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Clinical Policy Bulletin: Intravenous Immunoglobulins (IVIG)

Number: 0208

Policy

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

1. Primary humoral immunodeficiency diseases (such as congenital agammaglobulinemia (X-linked agammaglobulinemia), hypogammaglobulinemia, common variable immunodeficiency, X-linked immunodeficiency with hyperimmunoglobulin M, Wiscott-Aldrich syndrome, and severe combined immunodeficiency) (see Appendix)
2. Immune or idiopathic thrombocytopenic purpura (ITP) when a rapid rise in the platelet count is required, such as prior to surgery, to control excessive bleeding, or to defer or avoid splenectomy (see Appendix for criteria for ITP in adults, ITP in children, chronic ITP, and ITP in pregnancy)
3. Guillain-Barré syndrome (GBS) and GBS variants: IVIG is generally accepted as the treatment of choice for persons with Guillain-Barro syndrome, provided that they are so severely affected that they at least require aid to walk, that the disorder is diagnosed during the first 2 weeks of the illness, and that there are no contraindications to IVIG (see Appendix)
4. Multifocal motor neuropathy: for persons who have progressive, symptomatic multifocal motor neuropathy that has been diagnosed on the basis of electrophysiologic findings that rule out other possible conditions that may not respond to this treatment (see Appendix)
5. Kawasaki disease (see Appendix)
6. HIV infected children: bacterial control or prevention (see Appendix)
7. HIV-associated thrombocytopenia, pediatric or adult: considered medically necessary when criteria in Appendix are met (see Appendix)
8. Hemolytic disease of newborn, to decrease need for exchange transfusion (see Appendix)
9. B-cell chronic lymphocytic leukemia (CLL): for persons with hypogammaglobulinemia associated with CLL and recurrent infections or specific antibody deficiency (see Appendix)
10. Stem cell or bone marrow transplantation: IVIG is indicated for markedly hypogammaglobulinemic (IgG level less than 400 mg/dL) bone marrow or stem cell transplant recipients with severe infections (see Appendix and CPB 5.44 - Immune Globulins for Post-exposure Prophylaxis). IVIG is also indicated for steroid-resistant graft-versus-host disease in bone marrow transplant recipients 20 years of age or older, in the first 100 days post transplant, and who are hypogammaglobulinemic (IgG level less than 400 mg/dL).
11. Secondary immunosuppression associated with major surgery (such as cardiac transplants) and certain diseases (hematologic malignancies, extensive burns, or collagen-vascular diseases) (see Appendix)

Policy History

> Last Review: 08/21/2007
 Effective: 03/19/1998
 Next Review: 03/13/2008
 > Review History
 > Definitions

Additional Information

> Clinical Policy Bulletin Notes

12. Polymyositis in persons who are resistant to first and second line therapies (see Appendix)
13. Post-transfusion purpura (see Appendix)
14. Dermatomyositis in persons who are resistant to first and second line therapies (see Appendix)
15. Myasthenia gravis (see Appendix)
16. Multiple myeloma (see Appendix)
17. Moersch-Woltmann (Stiff-man) syndrome (unresponsive to other therapies) (see Appendix)
18. Neonatal alloimmune thrombocytopenia (NAIT) (also known as fetal alloimmune thrombocytopenia or FAIT) when criteria in Appendix are met
19. Opsoclonus-myoclonus (see Appendix)
20. Parvovirus B19 infection, chronic, with severe anemia (see Appendix)
21. Paraneoplastic opsoclonus-myoclonus-ataxia associated with neuroblastoma (see Appendix)
22. Lambert-Eaton myasthenic syndrome (see Appendix)
23. Hypoimmunoglobulinemia E syndrome, for treatment of severe infection (see Appendix)
24. Autoimmune mucocutaneous blistering diseases: IVIG is considered medically necessary for members with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (a.k.a., cicatricial pemphigoid), and epidermolysis bullosa acquisita if the member has either failed or has contraindications to conventional therapy, or the member has rapidly progressive disease in which a clinical response could not be affected quickly enough using conventional agents. When indicated for rapidly progressive disease, accepted guidelines indicate that IVIG should be given along with conventional treatment(s) and IVIG should be used only until conventional therapy could take effect. (See Appendix) Note: IVIG for the treatment of autoimmune mucocutaneous blistering disease is considered medically necessary only for short-term therapy and not as a maintenance therapy
25. Relapsing-remitting multiple sclerosis (MS) when standard approaches (i.e., interferons) have failed, become intolerable, or are contraindicated (see Appendix) (See also CPB 264... Multiple Sclerosis)
26. Systemic lupus erythematosus (SLE), for persons with severe active SLE for whom other interventions have been unsuccessful, have become intolerable, or are contraindicated (see Appendix)
27. Selective IgG subclass deficiencies with severe infection for persons meeting selection criteria (see Appendix)
28. Renal transplantation from live donor with ABO incompatibility or positive cross-match, where a suitable non-reactive live or cadaveric donor is unavailable (preparative regimen)
29. Churg-Strauss Syndrome (CSS) (allergic granulomatosis), for persons with severe active illness for whom other interventions have been unsuccessful, have become intolerable, or are contraindicated
30. Refractory autoimmune hemolytic anemia (see Appendix)
31. Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus (see Appendix)
32. Staphylococcal toxic shock syndrome (see Appendix)
33. Toxic epidermal necrolysis and Stevens-Johnson syndrome
34. Birdshot (vitelligenous) retinochoroidopathy
35. IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathy

36. Enteroviral meningoencephalitis

37. Neonatal sepsis, treatment.

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

III. Aetna considers the use of IVIG experimental and investigational for all other clinical conditions. See appendix for a current list of such indications.

Notes: The following criteria are considered in assessing the medical necessity of IVIG for the indications listed above.

1. The diagnosis of the disorder must be reasonably certain, and based on a thorough history and examination, and appropriate laboratory testing (e.g., electromyography (EMG), spinal fluid tests, serum tests and biopsy findings).
2. Previous treatment failures must be documented.
3. In some situations, IVIG may be used for medically necessary indications listed above for a person that has rapidly progressive disease in which a clinical response could not be effected quickly enough using conventional agents. In those situations, IVIG therapy would be given along with conventional treatment(s) and continued administration of IVIG is not considered medically necessary once conventional therapy takes effect.
4. Once treatment is initiated, there must be adequate documentation of progress. If there is initial improvement, and continued treatment is necessary, then some type of objective quantitative assessment to monitor the progress is required. Any accepted metric assessment may be used for objective monitoring of progress, such as MRC scale ** and activities of daily living (ADL) measurements. Changes in these measures should be clearly documented. Subjective or experiential improvement alone is generally insufficient to either continue IVIG or to expect coverage.
5. Clinical monitoring takes clear precedence over laboratory monitoring. If clinical improvement is evident, then laboratory monitoring solely to guide IVIG therapy is not considered medically necessary.
6. There should be, depending on the diagnosis and clinical circumstances, an attempt made to decrease/reduce the dosage when improvement has occurred. There should be, when clinically appropriate for the diagnosis, an attempt to stop the IVIG infusion if improvement is sustained with dosage reduction. If improvement does not occur with IVIG, continued infusion may not be considered medically necessary.

** The Medical Research Council (MRC) scale is the most commonly used grading of muscle strength.

Scale: 0 = no muscle movement; 1 = flicker of muscle movement; 2 = trace movement but not able to fully overcome gravity; 3 = just able to overcome gravity, but not against resistance; 4 = moves against resistance, but weak; 5 = full strength against resistance.

Background

This policy is consistent with guidelines on the use of immunoglobulin therapy from the Centers for Disease Control and Prevention (1999), and the United States Pharmacopoeial Convention (2007).

IVIG has been shown to be ineffective for the prophylaxis of, and as a treatment adjunct in, infections in some high-risk, preterm, low-birth-weight neonates (USPDI, 2002). Studies published before 1990 suggested that prophylactic IVIG reduced nosocomial infections in low-birth-weight infants. However, these studies enrolled small numbers of patients; employed varied designs, preparations, and doses; and included diverse study populations. The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network therefore performed a prospective, multicenter, randomized trial to test the hypothesis that the intravenous administration of immune globulin to infants with birth weights between 501 and 1500 grams would reduce the incidence of nosocomial infections (Fanaroff, et al., 1994). In this trial, the repeated prophylactic administration of IVIG failed to reduce the incidence of nosocomial infections significantly in premature infants weighing 501 to 1500 grams at birth. Furthermore, there were no significant differences in morbidity, mortality, or the duration of hospitalization between infants given IVIG

and Infants given no infusion or an infusion and placebo.

A recent multicenter, randomized, double-blind, placebo-controlled study (Cordonnier, et al., 2003) concluded that prophylactic immunoglobulin in allogeneic recipients of stem cell transplant from HLA-identical sibling donors is not recommended. However, the finding of this study does not question the use of immunoglobulin in hypogammaglobulinemic stem-cell transplant patients.

For a discussion of IVIG for recurrent spontaneous abortion, see CPB 348 - Recurrent Pregnancy Loss.

Gammagard Liquid 10 % is a slightly different version of the existing form of IVIG. It offers improved convenience because the ready-to-use, sterile preparation of Gammagard Liquid 10 % eliminates the need for reconstitution. Furthermore, its high concentration, compared to 5 % concentrations, allows for a reduction in the length of infusion.

Vivaglobin is an immune globulin [human] subcutaneous injection administered via a small, portable pump for the prevention of serious infection in children and adults with primary immunodeficiency.

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

Darabi et al (2006) noted that IVIG has been approved by the United States Food and Drug Administration (FDA) for use in 8 conditions: (i) immune thrombocytopenic purpura (ITP), (ii) primary immunodeficiency, (iii) secondary immunodeficiency, (iv) pediatric HIV infection, (v) Kawasaki disease, and (vi) prevention of graft versus host disease (GVHD) and infection in bone marrow transplant recipients. However, most usage of IVIG is for off-label indications, and for some of these comprehensive guidelines have been published. Common off-labeled uses for IVIG include chronic neuropathy (e.g., chronic inflammatory demyelinating polyneuropathy (CIDP) and multi-focal motor neuropathy), hypogammaglobulinemia, renal transplant rejection, myasthenia gravis, Guillain-Barre syndrome, necrotizing fasciitis, and autoimmune hemolytic anemia. The authors concluded that only a few indications account for most of the usage for IVIG. Reports concerning IVIG continue to grow at a tremendous pace but few high-quality randomized controlled studies have been reported. They noted that randomized controlled trials are especially needed for conditions such as CIDP, which consume large quantities of product.

Appendix

| Condition | Indications |
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| Autoimmune hemolytic anemia, refractory | IVIG may be considered medically necessary in persons with warm-type autoimmune hemolytic anemia that does not respond to corticosteroids or splenectomy, or those for whom the latter two treatments are contraindicated. |
| Bacterial infection in HIV-infected children | Consistent with recommendations of the Working Group on Antiretroviral Therapy of the National Pediatric HIV Resource Center IVIG is considered medically necessary in children with HIV-infection who meet any of the following criteria: <ol style="list-style-type: none"> I. Those with hypogammaglobulinemia, i.e., serum IgG concentration less than 250 mg/dL; II. Those with recurrent serious bacterial infections, i.e., defined as two or more infections such as bacteremia, meningitis, or pneumonia in a 1-year period; III. Those who fail to form antibodies to common antigens, such as measles, pneumococcal, and/or Haemophilus influenzae type b vaccine; IV. Those living in areas where measles is highly prevalent and who have not developed an antibody response after two doses of measles, mumps, and rubella virus vaccine live; |

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| | <p>V. Single dose for HIV-infected children who are exposed to measles;</p> <p>VI. HIV-infected children with chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy.</p> |
| <p>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), also known as Chronic Relapsing Polyneuropathy, including diabetes mellitus-CIDP and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant</p> | <p>Symmetric or focal neurologic deficits with slowly progressive or relapsing course over 2 months or longer with neurophysiological abnormalities.</p> <p>Note: A metaanalysis comparing the efficacy of IVIG, plasma exchange, and oral glucocorticoids found equivalence between all three, at least within the first 6 weeks of therapy (Van Schaik, et al., 2002). IVIG is considered under accepted guidelines as the preferred treatment, particularly in children, when there is difficulty with venous access for plasmapheresis, and those susceptible to the complications of long-term corticosteroid therapy (Orange, et al., 2006).</p> <p>Persons typically respond to IVIG or plasma exchange within the first several weeks of treatment and may demonstrate sustained improvement for many weeks or months. Relapses may require periodic isolated treatments with a single dose of IVIG or single plasma exchange. If a person responds successfully to infrequent booster treatments of either IVIG or plasma exchange, it is reasonable to maintain this form of treatment rather than adding corticosteroids or other immunosuppressants.</p> |
| <p>Chronic Lymphocytic Leukemia (CLL) in patients with hypogammaglobulinemia</p> | <p>IgG level less than 600mg/dL; and:</p> <ol style="list-style-type: none"> I. 1 severe bacterial infection within preceding 6 months or 2 or more bacterial infections in one year; or II. Evidence of specific antibody deficiency. |
| <p>Dermatomyositis, Polymyositis (includes Juvenile)</p> | <ol style="list-style-type: none"> I. Members presenting at least one item from the 1st criterion and four items from the 2nd through 9th criteria are said to have dermatomyositis. Patients presenting no items from the 1st criterion and at least four items from the 2nd through 9th criteria are said to have polymyositis. <ol style="list-style-type: none"> A. Skin lesions <ol style="list-style-type: none"> 1. Heliotrope rash (red purple edematous erythema on the upper palpebra) 2. Gottron's sign (red purple keratotic, atrophic erythema, or macules on the extensor surface of finger joints) 3. Erythema on the extensor surface of extremity joints: slightly raised red purple erythema over elbows or |

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- B. Proximal muscle weakness (upper or lower extremity and trunk)
- C. Elevated serum CK (creatine kinase) or aldolase level
- D. Muscle pain on grasping or spontaneous pain
- E. Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
- F. Positive anti-Jo-1 (histidyl tRNA synthetase) antibody
- G. Non-destructive arthritis or arthralgias
- H. Systemic inflammatory signs (fever: more than 37° C at axilla, elevated serum CRP level or accelerated ESR of more than 20 mm/h by the Westergren method)
- I. Pathological findings compatible with inflammatory myositis (inflammatory infiltration of skeletal evidence of active regeneration may be seen)

AND

- II. Member has severe active illness; and
- III. Member is intolerant or refractory to 1st and 2nd line therapies:
 - A. 1st line therapy - Corticosteroids (e.g., prednisone);
 - B. 2nd line therapy - Immuno-suppressants (e.g., methotrexate, azathioprine, cyclophosphamide, and cyclosporine).

Fetal Alloimmune Thrombocytopenia (FAIT)

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

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

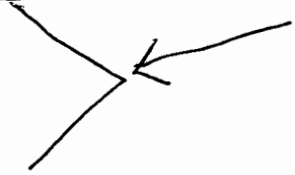
Guillain Barre Syndrome (GBS) - a.k.a. acute Inocive polyneuritis (includes GBS variants: Miller-Fisher syndrome [MFS], per autonomic polyneuropathy, acute pandysautonomia, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN))

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

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| Hematopoietic Stem Cell Transplant (HSCT) or Bone Marrow Transplant (BMT) | IVIg is considered medically necessary for treatment of markedly hypogammaglobulinemic (IgG level less than 400 mg/dL) HSCT or BMT recipients with severe infections. |
| HIV-associated Thrombocytopenia - Adult | <ol style="list-style-type: none"> I. Significant bleeding in thrombo-cytopenic patients or platelet count less than 20,000/ul; and II. Failure of RhIG in Rh-positive patients. |
| HIV-associated Thrombocytopenia - Pediatric | <p>Infants and children < 13 years of age whose IgG level is < 400 mg/dL; and</p> <ol style="list-style-type: none"> I. 2 or more bacterial infections in a 1-year period despite antibiotic chemoprophylaxis with TMP-SMZ or another active agent; or II. Child has received 2 doses of measles vaccine and lives in a region with a high prevalence of measles; or III. Member has HIV-associated thrombocytopenia despite antiretroviral therapy; or IV. Member has chronic bronchiectasis that is suboptimally responsive to antimicrobial and pulmonary therapy; or V. T4 cell count is greater than or equal to 200/mm³. |
| Hemolytic Disease of the Newborn | Not responding to phototherapy to decrease the need for exchange transfusion. Physician discretion important in deciding. |
| Hyperimmunoglobulin E Syndrome (Job's syndrome; Hyper IgE syndrome) | Recurrent staphylococcal abscesses and markedly elevated serum IgE with normal IgG, IgA, and IgM concentrations. |
| Idiopathic Thrombocytopenic Purpura (ITP) - Adult | <ol style="list-style-type: none"> I. Other causes of thrombocytopenia have been ruled out by history and peripheral smear; and Unresponsive to corticosteroid therapy; and Management of acute bleeding due to severe thrombocytopenia (platelet counts less than 30,000/ul); or II. To increase platelet counts prior to invasive major surgical procedures (e.g., splenectomy), or III. To defer or avoid splenectomy; or IV. In members with severe thrombocytopenia (platelet counts less than 20,000/ul) considered to be at risk for intracerebral hemorrhage. |
| Idiopathic Thrombocytopenic Purpura (ITP) - Pediatric | <p>Acute ITP:</p> <ol style="list-style-type: none"> I. IVIG as initial therapy if platelet count < 20,000/ul, especially when member has emergency bleeding or is at risk for severe life-threatening bleeding; or II. Persons with severe thrombo-cytopenia (platelet counts less than 20,000/ul) considered to be at |

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| | <p>risk for intracerebral hemorrhage.</p> <p>Note: IVIG not indicated if only mild manifestations of bleeding.</p> <p>Chronic ITP:</p> <p>In high risk persons when platelet count low or person symptomatic; and</p> <ol style="list-style-type: none"> I. Failure of other therapies, or II. Member is a high risk for post-splenectomy sepsis. |
| <p>Idiopathic Thrombocytopenic Purpura (ITP), Chronic Refractory</p> | <ol style="list-style-type: none"> I. Age of 10 years or older; and II. Duration of illness of greater than six months; and III. No concurrent illness/disease explaining thrombocytopenia; and IV. Prior treatment with corticosteroids and splenectomy has failed or member is at high risk for post-splenectomy sepsis. |
| <p>Immune Thrombocytopenic Purpura (ITP) in Pregnancy</p> | <ol style="list-style-type: none"> I. Refractory to steroids with platelet counts < 10,000/ul in the third trimester; or II. Platelet counts < 30,000/ul associated with bleeding before vaginal delivery or C-section; or III. Pregnant women who have previously delivered infants with autoimmune thrombocytopenia; or IV. Pregnant women who have platelet counts less than 50,000/ul during the current pregnancy; or V. Pregnant women with past history of splenectomy. |
| <p>Immunosuppressed Patients</p> | <p>To prevent or modify recurrent bacterial or viral infections (e.g., CMV) in members with iatrogenically induced, or disease associated immunosuppression (IgG < 400 mg/dL) with one of the following:</p> <ol style="list-style-type: none"> I. Solid organ transplants or extensive surgery with immunosuppression (Note: In particular, IVIG may be medically necessary in persons undergoing multiple courses of plasmapheresis as a treatment for allograft rejection or for other indications; these persons may receive IVIG at the completion of therapy if their IgG level is less than 400 mg/dL); or II. Hematological malignancy; or III. Extensive burns; or IV. Collagen-vascular disease. |
| <p>Kawasaki disease (Mucocutaneous Lymph Node Syndrome [MCLS])</p> | <p>Diagnosis must be established - no specific lab test - diagnosis is established by meeting the following criteria:</p> <ol style="list-style-type: none"> I. Fever present for at least five days; and II. Four of the following five conditions are met: |

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| | <ul style="list-style-type: none"> A. Mucous membrane changes such as a red tongue and dry fissured lips; B. Swelling of the hands and feet; C. Enlarged lymph nodes in the neck; D. Diffuse red rash covering most of the body; E. Redness of the eyes. |
| Lambert-Eaton Myasthenic Syndrome (LEMS) | <p>No response to anticholinesterases and Diaminopyridine); and</p> <ul style="list-style-type: none"> I. Used as an alternative to plasma exchange if weakness is severe; or II. When there is difficulty with venous access for plasmapheresis. |
| Myasthenia Gravis | <ul style="list-style-type: none"> I. Treatment of acute myasthenic crisis with decompensation (respiratory failure, or disabling weakness requiring hospital admission); and II. Other treatments have been unsuccessful or are contraindicated (e.g., azathioprine, cyclosporine, and cyclophosphamide). <p>Note: For management of myasthenic crises, IVIG is administered over 2 to 5 days. Use of IVIG as maintenance therapy is considered experimental and investigational.</p> |
| Moersch-Woltmann (Stiff-man) Syndrome | <ul style="list-style-type: none"> I. Presence of Anti-GAD antibody; and II. Benzodiazepines (e.g., Valium) and/or Baclofen, phenytoin, clonidine, tizanidine have failed. |
| Multifocal Motor Neuropathy with Conduction Block | <p>Progressive, symptomatic multifocal motor neuropathy that has been diagnosed on the basis of electrophysiologic findings that rule out other possible conditions that may not respond to IVIG treatment.</p> |
| Multiple Myeloma (MM) | <ul style="list-style-type: none"> I. "Plateau Phase" MM (> 3 months since diagnosis); and II. IgG level < 600mg/dL; and III. 2 or more significant infections in last year or a single life threatening infection; or <p>Evidence of specific antibody deficiency.</p> |
| Multiple Sclerosis (MS) - Relapsing-remitting <i>(not primary or secondary progressive MS)</i> | <ul style="list-style-type: none"> I. Severe manifestations of relapsing-remitting MS (not primary or secondary progressive MS); and II. Standard approaches (i.e., interferons – Betaseron, Avonex, Rebif) have failed, become intolerable, or are contraindicated. |
| Neuroblastoma associated paraneoplastic opsoclonus-myoclonus-ataxia syndrome | <p>Treatment of opsoclonus-myoclonus-ataxia associated with neuroblastoma.</p> |



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| <p>Opsoclonus-myoclonus</p> | <p>Medically necessary as last-resort treatment for refractory opsoclonus-myoclonus.</p> |
| <p>Erythrovirus (formerly parvovirus) B19 Infection, Chronic, with Severe Anemia (Pure Red Cell Aplasia)</p> | <p>Severe, refractory anemia with documented erythrovirus B19 viremia.</p> |
| <p>Autoimmune Mucocutaneous Blistering Diseases - includes Pemphigus vulgaris, Pemphigus foliaceus, Bullous Pemphigoid, Mucous Membrane Pemphigoid (a.k.a. Cicatricial Pemphigoid), and Epidermolysis bullosa acquisita</p> | <p>I. The diagnosis has been proven by biopsy and confirmed by pathology report; and II. The condition is rapidly progressing, extensive or debilitating; and III. Corticosteroids, immuno-suppressive agents have failed or the member has experienced significant complications from standard treatment, such as diabetes or steroid-induced osteoporosis.</p> |
| <p>Post-transfusion purpura (PTP)</p> | <p>I. Decreased platelets (usually < 10,000/ul); and II. 2 - 14 days post transfusion with bleeding.</p> |
| <p>Primary Humoral Immunodeficiencies</p> <p>I. Selective IgM Immunodeficiency II. Congenital hypogamma-globulinemia III. Immunodeficiency with near/normal IgM (absent IgG, IgA) – a.k.a. Hyper IgM syndrome IV. Other deficiency of humoral immunity V. Severe combined immunodeficiency disorders (e.g., X-SCID, jak3, ZAP70, ADA, PNP, RAG defects, Ataxia Telangiectasia, DiGeorge syndrome, common variable immunodeficiency)</p> | <p>I. Agammaglobulinemia (total IgG < 200 mg/dL); or II. Persistent hypogammaglobulinemia (total IgG < 400 mg/dL) with recurrent bacterial infections and/or lack of response to protein or polysaccharide antigens (inability to make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both):</p> <p>A. Serum antibody titres to tetanus and/or diphtheria should be obtained prior to immunization with diphtheria and/or tetanus vaccine and two to four weeks after immunization. An inadequate response is defined as less than a fourfold rise in antibody titre; and B. Serum antibody titres to pneumococcus should be measured prior to immunization and three to six weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax). An inadequate response is defined as less than a 2-fold rise in titer over baseline in at least one serotype tested.</p> <p>III. Selective IgG subclass deficiency (see criteria below); or IV. Normal total IgG levels with severe polysaccharide nonresponsiveness (deficient responses to 4 or more of 23 polysaccharide antigens included in Pneumovax vaccination) and evidence of recurrent severe difficult-to-treat infections (e.g., recurrent otitis media, bronchiectasis, recurrent infections requiring IV antibiotics, multiple antibiotic hypersensitivities)</p> |

with a documented requirement for antibiotic therapy:

- A. Further evidence of infection, including sinus and lung imaging, complete blood counts, C-reactive protein measurement, and erythrocyte sedimentation rate determination, may be required to support the need for IVIG supplementation.
- B. IVIG should be discontinued and the medical necessity of IVIG should be reevaluated 1 year after initiating therapy and every two years thereafter by reassessing immune response to protein and polysaccharide antigens. Immune response should be reevaluated at least 5 months after discontinuation of IVIG.

The use of IVIG may not be beneficial in certain secondary immunodeficiency states; correction of the underlying condition is the preferred approach.

Selective IgG Subclass Deficiency

- I. Member has unexplained recurrent or persistent severe bacterial infections; and
 - II. Infections fail to respond adequately to conservative measures, including meticulous hygiene and prophylactic antibiotics; and
 - III. Member has demonstrated an inability to mount an adequate response to protein and polysaccharide antigens, as determined by the following criteria, derived from Buckley (2002):
 - A. Member has documented inability to mount an antibody response to protein antigens: Serum antibody titres to tetanus and/or diphtheria should be obtained prior to immunization with diphtheria and/or tetanus vaccine and two to four weeks after immunization. An inadequate response is defined as less than a fourfold rise in antibody titre; and
 - B. Member has documented inability to mount an adequate antibody response to polysaccharide antigens. Serum antibody titres to pneumococcus should be measured prior to immunization and three to six weeks after immunization with polyvalent pneumococcal polysaccharide vaccine (e.g., Pneumovax). An inadequate response is defined as less than a 2-fold rise in titer over baseline in at least 20 percent of serotypes tested (e.g., 4 or more serotypes included in 23 valent Pneumovax vaccine).
- Note: Response to polysaccharide antigens is not reliable in children less than 2 years of age.
- IV. IVIG should be discontinued and the medical

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| | necessity of IVIG should be reevaluated 1 year after initiating therapy and every two years thereafter by reassessing immune response to protein and polysaccharide antigens. Immune response should be reevaluated at least 5 months after discontinuation of IVIG. |
| Staphylococcal Toxic Shock Syndrome | Severe cases of toxic shock syndrome that have not responded to fluids and vasopressors. |
| Systemic Lupus Erythematosus | Members with severe active SLE for whom first- and second-line therapies have been unsuccessful, have become intolerable, or are contraindicated. Note: Standard first-line therapy of active SLE include non-steroidal anti-inflammatory drugs, followed by low-dose corticosteroids and antimalarial compounds. Second-line therapeutic alternatives are the cytotoxic agents methotrexate, azathioprine, or cyclophosphamide. |
| Toxic shock syndrome or toxic necrotizing fasciitis due to group A streptococcus | IVIG is considered medically necessary in persons who are sufficiently ill to require critical care unit support and have documented presence of fasciitis and microbiological data consistent with invasive streptococcal infection (culture or Gram stain). |

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

| Normal Immunoglobulin Levels (mg/dl) | | | | Normal IgG Subclass Levels (mg/dl) | | | | |
|--------------------------------------|----------|------------|----------|------------------------------------|------------|-----------|----------|---------|
| AGE | IgA | IgG | IgM | AGE | IgG1 | IgG2 | IgG3 | IgG4 |
| 1 - 2 mo | 1 - 53 | 251 - 906 | 20 - 87 | cord | 435 - 1084 | 143 - 453 | 27 - 146 | 1 - 47 |
| 2 - 3 mo | 3 - 47 | 206 - 601 | 17 - 105 | 0 - 3 mo | 218 - 498 | 40 - 167 | 4 - 23 | 1 - 33 |
| 3 - 4 mo | 4 - 73 | 176 - 581 | 24 - 101 | 3 - 6 mo | 143 - 394 | 23 - 147 | 4 - 100 | 1 - 14 |
| 4 - 5 mo | 8 - 84 | 172 - 814 | 33 - 108 | 6 - 9 mo | 180 - 388 | 37 - 80 | 12 - 62 | 1 - 1 |
| 5 - 6 mo | 8 - 68 | 215 - 704 | 35 - 102 | 9 mo - 3 yr | 286 - 680 | 30 - 327 | 13 - 82 | 1 - 65 |
| 6 - 8 mo | 11 - 90 | 217 - 904 | 34 - 125 | 3 - 5 yr | 381 - 884 | 70 - 443 | 17 - 90 | 1 - 116 |
| 8 mo - 1 yr | 16 - 84 | 294 - 1069 | 41 - 149 | 5 - 7 yr | 282 - 816 | 83 - 513 | 8 - 111 | 1 - 121 |
| 1 - 2 yr | 14 - 106 | 345 - 1213 | 43 - 173 | 7 - 9 yr | 442 - 802 | 113 - 480 | 15 - 133 | 1 - 84 |
| 2 - 3 yr | 14 - 123 | 424 - 1051 | 48 - 168 | 9 - 11 yr | 458 - 938 | 163 - 513 | 28 - 113 | 1 - 121 |
| 3 - 4 yr | 22 - 159 | 441 - 1135 | 47 - 200 | 11 - 13 yr | 456 - 952 | 147 - 493 | 12 - 179 | 1 - 168 |
| 4 - 6 yr | 25 - 154 | 483 - 1236 | 43 - 196 | 13 - 15 yr | 347 - 993 | 140 - 440 | 23 - 117 | 1 - 183 |
| 6 - 9 yr | 33 - 202 | 633 - 1280 | 48 - 207 | 15 yr & up | 422 - 1292 | 117 - 747 | 41 - 129 | 1 - 291 |
| 9 - 11 yr | 45 - 236 | 608 - 1572 | 52 - 242 | | | | | |
| 11 yr & up | 70 - 312 | 639 - 1349 | 56 - 352 | | | | | |