**Medication Policy Manual**

**Topic:** Immune Globulin Replacement Therapy, (IVIG, SCIG):
- Bivigam®
- Flebogamma® DIF
- Gammagard S/D®
- Gamunex-C®
- Hyqvia®
- Privigen®
- Carimune® NF
- Gammagard®
- Gammaplex®
- Hizentra™
- Octagam®

**Date of Origin:** January 1996

**Committee Approval Date:** November 13, 2014

**Next Review Date:** March 2015

**Effective Date:** March 1, 2015

**IMPORTANT REMINDER**
This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**
Intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG; Hizentra® or Hyqvia®) are preparations containing antibodies purified from human blood. They are used in the treatment of many different conditions resulting from immune deficiencies or other immunologic conditions.
Policy/Criteria

I. Most contracts require prior authorization approval of immune globulins prior to coverage. Immune globulins may be considered medically necessary when at least one of criteria A through E below is met AND criterion F below is met.

A. **Immunodeficiency (primary or acquired),** as defined in criteria 1 or 2:
   1. A diagnosis of one of the following and documented hypogammaglobulinemia (a low baseline serum IgG level):
      a. Primary humoral immunodeficiency diseases (PID) (as defined in Appendix I)
      b. HIV infected children (< 13 years of age) with hypogammaglobulinemia
      c. Hematologic malignancy-related hypogammaglobulinemia
         i. Post-allogeneic bone marrow transplant (BMT)
         ii. B-cell medicated cancer [e.g., chronic lymphocytic leukemia (CLL), B-cell lymphoma]
      d. Hypogammaglobulinemic neonates, with a low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity.
   OR
   2. Multiple myeloma in patients with stable disease and high risk of recurrent infections despite prophylactic antibiotic therapy, patients with poor IgG response to the pneumococcal vaccine, or have low normal IgG levels during acute sepsis episodes.

B. **Hematologic disorders (immune-mediated),** not responding to alternative therapies, or at high risk of bleeding.
   1. Acquired Factor VIII inhibitor, when conventional therapy is ineffective or not tolerated. (e.g., immunosuppressive therapy with cyclophosphamide, steroids, or azathioprine).
   OR
   2. Autoimmune hemolytic anemia (AIHA) not responding to alternative therapies (e.g., steroids, immunosuppressive agents, plasmapheresis, rituximab and/or splenectomy).
   OR
   3. Fetal (neonatal) alloimmune thrombocytopenia (FAIT) with documented diagnosis
   OR
   4. Idiopathic thrombocytopenia purpura (acute; ITP), when a rapid increase in platelet count is necessary, such as in an acute bleeding episode or prior to surgery.
   OR
5. ITP (chronic), when the platelet count is dangerously low, defined as a platelet count less than 30,000 cells/mm³ in children, less than 20,000 cells/mm³ in adults, or less than 30,000 cells/mm³ along with signs/symptoms of bleeding in adults.

OR

6. ITP in pregnancy, when at least one of the following criteria are met:
   a. Platelet counts less than 10,000/mm³ in the third trimester, despite an adequate course of corticosteroids, unless use of steroids are contraindicated, or not tolerated.
   b. Platelet counts less than 30,000/mm³ associated with bleeding before vaginal delivery or C-section;

OR

7. Post-transfusion purpura (hemolytic transfusion reaction) in severely affected patients.

OR

8. Pure red cell aplasia (PRCA, viral) with documented parvovirus B19 infection and severe anemia.

C. Neuromuscular disorders, when significant functional impairment is present:

1. Acute inflammatory demyelinating polyneuropathy, including Guillain-Barré syndrome (GBS), when one of criteria a through d below are met:
   a. Deteriorating pulmonary function tests.
      OR
   b. Rapid deterioration with symptoms for less than 2 weeks.
      OR
   c. Rapidly deteriorating ability to ambulate.
      OR
   d. Inability to walk independently for 10 meters.

OR

2. Chronic inflammatory demyelinating polyneuropathy (CIDP) when all of criteria a, b, and c below are met:
      AND
   b. Documentation of slowing of nerve conduction velocity on EMG/NCS.
      AND
   c. Documentation of elevated spinal fluid protein on lumbar puncture OR a nerve biopsy confirming the diagnosis.

OR

3. Dermatomyositis, with documented EMG abnormalities and/or increased CPK levels, with associated severe disability when steroid therapy is ineffective or not tolerated.
OR
4. Lambert-Eaton myasthenic syndrome (LEMS) when other treatment options are ineffective or not tolerated. (e.g., pyridostigmine bromide, azathioprine, and/or prednisone).

OR

OR
6. Myasthenia gravis for the treatment of acute crisis (e.g., respiratory failure, swallowing difficulties) OR chronic decompensation, when other treatments are ineffective or not tolerated (e.g., plasmapheresis, pyridostigmine, azathioprine, cyclosporine, and cyclophosphamide).

OR
7. Paraneoplastic opsoclonus ataxia syndrome (Opsoclonus-myoclonus ataxia syndrome, OMS) in pediatric neuroblastoma patients with significant functional impairment and not responding to an adequate course of steroids (at least 3 to 7 days).

OR
8. Pemphigoid, refractory immunobullous disease (e.g., bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris) until conventional treatment takes effect (e.g., immunosuppressive agents and plasmapheresis).

OR
9. Polymyositis in patients with severe active illness when other treatments have been ineffective or not tolerated (e.g., corticosteroids, azathioprine, methotrexate, or cyclophosphamide).

OR
10. Stiff-Person Syndrome when treatment with other agents is ineffective or not tolerated. (e.g., diazepam, baclofen, clonazepam, valproic acid, and clonidine).

OR
11. Systemic lupus erythematosus, for severe active disease when other interventions are ineffective or not tolerated (e.g., corticosteroids and immunosuppressive agents, such as cyclophosphamide or azathioprine).

D. Transplant (solid organ), antibody-mediated rejection:

1. Prevention of antibody (Ab)-mediated rejection: Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ.

OR
2. Treatment of antibody-mediated rejection (a.k.a. vascular rejection, humoral rejection): following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs), if used in combination with plasmapheresis.

E. Other Miscellaneous conditions, when criteria are met

1. Kawasaki syndrome, during the first ten days of diagnosis.

OR

2. Pediatric intractable epilepsy in candidates for surgical resection or when other interventions are ineffective or not tolerated. Examples of other interventions include, but are not limited to, anticonvulsant medications, ketogenic diets, and steroids. [85]

AND

For Washington, Oregon, and Idaho commercial, fully insured members only

F. Immune globulin replacement therapy is administered in a non-hospital outpatient based setting (e.g. provider’s office, infusion center, or home infusion), unless both of the following criteria 1 and 2 below are met:

1. All non-hospital outpatient based settings are greater than 10 miles further from the member’s home than the hospital outpatient setting.

AND

2. The member’s home is not eligible for home infusion services (e.g. home is not within the service area or is deemed unsuitable for care by the home infusion provider).

II. Administration, Quantity Limitations, and Authorization Period

A. RegenceRx does not consider immune globulins to be self-administered medications.

B. When prior authorization is approved, immune globulins may be authorized in quantities as follows:

1. Initial Authorization: Immune globulins may be authorized for the period defined in Table 1, based on diagnosis.

2. Continued Authorization: If the diagnosis is eligible for re-authorization (as listed in Table 1), the maximum number of infusions that may be authorized per year are based on the diagnosis being treated.

C. Authorization shall be reviewed as follows to confirm that current medical necessity criteria are met and that the medication is effective.
1. Initial authorization shall be reviewed at the end of the initial authorization period (as defined in Table 1).

2. Continued authorization (after the initial period) shall be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided (such as decrease in infections or improvement of functional impairment from baseline). In addition, for patients with immunodeficiency (on replacement therapy) documentation of a current low/normal IgG trough level must be provided at least annually.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Frequency/Duration</th>
<th>Reauthorization Criteria/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Replacement Therapy - Immunodeficiency</strong> [with documented hypogammaglobulinemia (low IgG levels) or poor immune response (dysgammaglobulinemia)]</td>
<td></td>
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<tr>
<td>Primary humoral immunodeficiency disease (PID)</td>
<td>One dose per month x 12 months</td>
<td>Documented current IgG levels that are in the low to normal range and evidence of clinical improvement, such as decreased occurrence of infections; x 12 months</td>
</tr>
<tr>
<td>Hematologic malignancy-related hypogammaglobulinemia (e.g., CLL, post-BMT)</td>
<td>One dose per month x 12 months</td>
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<tr>
<td>HIV+ children with hypogammaglobulinemia</td>
<td>One dose per month x 12 months</td>
<td></td>
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<tr>
<td>Hypogammaglobulinemic neonates</td>
<td>One dose per month x 6 months</td>
<td></td>
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<tr>
<td><strong>Hematologic disorders (immune-mediated)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired Factor VIII Inhibitor</td>
<td>One dose per month x 6 months</td>
<td>Documented initial response and continued presence of Factor VIII inhibitor; x 12 months</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia, (AIHA)</td>
<td>One dose per month x 6 months</td>
<td>Documented initial response and recurrence of clinically significant, symptomatic anemia; x 12 months</td>
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<tr>
<td>Fetal (neonatal) alloimmune thrombocytopenia (FAIT)</td>
<td>One dose per week until the estimated date of delivery.</td>
<td>No reauthorization</td>
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<tr>
<td>ITP (acute)</td>
<td>Up to four doses (authorization is for up to a 6 month window).</td>
<td>May re-authorize under Chronic ITP; however, use of IVIG chronically is generally discouraged, given the short duration of action. On a chronic basis, IVIG may be indicated for intermittent use in patients with episodes of acutely low platelets.</td>
</tr>
<tr>
<td>ITP (chronic)</td>
<td>One dose per month x 6 months. IVIG treatment only covered until conventional therapy takes effect.</td>
<td>Authorization x 6 months. Documented initial response to IVIG and: -Continued thrombocytopenia, defined as a platelet count of &lt; 20,000 OR less than 30,000 cells/m³ and clinically significant bleeding. OR -Patient is scheduled for an invasive procedure with high risk of bleeding.</td>
</tr>
<tr>
<td>ITP in pregnancy</td>
<td>One dose per month until the estimated date of delivery.</td>
<td>May re-authorize under Chronic ITP</td>
</tr>
<tr>
<td>Post-transfusion purpura (hemolytic transfusion reaction)</td>
<td>Up to two doses in 2 weeks (authorization is for up to a 2 week window)</td>
<td>No reauthorization</td>
</tr>
<tr>
<td>Pure red cell aplasia (PRCA), viral</td>
<td>One dose per month x 6 months</td>
<td>Documentation of initial response, parvovirus, and recurrence of significant anemia; x 12 months</td>
</tr>
<tr>
<td>Indication</td>
<td>Frequency/Duration</td>
<td>Reauthorization Criteria/Duration</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td><strong>Neuroimmunologic disorders</strong></td>
<td></td>
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<tr>
<td>Acute inflammatory demyelinating polyneuropathy (including GBS)</td>
<td>One dose per month x 3 months</td>
<td>May re-authorize under Chronic IDP</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>One dose per month x 6 months</td>
<td>Documented functional improvement; x 12 months</td>
</tr>
<tr>
<td>Dermatomyositis, refractory</td>
<td>One dose per month x 3 months.</td>
<td>Documented improvement in muscle strength and/or decreased CPK levels; x 6 months</td>
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<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>One dose per month x 6 months</td>
<td>Documented improvement in muscle function/strength; x 12 months</td>
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<tr>
<td>Multifocal motor neuropathy (MMN)</td>
<td>One dose per month x 6 months</td>
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<tr>
<td>Myasthenia gravis (acute and chronic)</td>
<td>One dose per month x 6 months</td>
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</tr>
<tr>
<td>Paraneoplastic opsoclonus ataxia syndrome</td>
<td>One dose (authorization is for up to a 2 week window)</td>
<td>Documented functional improvement; x 6 months</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>One dose per month x 3 months</td>
<td>Documented improvement in muscle strength and/or decreased CPK levels; x 6 months</td>
</tr>
<tr>
<td>Pemphigoid, refractory</td>
<td>One dose per month x 6 months, until conventional therapy takes effect.</td>
<td>No reauthorization</td>
</tr>
<tr>
<td>Stiff-Person syndrome</td>
<td>One dose per month x 3 months</td>
<td>Documented functional improvement; x 6 months</td>
</tr>
<tr>
<td>Systematic lupus erythematosus</td>
<td>One dose per month x 6 months</td>
<td>Documented improvement in muscle strength and/or decreased CPK levels; x 6 months</td>
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<tr>
<td><strong>Transplant (solid organ)</strong></td>
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<tr>
<td>Prevention of acute rejection (pre- and peri-operative)</td>
<td>Up to 4 doses pre-transplant, then 1 dose weekly for 4 weeks post-transplant. (not to exceed 8 doses total; authorization is for up to a 3 month window)</td>
<td>Further authorization may be considered under “Treatment of Ab-mediated rejection”</td>
</tr>
<tr>
<td>Treatment of antibody (Ab)-mediated (humoral) rejection</td>
<td>One dose, once per rejection episode (authorization is for up to a 2 week window)</td>
<td>Documented improvement from previous course and confirmation of another episode of rejection; one dose.</td>
</tr>
<tr>
<td><strong>Other Miscellaneous disorders</strong></td>
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<tr>
<td>Kawasaki syndrome</td>
<td>Up to two doses given within 10 days of symptom onset (authorization is up to a 2 week window)</td>
<td>No reauthorization</td>
</tr>
<tr>
<td>Pediatric intractable epilepsy</td>
<td>One dose per month x 6 months.</td>
<td>Documented of significantly reduced frequency and/or duration of seizures; x 6 months</td>
</tr>
</tbody>
</table>
III. Subcutaneous administration of immune globulin (SCIG) is considered an alternative to intravenous administration of immune globulin and may be considered medically necessary when one of the criteria in Section I is met.

IV. **For Washington, Oregon, and Idaho commercial, fully insured members only**

Immune globulin replacement therapy is considered not medically necessary when administered in a hospital outpatient setting, except when the only non-hospital outpatient based setting is greater than 10 miles further from the member’s home than the hospital outpatient setting OR the member’s home is not eligible for home infusion services.

V. IVIG/SCIG is considered investigational when used for all other conditions, including, but not limited to:

1. Acute disseminated encephalomyelitis (ADEM)
2. Acute lymphocytic leukemia
3. Acute renal failure
4. Adrenoleukodystrophy
5. Adult HIV infection
6. Alzheimer's disease
7. Aplastic anemia
8. Asthma
9. Atopic dermatitis
10. Autism
11. Behçet's syndrome (Behçet’s disease)
12. Cardiomyopathy, recent-onset dilated
13. Chronic fatigue syndrome
14. Clostridium difficile, recurrent
15. Cystic fibrosis
16. Diabetes
17. Diamond-Blackfan anemia
18. Endotoxemia
19. Heart block, congenital
20. Hemolytic anemia (other than autoimmune)
21. Hemophagocytic syndrome
22. Human T-lymphocyte virus-1 myelopathy
23. Hyper IgE syndrome
24. Immune mediated neutropenia
25. Inclusion body myositis
26. Infectious disease in high risk neonates and adults following surgery or trauma
27. Lumbosacral plexopathy
28. Multiple sclerosis
29. Narcolepsy/cataplexy
30. Neonatal hemochromatosis
31. Neonatal hemolytic disease
32. Nephropathy, membranous
33. Nephrotic syndrome
34. Ophthalmopathy, euthyroid
35. Paraproteinemic neuropathy
36. Post-polio syndrome
37. Recurrent spontaneous abortion
38. Rheumatoid arthritis
39. Systemic Sclerosis, diffuse cutaneous (dcSS)
40. Stevens-Johnson Syndrome
41. Still's Disease (Systemic Juvenile Immune Arthritis, SJIA)
42. Surgery or trauma
43. Thrombocytopenia, nonimmune
44. Thrombotic Thrombocytopenic Purpura, including Hemolytic Uremic Syndrome (TTP/HUS), neonatal autoimmune and transfusion refractory.
45. Tic disorder (Based on DSM Criteria)
46. Toxic epidermal necrolysis (TEN)
47. Urticaria, delayed pressure
48. Uveitis
49. Vasculitic syndromes, systemic
50. Von Willebrand’s syndromeWegener's granulomatosis

Position Statement

Summary

Intravenous immune globulin (IVIG)

- All IVIG preparations are generally considered therapeutically interchangeable. [32-34]
- Minor immunoglobulin A (IgA) and immunoglobulin G (IgG) subclass differences exist. [32-34]
- IVIG preparations with low IgA content are used to minimize reactions in patients with hypogammaglobulinemia and concurrent IgA deficiency or when anti-IgA antibodies are present in a recipient. [32-34]
- Differences in formulation may guide product selection (e.g., pre-mixed liquid vs. lyophilized powder, 5% vs. 10%, low sucrose, low osmolarity).

Subcutaneous immune globulin (SCIG)

- Hizentra® is an immune globulin product for subcutaneous use, approved for patients with primary immune deficiency (PID). [81] It is available as a 20% solution for weekly subcutaneous infusion.
Hyqvia® is also an immune globulin product for subcutaneous use, approved for patients with PID, and is available as a 10 % solution for every three to four week subcutaneous infusion. \cite{105} Gammaked®, Gamunex-C®, and Gammagard liquid® are approved for both intravenous and subcutaneous use for treatment of PID. \cite{89-91} All three are available as a 10 % solution.

SCIG has a lower bioavailability than IVIG, so must be given in higher doses to achieve the same serum IgG concentrations.

However, subcutaneous delivery may result in higher steady-state IgG levels due to less variation in IgG levels.

Multiple injection sites (three to four) are necessary for weekly infusion (Hizentra, Gammaked, Gamunex-C, Gammagard) for an average patient because of the volume that must be infused, whereas Hyqvia may be infused monthly.

Hyqvia 10% is formulated with hyaluronidase, to allow for larger volume infusion at a single injection site. Up to 600 mL (60 grams) may be given per injection site (for patients > 40 kg) at an infusion rate up to 300 mL/hour. The recommended maximum dose per injection site for Hizentra 20% is 25 mL (5 grams), given over a maximum of 25 mL/hour.

None of these products have been approved for SC administration for any other indications, other than PID. Because other diagnoses usually require larger doses (based on grams per kilogram) with a high volume per dose, subcutaneous administration is generally not feasible.

Injection site swelling, redness, and itching were reported in the majority of patients.

**Dosing Considerations and Therapeutic Levels for Replacement Therapy for Treatment of Immunodeficiency with Hypogammaglobulinemia**

- A plasma IgG level of 200 mg/dL is often a common minimum target for patients being considered for IVIG replacement therapy. \cite{4}

- In patients with mild to moderate IgG deficiency with levels of 300 mg/dL-400mg/dL, the decisions to treat are based on clinical symptoms and antigenic challenge. \cite{31}

- Dosing adjustment in replacement therapy is based on clinical response and IgG levels. \cite{4}
  * The trough or steady state IgG level is obtained before scheduled infusions and frequently guides IVIG dose selection.
  * The minimum serum concentration of IgG necessary for protection has not been firmly established. However, maintenance of serum trough IgG levels above 500 mg/dL has been considered a sufficient target to prevent most systemic infections. \cite{4, 31} Some patients may require an IgG level of 400-500 mg/dL above their baseline value for protection.
  * In patients with severe hypogammaglobulinemia, IgG levels (trough) should be checked every three to six months in growing children and every six to twelve months in adults. \cite{56}

- Dosing of IVIG for conditions other than hypogammaglobulinemia do NOT require monitoring of IgG levels. Efficacy in conditions other than hypogammaglobulinemia is based on clinical response, including improvement or resolution of disease symptoms.
**Clinical Efficacy**

**IMMUNODEFICIENCY (Primary or Secondary) - Replacement Therapy for Hypogammaglobulinemia** [1, 4-5, 27, 34, 43]

**Primary humoral immunodeficiency diseases**

* All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID). [94]
* X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life.
* Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) is characterized by low to normal IgG levels and inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax). Most patients experience severe recurrent and/or chronic infections.
* Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, are rare, inherited syndromes.
* Immunoglobulin reference ranges vary depending on the age of the patient and the particular assay method used. The usual immune globulin maintenance dose is 100-800mg/kg/month and therapy is usually life-long.
* Serum trough levels should be maintained at 400 – 600 mg/dl. Documentation of the rationale should be provided in the event that a trough level greater than 600 mg/dl is required. [72]
* Hypogammaglobulinemic neonates
  - Treatment with IVIG is usually reserved for patients with recurrent severe infections, not responding to antibiotic prophylaxis.
  - The usual IVIG dose is 400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration. [67]

**Acquired Deficiencies:**

- Hematologic malignancy-related hypogammaglobulinemia (including B-cell cancers, multiple myeloma, and post-bone marrow transplant (BMT))
  * Use of immune globulin replacement in hypogammaglobulinemic patients with B-cell cancers (including CLL), multiple myeloma and post-allogeneic bone marrow transplant (BMT) is supported by guidelines. [83, 100]
  * IVIG therapy reduces the incidence of bacterial infections in patients with hematologic malignancies to approximately 50% of the incidence without IVIG administration. [4, 34]
  * Previously, use of IVIG prophylaxis post-BMT was common for prevention of graft versus host disease (GVHD); however, with improved immunosuppressant regimens, the use of routine IVIG prophylaxis is no longer supported. [100]
  * Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.
HIV-infected children < 13 years of age [92]
* Current guidelines recommend IVIG use among HIV-infected children who have hypogammaglobulinemia (IgG <400 mg/dL), to prevent serious bacterial infections (SBIs).
* IVIG is no longer recommended for primary prevention of SBIs in children, unless hypogammaglobulinemia is present. During the pre-HAART (highly-active antiretroviral therapy) era, IVIG was shown to decrease the frequency of bacterial infections and hospitalization in children with AIDS, however only in those not receiving daily Pneumocystis carinii pneumoniae (PCP) prophylaxis.

AUTOIMMUNE (IMMUNE-MEDIATED) DISORDERS
- Pooled immune globulin (IVIG) has been studied and found to be useful in a variety of autoimmune disorders, including hematologic, neuromuscular and infectious disease-related diseases. However, given the rarity of many of these disorders, the evidence for safety and efficacy in some diagnoses is insufficient at this time.
- The mechanism of action of IVIG in autoimmune disorders is thought to include acute neutralization of circulating autoantibodies, toxins, and cytokine modulation, as well as long-term reduction of antibody production and suppression of T-cell cytokines. [1]

Hematologic (immune-mediated) Disorders: [83]

Acquired Factor VIII inhibitor [21-25]
- A sufficient treatment course is usually 6-12 weeks before attempting a different immunosuppressive agent. Patients are generally treated until remission (elimination of the inhibitor) occurs, which may take several months.
- Treatment regimens of 1 gm/kg for 2 days or 400 mg/kg for 5 days have been studied. In one study, only 6 of 19 patients responded to IVIG within 40 days of treatment. [60]

Fetal (neonatal) alloimmune thrombocytopenia (FAIT): [58, 83]
- ACOG guidelines recommend IVIG as first line treatment for documented fetal thrombocytopenia. [58]
- A trial comparing IVIG treatment with and without dexamethasone in siblings showed that: [2]
  -- IVIG treatment was associated with an increase in mean platelet count of 69,000/mm³.
  -- There were no instances of intracranial hemorrhages, although hemorrhage had occurred previously in 10 untreated siblings.
- The recommended dose of IVIG is 1 gm/kg/week, increasing to 2 gm/kg/week in refractory cases. [59]

Idiopathic thrombocytopenia purpura (ITP) [5, 83, 84]
- Normal platelet count range is 115,000/mm³ to 440,000/mm³.
- **Acute ITP**
  * In various studies, 64% to 100% of IVIG recipients attained platelet counts greater than 100,000 cells/mm³ within 7 days. [4, 34]
  * A maximum of 1 gm/kg/day for three or four doses of IVIG on alternate days is recommended. Acute ITP is usually seen in children and typically resolves spontaneously within 2 months.

- **Chronic ITP** [4, 8-10]
  * Current evidence does not support that IVIG alters the natural course of chronic ITP, affects long-term morbidity/mortality, or increases the rate of long-term remission.
  * IVIG is not indicated for the maintenance of platelet counts in chronic ITP; however, IVIG may be used episodically in patients with chronic ITP, for acutely low platelet levels.
  * Steroids and/or splenectomy are considered the first-line treatment of choice for chronic ITP. Although the use of IVIG may be considered as a steroid-sparing adjunctive therapy for chronic ITP, [5,83,84] other therapies with a more durable response should be considered, such as splenectomy, rituximab (Rituxan), eltrombopag (Promacta) or romiplostim (Nplate). [5,84]
  * IVIG may be considered in patients with dangerously low platelet counts (less than 10,000 to 20,000 per mm³ in adults or less than 30,000 per mm³ in children) or patients undergoing an invasive procedure, and therefore may be at an increased risk for significant bleeding, such as intracranial hemorrhage.
  * The usual dose of IVIG is 1 to 2 gm/kg divided into equal amounts and given over 2 to 5 days.

- **ITP in pregnancy** [44,83,84]
  * The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia. [44]
  * Platelet function is typically normal so it is not necessary to maintain platelet count in the normal range.
  * The first line of treatment is prednisone, usual dose 1-2mg/kg/day.
  * IVIG is useful in cases that are resistant to steroids and when a rapid rise in platelets is necessary. A response typically occurs within 6 – 72 hours of IVIG treatment.

**Post-transfusion purpura** (hemolytic transfusion reaction)
- Post-transfusion purpura is a rare condition that can occur in patients undergoing blood transfusions. It typically develops approximately one-week after blood transfusion.
- IVIG may be considered first-line therapy in severely affected patients. [1, 83]
- The recommended dose of IVIG is 500 mg/kg/day for two consecutive days. Rapid platelet recovery has been seen within days of treatment.
Pure Red Cell Aplasia (PRCA), Viral [83]
- Parovirus B19 infects and lyses red cell precursors, which can cause pure red cell aplasia. IVIG therapy is usually reserved for patients with chronic parovirus infection and chronic anemia.
- Chronic parovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parovirus and anemia may spontaneously resolve.
- The usual dose of IVIG is 2-4 grams/kg, divided as 400 mg/kg/day for 5 – 10 days, 1 gm/kg/day for 3 days or 0.5 gm/kg weekly for 4 weeks. Initial treatment courses may be indicated with recurrence of anemia and increase in parovirus B19 DNA. [71,83]

Neuromuscular Disorders:
Inflammatory demyelinating polyneuropathy (IDP) [85, 86, 96]
- Acute IDP, including Guillain-Barré syndrome (GBS) [57,97]
  * IVIG appears to be effective in adult patients with Guillain-Barré syndrome when given within 2 weeks of symptom onset.
  * The recommended IVIG dose is 400 mg/kg/day for 5 days. If relapse occurs within 1-2 weeks of initial therapy, an additional treatment course of IVIG may be effective. Further treatment does not improve outcomes and is not recommended.
- Chronic IDP (CIDP)
  * Treatment options include plasmapheresis, IVIG, and corticosteroids.
  * The usual IVIG dose is 400 mg/kg/day for 5 days, repeated every 6 weeks.

Dermatomyositis (DM)
- High-dose IVIG is a safe and effective treatment for refractory dermatomyositis unresponsive to corticosteroid therapy. [5,7,27,33,36, 85,86,95]
- The recommended IVIG dose is 2 gm/kg per month.

Lambert-Eaton myasthenic syndrome (LEMS) [39, 85-87]
- LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes.
- Patients reported improved limb, respiratory muscle, and bulbar muscle strength with IVIG, compared to placebo in a small randomized crossover trial (n = 9). [73]
- The recommended dose of IVIG is 2 gm/kg administered over 2 – 5 days.

Multifocal motor neuropathy (MMN) [75-79, 85, 86]
- Small controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety. [6,26]
- The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.
- Conduction block is the hallmark of this disease. Additionally, patients with anti-GM1 antibodies show an increased chance of response to IVIG. However, anti-GM antibodies are present in only 30-80% of patients with MMN and are not specific to MMN. In addition, patients who lack anti-GM1 antibodies may have a favorable response to IVIG; therefore the clinical utility of monitoring anti-GM1 antibodies is uncertain. [75]
Myasthenia gravis (MG)\textsuperscript{[85,86]}
- Randomized trials examining short-term treatment of myasthenia gravis with IVIG have shown no difference between IVIG and plasma exchange or IVIG and methylprednisolone\textsuperscript{[69]}
- IVIG may be useful in treating patients with severe myasthenia gravis who fail to respond to the maximum tolerated doses of corticosteroids and/or immunosuppressants.\textsuperscript{[70]}
- There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.\textsuperscript{[69]}
- The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2 – 5 days.\textsuperscript{[69]}

Paraneoplastic opsoclonus ataxia syndrome (Opsoclonus-myoclonus)\textsuperscript{[85,101]}
- Opsoclonus-myoclonus is a rare neurological syndrome characterized by an unsteady gait, brief shock-like muscle spasms, and irregular rapid eye movements and can be a paraneoplastic (e.g., with neuroblastoma) or non-paraneoplastic syndrome.
- IVIG is a therapeutic option for pediatric neuroblastoma patients with paraneoplastic opsoclonus ataxia syndrome, along with other immunologic treatments, including glucocorticoids, cyclophosphamide, mycophenolate and plasma exchange.\textsuperscript{[85,101]}
- Evidence supporting the use of IVIG in this condition consists of retrospective chart reviews and case reports. However, a randomized phase II trial is currently investigating the use of IVIG in treating children with opsoclonus-myoclonus associated with neuroblastomas.\textsuperscript{[73,74,102]}

Refractory pemphigoid bullous (e.g., pemphigus foliaceus, pemphigus vulgaris)\textsuperscript{[27,38,88]}
- IVIG is typically given in combination with conventional treatments, such as immunosuppressive agents and plasmapheresis, and is discontinued once conventional treatment (such as corticosteroids, azathioprine, cyclophosphamide, etc.) takes effect. IVIG is not considered a maintenance therapy for pemphigus foliaceus, pemphigus vulgaris or other autoimmune mucocutaneous blistering diseases.
- The usual dose of IVIG is 1-2 gm/kg administered over 3 days. This regimen may be repeated every 3-4 weeks.

Polymyositis\textsuperscript{[85,86,95]}
- Polymyositis is an inflammatory myopathy with no unique clinical features. It is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness. Traditional therapies include immunosuppressive medications or steroids.
- IVIG may be considered for patients not responding to first-line immunosuppression.
- The recommended dose of IVIG is 2 gm/kg/month administered over 2 – 5 days.

Stiff Person Syndrome\textsuperscript{[37,85]}
- Sixteen patients were randomized to IVIG or placebo for 3 months, and then crossed over to the alternate treatment after a 1 month washout period. IVIG patients demonstrated decreased stiffness scores, decreased frequency of falls, ability to walk more easily without assistance, and improved ability to perform work-related tasks. Benefits lasted 6 weeks to 1 year without additional treatment.
- The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.
Systemic Lupus Erythematosus
- Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide.
- The usual dose of IVIG is 400 mg/kg/day for 5 days.

Transplant (Solid Organ) –

Antibody-mediated rejection\^[27, 98]\]
- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
- Pre-treatment with IVIG (desensitization) may reduce the risk of AMR in highly sensitized renal transplant patients.\^[27,98]\]
- A randomized, double-blind trial comparing IVIG to placebo in 101 highly sensitized renal transplant candidates concluded that IVIG is better than placebo in improving transplantation rates.\^[68]\]
- Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIG, pheresis or a combination of modalities.
- A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant.\^[27,98]\]

Other Miscellaneous Disorders:

Kawasaki syndrome
- IVIG in conjunction with aspirin given within the first 10 days of illness can reduce the incidence of coronary artery abnormalities by 65% - 78%, compared with treatment with aspirin alone.\^[4, 34-35,99]\ IVIG is not effective if more than ten days have elapsed from onset of symptoms.
- The usual dose of IVIG is 2 gm/kg as a single dose, but may be repeated if the patient fails to defervesce.\^[99]\]

INVESTIGATIONAL CONDITIONS\^[1, 5, 13-15, 17-20, 27, 46-52]\]
- The University Hospital Consortium (UHC), an alliance of 68 academic health centers, performed a critical assessment of off-label IVIG uses.
- The UHC determined published data to be inadequate to support the use of IVIG in various conditions.\^[1]\]
- Asthma: Further trials in asthma patients are necessary to delineate patient subsets that would best benefit from IVIG therapy, and define optimal dosing in this condition.\^[17-20]\]
- HIV (adults): The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes.\^[3]\]
- **Multiple sclerosis, progressive:** There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis. [28-30, 64]

- **Multiple sclerosis; relapsing-remitting type:** IVIG may provide some benefit in reducing the acute exacerbation rate in relapsing-remitting multiple sclerosis. [5, 27, 54]
  * Trials are generally limited to small numbers of patients and have lacked complete data on clinical outcomes.
  * Current evidence suggests little benefit with regard to slowing disease progression.
  * The American Academy of Neurology does not consider IVIG to be a first-line therapy in the treatment of relapsing-remitting multiple sclerosis.

- **Post-Polio:** Two published trials of post-polio syndrome failed to demonstrate a statistically significant benefit compared to placebo in improvement of muscle strength. [65, 66]

- **Recurrent pregnancy loss, or recurrent spontaneous abortion (due to anti-phospholipid or anti-cardiolipin antibodies):**
  * Recurrent pregnancy loss is defined as three or more pregnancies resulting in spontaneous abortion prior to 20 weeks of gestational age. These women often have immunologic abnormalities, particularly antiphospholipid antibodies. [27]
  * IVIG has not been established as a safe or effective therapy to prevent recurrent spontaneous abortion in women with immunologic abnormalities, such as elevated natural killer cells, defective cytokines, or defective growth factors. [13-15, 62]
  * One randomized controlled trial comparing IVIG to thyroid replacement therapy for the prevention of miscarriages found IVIG to be less effective. There was a statistically significant higher rate of live birth among women treated with thyroid replacement therapy. [61]
  * A small randomized controlled trial in 85 women with a history of three or more spontaneous abortions before 10 weeks of gestation compared low molecular heparin (LMW) plus aspirin with IVIG therapy. The percentage of live births in the LMW plus aspirin versus the IVIG treatment group was 72.5% and 39.5%, respectively. [80]
  * A randomized controlled trial in 82 women with a history of idiopathic secondary miscarriage compared live birth rates in those who received intravenous immune globulin versus placebo infusion (saline). There was no statistical difference between treatment groups. [82]
  * ACOG recommendations state:
    -- If results are positive for the same antibody on two consecutive tests 6 to 8 weeks apart, initiate heparin and low-dose aspirin with next pregnancy attempt.
    -- IVIG is not effective in preventing recurrent pregnancy loss. [55]
- **Additional conditions** for which published data is determined to be inconclusive or inadequate to support the use of IVIG include Alzheimer's disease, atopic dermatitis, recurrent *C. difficile*, narcolepsy/cataplexy, neonatal hemochromatosis, chronic sinusitis, tic disorder, delayed pressure urticaria, systemic sclerosis (diffuse cutaneous, dcSS) and toxic epidermal necrolysis. [27, 46-52, 63,103, 104]

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Appendix I: Primary Humoral Immunodeficiencies, as defined by the following diagnostic criteria:

1. X-linked agammaglobulinemia (congenital agammaglobulinemia) diagnosis accompanied by marked deficits or absence of all five immunoglobulin classes (IgG, IgM, IgA, IgE, and IgD), decreased circulating B lymphocytes, and normal numbers of functioning T lymphocytes.

OR

2. Hypogammaglobulinemia (a general term describing serum levels of IgG which are below the lower limits of normal).

OR

3. Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) documented with low to normal IgG levels and the inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax).

OR

4. Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM) accompanied by very low serum concentrations of IgG, IgA, and IgE, with normal or, more frequently, greatly elevated polyclonal IgM concentrations.

OR

5. Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, accompanied by marked deficits in IgG, IgA and IgM, low lymphocyte counts, and absent or below normal levels of both B- and T-lymphocytes.