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# Position statement on the appropriate use of intravenously administered immunoglobulin (IGIV)

Generated by the primary immunodeficiency committee of the American Academy of Allergy, Asthma and Immunology.

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## Introduction

Immunoglobulin (IG) for intravenous (IV) administration, or IGIV (also commonly referred to as IVIG, although licensed in the US as IGIV) is currently approved by the US Food and Drug Administration (FDA) for 6 indications: 1) treatment of primary immunodeficiencies; 2) prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia; 3) prevention of coronary artery aneurysm in Kawasaki disease; 4) prevention of infections and graft versus host disease after bone marrow transplantation; 5) reduction of serious bacterial infection in HIV-infected children; and 6) increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding. Not all currently available products are approved for each of these indications and physicians should review specific product information. The use of IGIV for these purposes can be variable and there are notable disparities in current clinical practices. Furthermore, there have been developments regarding IGIV usage, which warrant consideration.

IGIV has been utilized for other conditions without FDA approval. Some of these uses are based entirely upon theory and/or anecdotal reports, while others are based upon quality evidence. A comprehensive review of the evidence supporting the use of IGIV in specific indications is beyond the scope of this document, but was reviewed in detail in its preparation. The entire summary of evidence and detailed recommendations regarding the use of IGIV will be published elsewhere and the reader is referred to that document as well as other more comprehensive discussions of IGIV usage.[1]

In this position statement the major uses of IGIV are reviewed and specific recommendations are provided where appropriate. These recommendations should not be

considered absolute, but should help prompt each prescribing physician to consider and review the data supporting any particular use of IGIV. The indications discussed are: primary immunodeficiency; secondary immunodeficiency; autoimmune disease; asthma; neurologic disorders; transplantation; infectious disease; Kawasaki disease; and other uses. Practical considerations in using IGIV are also raised.

**Primary Immunodeficiency**

IGIV is indicated to reduce the susceptibility to infections in patients with primary immunodeficiencies affecting the quantity and/or quality of humoral immunity. Primary humoral immunodeficiencies include agammaglobulinemia, hyper IgM syndrome, common variable immunodeficiency as well as other deficiencies of immunoglobulin and specific antibody production (hyper IgE syndrome, Wiskott-Aldrich Syndrome and specific antibody deficiency).[2] Patients markedly deficient in humoral immunity are dependent on IGIV for survival. Benefits of IGIV in patients not able to produce antibodies normally include: a reduction of the severity and frequency of infections,[3] prevention of chronic lung disease[4] and prevention of enteroviral meningoencephalitis.[3] The decision to administer IGIV to patients with primary deficiencies in antibody production should be based on: 1) abnormalities of serum immunoglobulin concentrations; 2) clinical history of infections; and, when appropriate, 3) the demonstrated inability to produce antibody normally following antigenic stimulation.

An additional consideration is the route of administration. In the United States, at the present time, available immunoglobulin products are licensed only for administration by the intravenous or intramuscular route. Subcutaneous administration of intravenous or intramuscular preparations of immunoglobulin which is widely employed in Europe, has therapeutic equivalence with intravenous therapy.[5, 6]

**Secondary immunodeficiency**

IGIV has also been used in a number of diseases that result in secondary immunodeficiency. IGIV administration may be appropriate for selected patients with B cell chronic lymphocytic leukemia.[7] A well controlled trial of IGIV in HIV infected children demonstrated a significant reduction in bacterial infections but the benefit of IGIV was not seen in patients treated with trimethoprim/sulfamethoxazole for *Pneumocystis* pneumonia prophylaxis.[8] The use of IGIV as an adjunct to enhance the antibacterial defenses of premature newborn infants remains controversial, but may diminish the incidence of sepsis.[9] Other uses of IGIV for secondary immunodeficiencies, including sepsis beyond the neonatal period, multiple trauma and post-operative wounds are not well supported by published data.

**Autoimmune Diseases**

IGIV remains an important treatment modality in immune thrombocytopenic purpura, and it has been shown to improve platelet counts in controlled studies.[10] Despite the lack of vigorous scientific evidence for benefit in post-transfusion purpura, IGIV administration is recommended given the potential life threatening nature of the disease.[11] Anecdotal reports also suggest utility for IGIV in autoimmune neutropenia, autoimmune hemolytic anemia, Evans syndrome and acquired hemophilia especially when other therapeutic modalities fail.[12, 13]

IGIV has been used with varying efficacy in several other autoimmune diseases. The results in rheumatoid arthritis are controversial, but some benefit was suggested from case reports and open label trials.[14] Although high dose IGIV was reported to improve specific organ-related complications of systemic lupus erythematosus including nephritis, myocarditis, polyradiculopathy, and bone marrow suppression, its potential

prothromboembolic effects necessitate extreme caution in its therapeutic application.[15] IGIV also anecdotally helped patients with antiphospholipid antibody syndrome experiencing recurrent spontaneous abortion and those undergoing *in vitro* fertilization.[16] Some case reports and open label studies additionally report benefit from IGIV as an alternative therapeutic agent in patients with anti-neutrophil cytoplasmic antibody disorders,[17] systemic sclerosis/scleroderma,[18] and Still's disease.[19] Although IGIV may be useful in the inflammatory myopathies, polymyositis and dermatomyositis,[20] it is unlikely to be beneficial in inclusion body myositis[21] and thus specific recommendations for treatment of these diseases are not possible. IGIV has been successfully used in some other organ specific autoimmune diseases including Graves' opthalmopathy,[22] autoimmune uveitis,[23] and autoimmune chronic active hepatitis,[24] but lack of convincing evidence prevents a recommendation for its routine use.

**Asthma**

Asthma is a disease of pulmonary inflammation, which is effectively treated in most individuals with regimens that include low to moderate doses of inhaled corticosteroids, or non-steroidal anti-inflammatory agents. In some patients, very high doses of inhaled and oral steroids are required to control asthma symptoms, leading to intolerable adverse effects. In this setting, IGIV has been employed as a steroid-sparing agent in both open trials [25-28] Two subsequent placebo-controlled studies have had contradictory results; one failed to show any benefit of IGIV,[29] while the other demonstrated decreases in steroid requirements in steroid-dependent asthmatics.[30] Other smaller studies that have used low doses of IGIV, or that have only evaluated patients requiring inhaled steroids have not shown significant differences.[28, 31]

The inconsistent data from randomized controlled studies combined with the cost and availability of IGIV, does not support a recommendation for routine use in severe asthma. The efficacy in select groups, suggests that it may be used as a treatment for carefully defined asthmatic patients with persistent requirements for high doses of systemic steroids. Although, IGIV cannot be presently recommended for routine treatment of asthma, individuals with antibody deficiency who have asthma-like symptoms can benefit from IGIV therapy through its ability to decrease the incidence of infections that may trigger bronchospasm.

**Neurological Disorders**

IGIV has demonstrated effectiveness in inflammatory demyelinating disorders of the peripheral and central nervous systems.[32, 33] Despite the lack of an FDA indication, IGIV has become first-line therapy for demyelinating neuropathies such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, and has demonstrated similar efficacy and less adverse effects than plasma exchange or corticosteroids.[34-36] In myasthenia gravis[37] and Lambert Eaton myasthenic syndrome,[38] IGIV may be used as an alternative treatment when patients fail to respond or do not tolerate other treatments. IGIV may also be a potentially effective second line treatment in relapsing-remitting multiple sclerosis, although the optimal dosage remains to be established.[39]

Due to the paucity of reliable studies that demonstrate substantial efficacy of IGIV in intractable childhood epilepsy syndromes, its routine use cannot be recommended. However, the poor prognosis and quality of life of children who do not improve with anti-epileptic drugs and corticosteroids would justify a role for IGIV especially in patients who may be candidates for surgical resection.[40, 41] Many case reports exist in which IGIV therapy was

tried with varying success in other less common neurological disorders but more clinical research is needed to establish its usefulness.

**Hematopoietic Stem Cell and Solid Organ Transplantation**

IGIV is currently indicated as an adjunct treatment for selected patients undergoing allogenic hematopoetic stem cell transplantation for the treatment of hematologic malignancy.[42] Treatment is provided to prevent infection during the period in which patients are rendered most immunodeficient due to chemoablation, typically during the first 100 days. Similarly IGIV is effective in the management of primary immunodeficient patients undergoing allogeneic transplantation.[43] In particular, IGIV offers protection against interstitial pneumonia secondary to CMV, especially when given in conjunction with antiviral chemoprophylaxis.[44]

The benefit of IGIV as adjunct therapy for patients transplanted in the era of improved molecular HLA matching, anti-CMV chemoprophylaxis, gram-negative antimicrobial prophylaxis, nonablative conditioning regimens and improvements in graft versus host immunoprophylaxis is not known. Thus, a re-evaluation of practices is warranted. In this regard a recent double-blind placebo-controlled multi-center trial of IGIV in allogeneic bone marrow transplantation failed to demonstrate utility of IGIV administration.[45] As a result, its routine use in patients undergoing allogeneic matched related bone marrow transplantation may not be necessary.

IGIV had also been considered to reduce the incidence and severity of acute graft versus host disease (GVHD).[46] More recent studies, however have failed to demonstrate this benefit, thus preventing a recommendation of IGIV for this indication.[42, 45] In contrast, data have never supported the use of IGIV to prevent chronic GVHD.[47] Further trials are needed to resolve data supporting contrasting practices. Studies are also needed to

determine whether IGIV is beneficial in the case of HLA-matched unrelated donor bone marrow or cord blood transplants.

IGIV can be useful for solid organ transplant recipients who experience acute rejection, or who are HLA-sensitized for acute rejection, and may be justified for appropriately selected renal transplantation.[48] Although less data exist, there may also be a role for IGIV in autoimmune cytopenias that can occur post-transplant.[49]

**Kawasaki Disease (KD)**

KD is an acute febrile vasculitis of medium-sized vessels that commonly affects the coronary arteries and is believed to have a post-infectious origin. IGIV (single dose of 2g/kg) in conjunction with aspirin is the standard of care for patients with KD during the first 10 days of the syndrome to prevent the development of coronary aneurysms.[50] Although there are some data suggesting that there may be benefit to treatment on or prior to day 5,[51] they have been challenged.[52] Most importantly, therapy should be provided when the diagnosis is established in attempt to prevent coronary aneurysm, even after 10 days of onset of fever.

**Treatment of infectious disease**

Although IGIV does not have a major role in the treatment of infections, a beneficial role has been shown in the following settings. Adjunct treatment of established bacterial septic shock and group B streptococcal disease with IGIV provides benefit and reduces mortality.[53-57] High dose IGIV administered intravenously or intrathecally may be useful for treatment of meningoencephalitis caused by enteroviral infection in patients with agammaglobulinemia.[58] Orally administered IGIV can reduce the duration of diarrhea, viral shedding and hospitalization in children with acute rotaviral gastroenteritis.[59] Treatment of pneumonitis caused by CMV with high dose IGIV,[60] or high-titer anti-CMV IGIV[44] combined

with ganciclovir has resulted in improved outcomes. IGIV or hyperimmune respiratory syncytial virus (RSV) IGIV has provided some benefit in combination with ribavirin to treat RSV pneumonitis in immunodeficient patients.[61, 62] IGIV has also been effectively administered in anemia caused by chronic erythrovirus B-19 infection,[63] *Campylobacter jejuni* infection,[64] and in pseudomembneous colitis caused by *Clostridium difficile*,[65] but its widespread use in these conditions is not supported by extensive data. IGIV has not been found to have clinical efficacy in other infection-related conditions including, suspected sepsis, CMV gastroenteritis, or established bacterial pneumonia,[66, 67] and should not be used to treat these illnesses

**Other Uses**

Conflicting reports exist regarding the efficacy of IGIV in toxic epidermal necrolysis and Stevens-Johnson syndrome, but given the risk of mortality, the majority of evidence support the use of high-dose IGIV as an early therapeutic intervention.[68] The evidence for IGIV use in the autoimmune blistering disorders, such as bullous pemphigoid, is outlined in a consensus statement published by the American Academy of Dermatology,[69] and is primarily based on case reports or prospective studies of “last resort” treatment. There has been an open trial of IGIV use for delayed pressure urticaria and two thirds of the patients had remission, or some benefit.[70] The evidence for IGIV use in other chronic urticarias is unclear and does not currently support its use.[71, 72] Likewise the data for atopic dermatitis, which includes one small, randomized, evaluator blinded trial, does not support the use of IGIV.[73] There are case reports, but no controlled trials supporting the use of IGIV in psoriasis.[74]

Several neurocognitive disorders are proposed to have immunological components including childhood autism, chronic fatigue syndrome and the pediatric autoimmune neuropsychiatric disorders with associated streptococcal infection (PANDAS). Despite the

abundance of anecdotal reports of IGIV utility in these disorders, a double-blind placebo controlled trial has only been performed in chronic fatigue syndrome and demonstrated a lack of efficacy.[75] In PANDAS, a single case controlled prospective trial did demonstrate efficacy of 1g/kg/d treatment with IGIV on 2 consecutive days for rigorously defined patients.[76] In contrast, studies of IGIV in autism have at best, been case series and have not provided suggestion of benefit.[77]

IGIV has also been evaluated in certain other organ specific diseases. In selected patients with cystic fibrosis there have been some encouraging observations regarding IGIV therapy, but effects are marginal and probably do not justify the resources and risk.[78] High dose IGIV treatment appeared promising in numerous case reports of acute myocarditis,[79] but has been found ineffective in treatment of the carditis of acute rheumatic fever[80] as well as in recently diagnosed dilated cardiomyopathy,[81] as determined by randomized placebo controlled trials. Finally, IGIV has been suggested to promote successful pregnancy in women who experience recurrent spontaneous abortion, but meta-analysis of existing randomized controlled trials failed to demonstrate any benefit[82] and thus therapy is not recommended for this indication.

**IGIV Products**

There are currently a number of IGIV products that provide chemically unmodified lyophilized or liquid forms of IgG produced from plasma recovered from whole blood donations or from plasmapheresis donors. Lots may contain plasma obtained from more than 50,000 donors, which is pooled and then treated to precipitate the immunoglobulin-containing fraction. The resulting solutions may contain sodium, maltose, albumin, polyethylene glycol, D-mannitol, D-sorbitol, sucrose, glucose, and/or albumin among other substances to prevent aggregation. Donors are screened and tested for multiple infectious

agents to reduce the risk of pathogen contamination. In addition, several different pathogen inactivation steps are also utilized in the preparation of the various IGIV products and can include solvent/detergent treatment, acid incubation, pasteurization, filtration, and precipitation/chromatography. IGIV solutions have final IgG concentrations of 3,5,6,10 or 12% depending on the product. The osmolarity of these solutions lies between 253 mOsm/L and 1250 mOsm/L. The IgA content of current brands varies between <0.4μg/ml to 720 μg/ml.

**IGIV dosing**

For antibody replacement IGIV therapy is typically administered every 3 to 4 weeks at an initial dose of as much as 400-600 mg/kg.[83] The dose or dosing interval should be adjusted (based on the clinical response) to achieve optimal clinical results. Some studies suggest that doses as high as 800 mg/kg/month may be useful, particularly in primary immunodeficiency patients with chronic lung disease.[84, 85] Measurement of trough IgG levels may be helpful. Trough levels greater than 500 mg/dl are associated with fewer infections and improved outcomes.[3, 86] The target trough level for patients with pre-treatment IgG levels between 200 and 500mg/dl should be at least the pre-treatment IgG plus 300. Higher trough levels (>800 mg/dL) have the potential to further reduce the incidence of infection.[3] Patients with normal IgG levels, but impaired specific antibody production may also benefit from doses ≥400mg/kg.[87] Ultimately, the dose must be individualized and titrated to achieve clinical benefit for the patient being treated. Immunomodulatory doses are typically higher than those used for antibody replacement and range between 400 mg/ kg for 5 days, or a more rapid course of 1 or 2 g/kg given in one or two days.

## Infusion methods

The first infusion in an immunodeficient patient should be given in a setting with cardiovascular and pulmonary monitoring and should be administered slowly, starting with a rate of 0.4 mg/Kg/min. After 15 to 30 minutes the rate can be increased to 1.2 to 1.6 mg/Kg/min, and increased as tolerated to a maximum of 3.3 mg/kg/min (certain IGIV products are licensed for greater rates of infusion). Considerations of the sodium or sucrose content, total volume to be administered, and the osmolarity of the product are important in patients with pre-existing medical conditions such as renal[88] or cardiovascular disease.[33, 89-91] IGIV preparations should not be considered to be generically equivalent, and substitution should generally not be allowed without careful monitoring of the patient. Infusions of IGIV are commonly given in outpatient infusion centers, outpatient clinics, or in the home. The latter is facilitated by the involvement of home care nurses, but alternatively can be provided by self infusion.[92] In most cases the IV route is used, subcutaneous infusion (not yet FDA approved), has been found similarly satisfactory at least in primary immunodeficiency.[93] The placement and use of indwelling venous access for IVIG administration should be carefully weighed against the thrombotic and infectious risks inherent to these devices that may be further amplified in immunodeficient patients, or by administration of IGIV.

## Adverse effects

Mild adverse reactions, myalgias, chills, low grade fever, and/or headache are relatively common. They occur more commonly in the first few infusions and are treated by slowing or stopping the infusion for 15 to 30 minutes. Pre-treatment with diphenhydramine, acetaminophen, aspirin or ibuprofen, or IV hydration may also be helpful. Prophylaxis of more severe reactions can be provided with 1mg/kg IV hydrocortisone. Serious adverse

events are rare, but include aseptic meningitis, renal failure, thrombosis, and neurodegeneration amongst others.[94] Of these, renal failure has been associated with the sucrose content of a given product and thrombosis may be associated with high osmolarity products or high viscosity states.[92, 95] There is also a risk of reactions from anti-IgA antibodies generated in patients with complete IgA deficiency.[96] This includes rare IgE-mediated anaphylactic reactions against IgA,[97] and may be addressed to some degree by the use of IgA-depleted IGIV products. Finally, the theoretical and actual possibility of transmission of blood-borne infection needs to be considered. Thus, the risks of IGIV administration must be carefully weighed against potential benefits. The appropriate use of IGIV, however, can be life-saving and should not be withheld for patients in justifiable need.

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