsed thereafter and have severe ITP or have a risk of bleeding that requires therapy are classified as having refractory ITP. ASH does not recommend therapy in patients with platelet counts > 30,000 per mm\textsuperscript{3} in the absence of bleeding after splenectomy.

ITP is usually chronic in adults. There is no clear age at which children should be treated in a manner more like adults.\textsuperscript{40} Although data suggest that adolescents are more likely than younger children to develop persistent or chronic disease, there have been no studies investigating a benefit to altered treatment in this age group or the age at which point this effect is likely to be most present. Therefore the management of adolescents should follow the usual management for children. Children with no or mild bleeding are managed with observation alone regardless of platelet count.

In children and adolescents ≤ 17 years of age, use of IVIG is based on risk of bleeding and not on platelet counts. Most children do not require therapy with IVIG.\textsuperscript{39,42} In emergency situations, platelet transfusions given with IV corticosteroids and IVIG should be given for intracranial hemorrhaging or other life-threatening or serious bleeding.\textsuperscript{32}

Studies in children with ITP suggest the majority of children experience no bleeding or mild bleeding regardless of whether or not they initially receive drug therapy.\textsuperscript{40} ASH notes the decision to manage with observation requires a detailed discussion between the healthcare provider, patient and family. Treatment may be appropriate if follow-up cannot be assured, if there are other societal concerns (e.g., travel, distance from hospital), if there are concerns attributed to activity level or risk of bleeding, or there is a need for upcoming procedures associated with a risk of bleeding. For pediatric patients requiring treatment, a single dose of IVIG or a short course of corticosteroids are recommended as first-line treatment (long-term use of corticosteroids should be avoided). IVIG can be used if a more rapid rise in platelet count is desired.\textsuperscript{40,42}

ASH recommends pregnant patients requiring treatment for ITP receive either a corticosteroid or IVIG.\textsuperscript{40} Newborns of mothers with ITP are hospitalized.

In pregnant women, corticosteroids and IVIG are considered safe with regard to teratogenicity but may have maternal side effects including exacerbation of gestational diabetes and postpartum psychiatric
The ASH guideline recommends IVIG or corticosteroids in pregnant patients requiring treatment with no recommendations for specific platelet counts at which patients should be treated. During labor and delivery, ITP management is based on assessment of maternal bleeding risks associated with delivery and epidural anesthesia, and the minimum platelet counts required to undergo these procedures.