Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology

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Human immunoglobulin prepared for intravenous administration (IGIV) has a number of important uses in the treatment of disease. Some of these are in diseases for which acceptable treatment alternatives do not exist. In this review we have evaluated the evidence underlying a wide variety of IGIV uses and make specific recommendations on the basis of these data. Given the potential risks and inherent scarcity of IGIV, careful consideration of the indications for and administration of IGIV is warranted. (J Allergy Clin Immunol 2006;117: S525-53.)

Key words: *Immunoglobulin, IGIV, intravenous immunoglobulin, transfusion, adverse events, primary immunodeficiency, immunomodulation, autoimmunity*

Abbreviations used

APS: Antiphospholipid antibody syndrome
CMV: Cytomegalovirus
CVID: Common variable immunodeficiency
FDA: US Food and Drug Administration
GBS: Guillain-Barré syndrome
GVHD: Graft-versus-host disease
IDF: Immune Deficiency Foundation
IGIV: Immunoglobulin, intravenous
KD: Kawasaki Disease
LEMS: Lambert-Eaton myasthenic syndrome
MG: Myasthenia gravis
MMN: Multifocal motor neuropathy
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
PE: Plasma exchange
RSV: Respiratory syncytial virus
SLE: Systemic lupus erythematosus

INTRODUCTION

Over the past 2½ decades, administration of exogenous pooled human immunoglobulin for intravenous use (IGIV; commonly referred to as IVIG, although licensed

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Cover artwork depicts a structural model of IgG. This image was created by Michael Clark, PhD, Department of Pathology, Cambridge University, Cambridge, United Kingdom. Reproduced with permission.

Received for publication December 22, 2005; accepted for publication January 17, 2006.

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0091-6749
doi:10.1016/j.jaci.2006.01.015

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in the United States as IGIV) has become an important therapy in clinical medicine. The original use of these immunoglobulin preparations, which contain a broad range of antibody specificities (as opposed to the use of mAbs or sera or immune globulin preparations with high titers of selected specific antibodies), was in antibody replacement therapy. However, a number of other clinical benefits of IGIV treatment have been demonstrated. Many of these other uses result from anti-inflammatory and immunomodulatory effects, which were not anticipated when these polyclonal preparations were first developed. Unfortunately, some frequent or proposed uses are based on relatively little data or anecdotal reports. Because currently available IGIV preparations are produced from human plasma by using a number of preparatory steps, supply of products is finite, and its use should be carefully considered.[1] Furthermore, the administration of IGIV can lead to numerous side effects and potential additional adverse consequences.[2-6] Despite this, the appropriate use of immunoglobulin can be life-saving.

This document is focused on the use of standard immunoglobulin preparations specifically manufactured for intravenous administration. These preparations have been in clinical use for more than 20 years and have improved the management of certain disease states. There are currently 6 clinical indications for which IGIV has been licensed by the United States Food and Drug Administration (FDA), as outlined in Table I. These can be summarized as follows: (1) treatment of primary immunodeficiencies; (2) prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia; (3) prevention of coronary artery aneurysms in Kawasaki disease (KD); (4) prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) after bone marrow transplantation; (5) reduction of serious bacterial infection in children with HIV; and (6) increase of platelet counts in idiopathic thrombocytopenic purpura to prevent or control bleeding.

This document reviews the basis for the FDA-approved indications and will discuss other disease states in which IGIV has been used. Some of these other conditions are extremely rare, making randomized controlled investigations difficult. Others, however, are quite common, and rigorous scientific evaluation of IGIV utility has been possible. IGIV holds great promise as a useful therapeutic agent in some of these diseases, whereas in others it is ineffectual and might actually increase risks to the patient. Thus the evidence supporting the use of IGIV in these conditions has been reviewed and categorized (Table II). Current recommendations for the appropriate use of IGIV are outlined in this summary.

It is noteworthy that this summary is current as of November 2005 and does not reflect clinical research or reports that have become available since that time. Although prior reviews of evidence were considered to arrive at the conclusions contained in this document, primary literature for review on each subject was derived from searching the National Center for Biotechnology Information Pubmed database using the key words ''IVIG,'' ''IGIV,'' and ''intravenous immunoglobulin,'' along with key words specific for each disease-related topic. The recommendations for appropriate use of IGIV stated here are based on this literature review but will most certainly change over time as experience and understanding of these diseases increases.

TABLE I. FDA-approved indications for IGIV

No. of FDA-licensed products*	Disease state	Indication†
11	Primary immunodeficiency disease or primary humoral immunodeficiency	Indicated for the treatment of primary immunodeficiency states or for increase of circulating antibody levels in primary immunodeficiency diseases or for replacement therapy of primary immunodeficiency states in which severe impairment of antibody-forming capacity has been shown
5	Idiopathic thrombocytopenic purpura	Indicated when a rapid increase in platelet count is needed to prevent bleeding, control bleeding, or both in idiopathic thrombocytopenic purpura or to allow a patient with idiopathic thrombocytopenic purpura to undergo surgery
3	Kawasaki disease (syndrome)	Indicated for the prevention of coronary artery aneurysms associated with Kawasaki disease
2	B-cell chronic lymphocytic leukemia	Indicated for the prevention of bacterial infections in patients with hypogammaglobulinemia, recurrent bacterial infections, or both associated with B-cell chronic lymphocytic leukemia
1	HIV infection	Indicated for pediatric patients with HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization and increase time free of serious bacterial infection
1	Bone marrow transplantation	Indicated for bone marrow transplant recipients $\geq$20 years of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic causes, and acute GVHD in the first 100 days after transplantation

*Refer to Table IX for specific details regarding individual products.
†Note the indications listed represent a cumulative summary of the indications listed for the range of products that carry that indication. For the specific details relating to a given indication, refer to the prescriber information for each individual product.

PRIMARY AND SECONDARY IMMUNODEFICIENCY

IGIV is indicated as replacement therapy for patients with primary and selected secondary immunodeficiency diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infections (Table III).[7,8]

Agammaglobulinemia

Among the immunodeficiencies, the clearest indication for IGIV is for patients who produce no antibody, which can occur because of the absence of functionally mature B cells. Evaluation of IGIV use in patients lacking immunoglobulin has demonstrated a clear benefit in terms of reducing both acute and chronic infections.[7,9,10] Retrospective analyses of agammaglobulinemic children have revealed that the number and severity of infectious complications is inversely correlated with the dose of IGIV administered.[10,11] In particular, when IgG trough levels were maintained at greater than 800 mg/dL, serious bacterial illness and enteroviral meningoencephalitis were prevented.[10] Although agammaglobulinemia is rare, it provides insight into the value of immunoglobulin replacement in preventing disease caused by defective humoral immunity that can be extrapolated to other antibody-deficient states.

Another group of patients who are often effectively agammaglobulinemic are the recipients of hematopoietic stem cell transplants for severe combined immunodeficiency. The engrafted marrow often does not allow for functional B-cell reconstitution, and thus these patients do not produce functional antibody and should be treated as if they were agammaglobulinemic.

TABLE II. Categorization of evidence and basis of recommendation and strength of recommendation

Categorization of evidence and basis of recommendation	
Ia	From meta-analysis of randomized controlled studies
Ib	From at least one randomized controlled study
IIa	From at least one controlled trial without randomization
IIb	From at least one other type of quasiexperimental study
III	From nonexperimental descriptive studies, such as comparative, correlation, or case-control studies
IV	From expert committee reports or opinions or clinical experience of respected authorities or both
Strength of recommendation	
A	Based on category I evidence
B	Based on category II evidence or extrapolated from category I evidence
C	Based on category III evidence or extrapolated from category I or II evidence
D	Based on category IV evidence or extrapolated from category I, II, or III evidence

Hypogammaglobulinemia with impaired specific antibody production

Deficient antibody production is usually defined by decreased immunoglobulin concentrations, or a significant inability to respond with IgG antibody production after antigenic challenge, or both. Reduced levels of serum

TABLE III. Uses of IGIV in primary and secondary immune deficiencies

Benefit	Disease	Evidence category	Strength of recommendation
Definitely beneficial	Primary immune defects with absent B cells	IIb	B
	Primary immune defects with hypogammaglobulinemia and impaired specific antibody production	IIb	B
Probably beneficial	Chronic lymphocytic leukemia with reduced IgG and history of infections	Ib	A
	Prevention of bacterial infection in HIV-infected children	Ib	A
	Primary immune defects with normogammaglobulinemia and impaired specific antibody production	III	C
Might provide benefit	Prevention of neonatal sepsis	Ia	A
Unlikely to be beneficial	Isolated IgA deficiency	IV	D
	Isolated IgG4 Deficiency	IV	D

immunoglobulin in patients with recurrent bacterial infections coupled with a lack of response to protein or polysaccharide vaccine challenges (ie, patients who cannot make IgG antibody against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine, or both) is a clear indication for IgG replacement. The prototype of this disorder is common variable immunodeficiency (CVID), which can result from several different genetic abnormalities. Early studies of IGIV in this setting have shown that it reduces the incidence of infection in patients when compared with their infection rates before IGIV treatment.[12] IGIV has also been shown to be superior to intramuscular immunoglobulin for these patients in direct comparison studies.[13,14] Because patients with CVID are predisposed to chronic lung disease and pulmonary deterioration as a result of chronic or subclinical infection,[15,16] early recognition of the diagnosis and initiation of IGIV therapy are critical.[15] Adequate replacement of IGIV has been shown to reduce the incidence of pneumonia[17] and prevent the progression of lung disease in patients with CVID.[18] Although double-blind placebo-controlled studies demonstrating the benefits of IGIV for patients with CVID do not exist, the historical evidence and existing studies are compelling enough to indicate this therapy to prevent recurrent infection in the setting of CVID.

Hyper-IgM syndromes are a group of disorders characterized by hypogammaglobulinemia with severely impaired production of specific antibody. Children with hyper-IgM syndrome have decreased levels of IgG and IgA and increased or normal levels of IgM. Although B cells are present, there is an inability to generate specific antibody. As a result, these individuals have recurrent infections similar to those of patients with agammaglobulinemia. Regular replacement therapy with IGIV is crucial for individuals with this disorder, whether it be due to the X-linked or autosomal recessive varieties, as reported in the 2 largest series of patients.[19-21] Patients treated with IGIV did not get meningitis, and the incidence of pneumonia was reduced from 7.6% to 1.4% per year. Similar trends were found with other infectious diseases in these patients.

Normogammaglobulinemia with impaired specific antibody production (selective antibody deficiency)

Patients who have normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens after vaccination, can present a diagnostic challenge. IgG replacement therapy should be provided when there is well-documented severe polysaccharide nonresponsiveness and evidence of recurrent infections with a documented requirement for antibiotic therapy.[22] Further evidence of infection, including sinus and lung imaging, complete blood counts, C-reactive protein measurement, and erythrocyte sedimentation rate determination, would support the need for IGIV supplementation. In this setting IGIV therapy is appropriate for patients with difficult-to-manage recurrent otitis media with risk for permanent hearing loss, bronchiectasis, recurrent infections necessitating intravenous antibiotics, or multiple antibiotic hypersensitivities that interfere with treatment.

When the severity of infection warrants the use of IGIV for this form of antibody deficiency, patients, their parents, or both should be informed that the treatment might be stopped after a period of time (preferably in the spring in temperate regions) and that the immune response will have to be re-evaluated at least 5 months after discontinuation of IGIV. Although some patients, usually children, show improved responses to antigenic challenge (typically with pneumococcal polysaccharide vaccine) and improve clinically, others require restarting the IGIV therapy because of recurrence of infections.[23,24]

Selective IgA deficiency is not an indication for IGIV replacement therapy, although in some cases poor specific IgG antibody production, with or without IgG2 subclass deficiency, might coexist; in these patients IGIV might be required. At least one such patient has been found to have a mutation in the *TNFRSF13B* gene encoding the

transmembrane activator and calcium modulator and cyclophilin ligand interactor, which is associated with CVID.[25] Intravenous administration of IGIV can pose a risk of anaphylaxis for IgA-deficient patients who have IgE anti-IgA antibodies[26] or reactions caused by complement activation if IgG anti-IgA antibodies are present.[27,28] The vast majority of patients who have low serum IgA levels, with or without IgG anti-IgA antibodies, however, receive IGIV without difficulty, regardless of the IgA content.[27,28] If there is a specific concern, IgA-depleted IGIV has also been safely used.[27]

Patients with the hyper-IgE syndrome usually have normal serum IgG, IgM, and IgA levels, but some have been reported to have various defects in antibody responses. These include poor anamnestic antibody responses to booster immunization with ΦX174, diphtheria and tetanus toxoids, and pneumococcal and *Haemophilus influenzae* vaccines, as well as poor antibody and cell-mediated responses to neoantigens, such as keyhole limpet hemocyanin.[29,30] There is significant phenotypic variation in the severity of pulmonary infections that is not necessarily predicted by deficits in antigen-specific antibody responses. Despite this, some patients with hyper-IgE syndromes with recurrent respiratory infections might benefit from IgG replacement therapy.[31,32]

Wiskott-Aldrich syndrome is another disease typically characterized by normal total IgG levels but with impaired specific antibody responses against both protein and polysaccharide antigens.[33,34] Half of the centers caring for patients with Wiskott-Aldrich syndrome treat all patients with IGIV infusions,[35] which appear to be effective in reducing the incidence of infection.[36]

Secondary immunodeficiency

IGIV has also been used in a number of diseases that result in a secondary humoral immunodeficiency. Although there are anecdotal reports of the use of IGIV in conditions that have the potential to impair humoral immunity, our discussion is limited to 3 diseases, B-cell chronic lymphocytic leukemia, pediatric HIV infection, and prematurity, the first 2 of which are FDA-approved indications for IGIV use in the United States.

IGIV administration in a dose of 0.4 g/kg per month significantly reduces the number of infections compared with placebo treatment in patients with chronic lymphocytic leukemia.[37,38] In most cases IGIV is used in patients with serum IgG levels of less than 500 mg/dL and who have experienced significant infections. Randomized double-blind trials do not discern a difference between replacement with 0.25 to 0.5 g/kg per month.[39]

Symptomatic HIV-infected children can be given replacement doses of IGIV to prevent bacterial (especially pneumococcal) infections.[40] Symptomatic HIV disease can lead to impaired specific antibody production, although these children only rarely have hypogammaglobulinemia (hypergammaglobulinemia is more frequent with symptomatic untreated disease). Placebo-controlled trials have found that IGIV treatment (0.4 g/kg every 28 days) reduces serious and minor bacterial infections, with decreased acute-care hospitalizations.[41,42] In those studies the benefit of IGIV was not seen in patients treated with trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* (formerly *carinii*)–induced pneumonia prophylaxis. It is also important to note that these studies occurred before the era of highly active antiretroviral treatment for HIV.

The use of IGIV as an adjunct to enhance the antibacterial defenses of premature newborn infants remains controversial, but several studies suggest that IGIV might diminish the incidence of sepsis.[43] This finding might be most apparent in low-birth-weight neonates.[44] Despite encouraging trials, there are substantial contradictory data and insufficient overall evidence to support the routine administration of IGIV in infants at risk for neonatal infection.[43,45]

Considerations of dosage, interval, and route of administration

After deficient antibody production has been documented, infusions are usually given every 3 to 4 weeks at an initial dose of 0.4 to 0.6 g/kg, titrating the dose and interval between infusions to achieve a trough IgG level at least greater than 500 mg/dL in agammaglobulinemic patients.[46] Many practitioners target a serum IgG level equal to the pretreatment level plus 300 mg/dL for patients with CVID. A specific maintenance of trough level greater than 500 mg/dL has been associated with fewer infections and improved outcomes.[10,18,47] Higher trough levels (>800 mg/dL) also have the potential to improve pulmonary outcome.[10,48] Monitoring preinfusion trough levels at no greater than 3-month intervals, and preferably no greater than every 6 months, might be helpful in patients who are hypogammaglobulinemic, particularly when infections are not well controlled. Because there is significant variability among patients in the pharmacokinetics of IgG, a given IGIV dose has the potential to result in different trough levels in different patients having similar body mass.[49] An acceptable starting point for maintenance dosing is 0.4 g/kg every 3 to 4 weeks. Although some clinicians measure trough IgG levels frequently, others measure serum IgG levels annually or whenever there is a significant infection and when the clinical response to treatment does not meet expectations. After the sixth infusion, a steady state will have been achieved, and the dose or dosing interval should be adjusted to achieve the optimal clinical result. Trough IgG levels should be considered in optimizing therapy for agammaglobulinemic and potentially hypogammaglobulinemic patients. Treating physicians must be mindful of patients' changing body mass (particularly children and pregnant patients), the possibility of protein-losing conditions, or both, and dose adjustments need to be made accordingly. When initiating therapy, patients with extremely low IgG levels at presentation might benefit from a larger loading dose before the initiation of regular maintenance dosing. Some centers use an initial dose of 1 g/kg administered slowly for agammaglobulinemic patients. Other centers prefer smaller doses given more frequently to initially provide agammaglobulinemic patients with adequate levels of IgG.

TABLE IV. Uses of IGIV in autoimmune diseases

	Indication	Evidence category	Recommendation
Definitely beneficial	Graves ophthalmopathy	Ib	A
	Idiopathic thrombocytopenic purpura	Ia	A
Probably beneficial	Dermatomyositis and polymyositis	IIa	B
	Autoimmune uveitis	IIa	B
Might provide benefit	Severe rheumatoid arthritis	IIb	B
	Autoimmune diabetes mellitus	IIb	B
	Posttransfusion purpura	III	C
	Vasculitides and antineutrophil antibody syndromes	III	D
	Autoimmune neutropenia	III	D
	Autoimmune hemolytic anemia	III	D
	Autoimmune hemophilia	III	D
	SLE	III	D
	Fetomaternal alloimmune thrombocytopenia	III	D
	Neonatal isoimmune hemolytic jaundice	III	D
Unlikely to be beneficial	Inclusion body myositis	IIb	B
	APS in pregnancy	III	D

When IgG production is deficient but not completely absent, such as in CVID, dosing IGIV is more complex. In this setting, IgG trough levels can be unreliable and should not be used as primary benchmarks for guiding therapy. Dose comparison studies in these types of patients have been performed, however, and a particular double-blind, multicenter crossover trial is worthy of specific mention.[50] In this study, children were randomized to receive either 0.4 g/kg or 0.8 g/kg every 4 weeks (adults in the study received 0.3 g/kg or 0.6 g/kg). The number of immunodeficiency-related infections was reduced in the high-dose IGIV group ($P < .004$), demonstrating a definitive benefit to more substantial doses. Interestingly, the IgG trough level in the low-dose group was 640 mg/dL compared with 940 mg/dL in the high-dose group, suggesting an importance in maintaining a higher trough level. Ultimately, however, a dose must be individualized and titrated to achieve clinical effect in the patient being treated.

The issue of IgG dose for patients with normal IgG levels but impaired specific antibody production is more difficult because IgG trough levels are not particularly useful. In fact committing these patients to trough-based dosing will afford them a disservice and is not advised. Several studies comparing different maintenance doses have yielded conflicting results.[51] Most studies, however, demonstrate that doses of 0.4 g/kg or greater have improved efficacy over lower doses in reducing the incidence of infection.[11,47,50,52,53]

Despite the number of studies comparing different IgG doses for primary immunodeficiency, none have directly compared different dosing intervals. Without additional data, the dosing interval should be selected according to the ability of a given regimen to maintain an adequate IgG trough level, an acceptable clinical effect, or both. If patients who are receiving IGIV every 28 days experience malaise or upper respiratory tract symptoms in the week before infusion, practitioners should consider a more frequent dosing schedule.

An additional consideration that has numerous implications is the route of administration. In the United States immunoglobulin products are licensed as therapy for primary immunodeficiency when administered through the intravenous or intramuscular routes (see ''Note added in proof'' section at the end of this article). In other countries, however, there has been significant experience with the administration of immunoglobulin through the subcutaneous route for treatment of primary immunodeficiency.[54,55] Additional discussion of the subcutaneous route of immunoglobulin administration will be given in the ''Immune globulin products, infusions, and practical considerations'' section, but retrospective case-control studies,[54] as well as open-label crossover studies,[55] have demonstrated therapeutic equivalence between the intravenous and subcutaneous routes.

AUTOIMMUNE DISEASES

Intravenous immune globulin has been used with varying efficacy in a number of systemic autoimmune diseases, as outlined in Table IV. These applications are reviewed below.

Hematologic autoimmune disease

Immune thrombocytopenic purpura. Immune thrombocytopenic purpura is a disorder that affects children and adults. Pharmacologic treatment of children with immune thrombocytopenic purpura is an actively debated issue because the vast majority of children recover spontaneously.[56-58] Regardless, treatment is usually provided for those children at the greatest risk for complications relating to bleeding or those having chronic refractory disease. Commonly used therapeutic modalities for this disorder include systemic corticosteroids, anti-D IgG, or both or IGIV.[57] This is one of the FDA-approved indications for IGIV, and the ability of IGIV to increase platelet counts in this setting is supported by numerous data.[59-62] The mechanism of action is believed to be mediated by immunomodulatory capacity exerted by Fc receptor blockade and potentially through ligation of inhibitory Fc receptors.[63] Importantly, high-dose IGIV has been compared with systemic corticosteroids in randomized multicenter trials and was found to provide a clinically relevant advantage over corticosteroids.[59,60] Thus at present, IGIV remains an important and useful treatment modality in the severe presentations of this disorder.

There are anecdotal data supporting the use of IGIV for antenatal therapy of fetomaternal alloimmune thrombocytopenia.[64] Although there are no randomized trials to support this practice, use of IGIV has become routine first-line therapy in this setting.

Posttransfusion purpura. Posttransfusion purpura is a rare and potentially fatal disorder characterized by severe thrombocytopenia developing 7 to 10 days after transfusion of platelet-containing blood components. Most cases of posttransfusion purpura are caused by alloantibodies directed against human platelet antigen 1a.[65] The standard therapy has included systemic corticosteroids, IGIV, or both. A few case reports showed benefit from combination therapy of corticosteroids with IGIV, but no controlled studies have been conducted.[65-70] Despite the lack of rigorous scientific evidence for benefit, therapy with IGIV can be considered given the potential life-threatening nature of the disease.

Autoimmune neutropenia. Clinical responses (increased neutrophil counts) have been described in several small series of patients with autoimmune neutropenia who were treated with IGIV.[71-74] It is unclear whether the beneficial effects are due to the ability of IGIV to induce neutrophil egress from the bone marrow or to prolong the survival of neutrophils. Because corticosteroids are also an effective therapy for this disorder, it is unclear whether IGIV offers any advantage over corticosteroid therapy. Anecdotal reports also suggest utility for IGIV in post–bone marrow transplantation neutropenia, which might be autoimmune in nature.[75-77]

Other autoimmune cytopenias. Multiple anecdotal reports demonstrate benefit from the use of IGIV in autoimmune hemolytic anemia,[73,78,79] but the use of IGIV should be considered only when other therapeutic modalities fail.[80] IGIV might decrease the need for exchange transfusion in neonates with isoimmune hemolytic jaundice.[81-83] However, there are methodologic flaws with these studies, and routine use in this setting is not recommended.[84]

IGIV might have some benefit when combined with other therapies for Evans syndrome, which is defined as the autoimmune destruction of at least 2 of the 3 hematopoetic lineages.[85] Other anecdotal reports have suggested a benefit for IGIV in malignancy[86,87] or lupus-associated[88,89] cytopenias as well.

Acquired hemophilia. Acquired hemophilia is a coagulopathy caused by the development of autoantibodies directed against specific domains of the coagulation Factor VIII molecule. This results in the inhibition of Factor VIII binding to its ligands in the coagulation cascade and causing systemic bleeding.[90] Treatment modalities include corticosteroids, cyclophosphamide, and cyclosporine. Patients who do not respond to immunosuppressive regimens might benefit from high-dose IGIV.[91,92] The mechanism of action could be through anti-idiotypic antibodies in the IGIV preparation.[93,94]

Autoimmune inflammatory myopathies

The pathogenesis of the inflammatory myopathies polymyositis and dermatomyositis appears to be immune mediated,[95] but the treatment remains empiric and usually includes systemic corticosteroids and immunosuppressive therapies. High-dose IGIV holds promise for selected patients with resistant disease. IGIV has reported efficacy in dermatomyositis in both controlled[96] and open-label[97] studies. In another report IGIV was added to the therapeutic regimens of 9 children with refractory juvenile dermatomyositis. Clinical improvement was seen in all, and the maintenance dose of corticosteroids could be reduced in 6.[98] In inclusion body myositis, however, a controlled trial failed to demonstrate objective improvement in those treated with IGIV.[99] Thus although IGIV might be useful in other inflammatory myopathies, generalized conclusions or recommendations are not presently possible.

Rheumatologic disease

Rheumatoid arthritis. The benefit of IGIV therapy after double-filtration plasmapheresis was evaluated in 29 patients with rheumatoid arthritis. IGIV was most effective in patients whose serum IgG levels after infusion increased to 1000 to 1800 mg/dL.[100] Case reports and open-label trials with high-dose IGIV showed some benefit for patients with rheumatoid arthritis.[101,102] In a different randomized, double-blind, placebo-controlled trial of 20 patients with refractory rheumatoid arthritis, no benefit of very low-dose (5 mg/kg per 3 weeks) IGIV was seen.[103]

Systemic lupus erythematosus. In a retrospective study of 59 patients with systemic lupus erythematosus (SLE), IGIV therapy (n = 31) resulted in clinical improvement of 65% of the patients treated, but the response was transient in each case.[104] In case reports high-dose IGIV was associated with disease resolution in patients with lupus affecting specific organs. The

reports include patients with lupus-induced nephritis,[105,106] lupus-induced myocarditis,[107] polyradiculopathy,[108] lupus-induced bone marrow suppression,[88] and lupus-induced multiorgan disease.[109] Because of this limited anecdotal experience and potential prothromboembolic effects of IGIV, caution is advised in the therapeutic application of IGIV in SLE and other autoimmune disease.[102] Furthermore, reports of IGIV-associated azotemia in SLE are an additional cause for concern.[110]

Antiphospholipid antibody syndrome. There are several reports supporting a beneficial role for IGIV in antiphospholipid antibody syndrome (APS).[111,112] Most reports focus on the use of IGIV in the obstetric complications of APS. Several patient series demonstrated that the use of IGIV resulted in successful pregnancy outcome in patients with APS with recurrent abortions. IGIV also benefited patients with APS undergoing *in vitro* fertilization.[111] However, a meta-analysis of several modes of therapy (heparin, aspirin, glucocorticosteroids, and IGIV) in this clinical setting did not support any improved outcome with IGIV and a possible association with increased pregnancy loss or prematurity.[112]

Systemic vasculitides and antineutrophil cytoplasmic autoantibody disorders. IGIV was found to be beneficial in individual cases[113] and open-label studies[114] when used as an alternative therapeutic agent in patients with antineutrophil cytoplasmic autoantibody–positive vasculitis. In the open-label trial IGIV induced a remission in 15 of 16 patients, which was only transient in 7 but was sustained in 8. In another study 10 patients with treatment-resistant systemic vasculitis were given 1 to 6 courses of a high-dose (2 g/kg) 5-day regimen of IGIV monthly, and 6 achieved remission from disease.[115] The role of IGIV in systemic sclerosis-scleroderma[116] or Still disease[117] has been anecdotally suggested but remains unclear.

Organ-specific autoimmune disease

Autoimmune diabetes mellitus. Antibodies against islet cell antigens, including glutamic acid decarboxylase II, are implicated in the autoimmune pathogenesis of insulin-dependent (type 1) diabetes mellitus. A case report of a patient with newly diagnosed type 1 diabetes treated with immunoglobulin apheresis showed a decrease in those antibodies correlated directly with a decreased requirement for insulin.[118] A review of IGIV administration to 77 subjects with newly diagnosed diabetes was summarized from 6 different studies and compared with 56 newly diagnosed diabetic case control subjects also reported in those studies.[119] In most patients no benefits were found, but 2 of the 6 studies reported decreased insulin requirements in the IGIV-treated patients. All 6 studies, however, identified subpopulations of patients who responded to IGIV therapy with a preserved C-peptide release, higher rate of remission, and longer duration of remission.[119] In contrast, a single randomized controlled trial evaluating the effect of IGIV administered every 2 months to children and adults with type 1 diabetes failed to demonstrate any benefits associated with IGIV therapy.[120]

Autoimmune Graves ophthalmopathy. A randomized trial of patients with active Graves ophthalmopathy compared systemic corticosteroids with 6 courses of IGIV at 1 g/kg body weight for 2 consecutive days every 3 weeks. Both treatment modalities were equally successful, but the side effects were more frequent and severe in the steroid-treated group.[121] In a separate case report IGIV was also noted as being superior to systemic corticosteroids in controlling Graves ophthalmopathy.[122]

Autoimmune uveitis. Birdshot retinochoroidopathy is an autoimmune posterior uveitis that frequently requires immunosuppressive therapy. An open trial with IGIV treatment for 6 months (1.6 g/kg every 4 weeks with transition to every 6-8 weeks) has shown promise.[123] Visual acuity improved in 53.8% and decreased in 7.7% of the eyes of patients during treatment. When present, macular edema improved in half of the eyes during treatment. In another trial with therapy-resistant autoimmune uveitis, clinical benefit was seen in half of the patients treated with IGIV.[124] These data suggest that IGIV therapy might be an effective alternative for patients with this disease.

Autoimmune liver disease. In one case report of a patient with autoimmune chronic active hepatitis, IGIV treatment was used with a successful outcome.[125] Specifically, liver enzymes normalized, circulating immune complexes were no longer detectable, and periportal mononuclear cell infiltrates improved after treatment.

USE OF IGIV IN ASTHMA

Asthma is a heterogeneous disease. In some patients upper or lower respiratory tract infections might trigger bronchospasm and excessive mucus production, whereas in others chronic or recurrent bronchial infections might manifest as wheezing and air trapping. Patients who fit these descriptions are occasionally found to have antibody deficiency.[126-133] In some patients with immune abnormalities and infection-associated asthma, replacement doses of IGIV might eliminate the triggering infections, reduce the frequency and severity of their pulmonary symptoms, or both. This in turn might decrease the symptoms and morbidity of asthma.[133,134]

The majority of asthmatic subjects, however, do not have a humoral immunodeficiency; rather, they have acute and chronic lower airway inflammation. Although the mainstay of treatment for this condition is low- to moderate-dose inhaled corticosteroids, severely affected individuals might require high doses of inhaled and oral steroids, which lead to unacceptable secondary effects. The potent anti-inflammatory properties of IGIV have lead to open trials of its use as an anti-inflammatory or ''steroid-sparing'' agent. An open-label trial of 2 g/kg per month IGIV in 8 steroid-dependent asthmatic children demonstrated a significant reduction in steroid dosage and improvements in peak expiratory flow rate and symptom scores. This was accompanied by a reduction in reactivity to titrated skin tests.[135] Subsequently, another open-label study from the same institution found that an identical

IGIV treatment regimen allowed significant reductions in oral steroid requirements and requirement for burst doses of oral steroids and decreased hospitalizations in 11 children. The effects of IGIV were attributed to increasing the responsiveness of patients' lymphocytes to dexamethasone and increased glucocorticoid receptor binding affinity *in vitro*.[136] Other *in vitro* studies have demonstrated a suppressive effect for IGIV on IgE production[137,138] and neutralization of inflammatory mediators that induce bronchospasm.[139] This has led to further attempts at determining the steroid-sparing effect of IGIV in asthma.

Three additional open trials of IGIV administration for severe asthma have been performed.[140-142] In the first of these, 9 of 14 IGIV-treated patients completed the trial (2 withdrew because of severe IGIV-associated headaches). Of the 9 who completed the trial, 6 had a reduction in steroid dose, and 2 more had decreased bronchial reactivity without a reduction in steroid dose. The second study evaluated the treatment of 11 patients (mean age, 14 years) and reported a significant decrease in steroid use (from 31.6 to 5.5 mg/d, $P < .0001$), increases in peak expiratory flow rate and FEV_1 percentages ($P = .01$), and improvement in overall symptom score ($P < .008$).[141] The third and most recent series included 7 highly refractory adult asthmatic subjects (mean age, 38 years), all of whom had previously been given immunosuppressive drugs, such as methotrexate or azathioprine. They were treated with 1 g/kg IGIV per month and experienced a small but statistically significant reduction in daily prednisone (from 56 ± 31 mg to 39 ± 35 mg, $P < .04$) and in the number of hospital admissions (from 5.9 ± 2.9 days to 3.6 ± 3.5 days, $P < .04$) but no significant improvement in lung function.[142] Thus open-label studies, which include a total of 56 patients, suggest that IGIV might have beneficial steroid-sparing effects in some patients with asthma.

There have been 3 double-blind, placebo-controlled studies of IGIV in asthma.[143-145] The first included 31 patients (mean age, 14 years) randomized to receive a loading dose of 2 g/kg IGIV, followed by 2 monthly doses of 1 g/kg each or the equivalent amount of albumin as a control. Although there was no difference in number of days of systemic steroid treatment, dose of inhaled steroid, pulmonary function, or symptom scores, there were fewer days with symptoms of respiratory infection in the IGIV group.[143] It should be noted that the duration of this study was only 2 months compared with most of the others, which were 6 months.

A second study had 3 arms in which 40 patients were randomized to receive either 2 g/kg IGIV per month, 1 g/kg IGIV per month, or 2 g/kg albumin per month. Oral steroid dosages were reduced in all 3 groups during the course of the study, and there were no significant differences among the groups.[144] There was a slight decrease in FEV_1 percentages in all 3 groups, with no significant differences among them. Important toxicity was observed: 3 patients in the high-dose IGIV group required hospitalization for symptoms suggestive of infusion-associated aseptic meningitis, and severe headaches were reported at a significantly higher rate in both IGIV groups ($P = .02$). These adverse effects resulted in premature termination of the study, and data were presented only for those 40 patients who completed at least 6 months of treatment.[144]

The third study evaluated 28 patients (mean age, 17.3 years) who could not be weaned off steroids during an initial treatment-optimization phase, followed by randomization to receive a loading dose of 2 g/kg IGIV, followed by 400 mg/kg every 3 weeks for 9 months. An equivalent dose and regimen of albumin was administered to control subjects as a placebo.[145] Oral steroid doses were reduced in the IGIV and albumin groups during the study period, from 10.5 to 3.5 mg/d and 9.3 to 8.8 mg/d, respectively. Although the difference between the doses at the beginning and end of the treatment phase were significant within each group, the difference between the groups was not significant. Post-hoc analysis of a subgroup of 17 patients who required high doses of oral steroids (>5.5 mg/d) in the year before participating did show a significant reduction in the dose required in those receiving IGIV. In contrast, there was no difference in the steroid dose in patients within that subgroup who received placebo. Furthermore, no differences were found in pulmonary function test results, inhaled steroid or β-agonist use, symptom score, or days lost from work or school.[145] Adverse effects were not reported.

Despite data suggesting efficacy in uncontrolled studies, 2 of 3 randomized controlled studies showed no significant effect of IGIV in asthma. A third reported a significant steroid-sparing effect in a subgroup that required relatively high daily doses of oral steroids. This existing literature therefore does not support a recommendation for the routine use of IGIV in patients with severe asthma. The efficacy in select groups and the fact that adverse effects were limiting in only one trial suggest that additional studies of IGIV in carefully defined groups of asthmatic patients with persistent requirements for high doses of systemic steroids might be of interest. It will be essential, however, that subsequent studies use randomized and controlled study designs.

IGIV IN NEUROLOGIC DISORDERS

IGIV has demonstrated some degree of effectiveness in a number of inflammatory or immune-mediated demyelinating disorders of the peripheral and central nervous systems (Table V). Mechanisms of action reflect the ability of IGIV to interfere with the activity of humoral components, such as antibody and complement, and to limit cytokine production.[146-148]

Demyelinating peripheral neuropathies

Guillain-Barré syndrome. Guillain-Barré syndrome (GBS) is a polyradiculopathy characterized by acute progressive motor weakness of the extremities, bulbar and facial musculature, and sometimes sensory or autonomic dysfunction. It is thought to result from immunologic destruction of myelin or Schwann cells within the

TABLE V. Uses of IGIV in neuroimmunologic disorders

Benefit	Disease	Evidence category	Strength of recommendation
Definitely beneficial	GBS	Ia	A
	Chronic demyelinating polyneuropathy	Ia	A
	MMN	Ia	A
Probably beneficial	LEMS	Ib	A
	IgM antimyelin-associated glycoprotein paraprotein–associated peripheral neuropathy	Ib	A
	MG	Ib-IIa	B
	Stiff-man syndrome	Ib	A
Might provide benefit	Monoclonal gammopathy MS	Ia	A
	Intractable childhood epilepsy	Ia	A
	Rasmussen syndrome	IIb	B
	Acute disseminated encephalomyelitis	III	C
	HTLV-1–associated myelopathy	III	C
	Cerebral infarctions with antiphospholipid antibodies	III	C
	Demyelinative brain stem encephalitis	III	C
	Lumbosacral or brachial plexitis	III	C
	Paraproteinemic neuropathy	III	C
	Opsoclonus myoclonus	III	C
	Postinfectious cerebellar ataxia	III	D
	Acute idiopathic dysautonomia	III	D
Unlikely to be beneficial	Demyelinating neuropathy associated with monoclonal IgM	Ib	A
	Adrenoleukodystrophy	Ib	A
	Amyotrophic lateral sclerosis	III	C
	POEMS syndrome	III	C
	Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy	III	C

HTLV-1, Human T-cell lymphotrophic virus 1; *POEMS*, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

peripheral nervous system. Therefore it is commonly treated with corticosteroids, plasma exchange (PE), and IGIV. Data from the first large, randomized, open controlled trial of IGIV (0.4 g/kg day for 5 days) versus PE suggested that the clinical outcomes were at least comparable.[149] A more recent multicenter, randomized, controlled, blinded trial involving 383 patients from Europe, Australia, and North America revealed no significant differences in the mean disability grade of patients treated with PE, IGIV, or PE followed by IGIV.[150] The addition of methylprednisolone (0.5 g/d for 5 days) after a course of IGIV did not show a significant benefit in a multicenter, randomized, double-blind, placebo-controlled study of 233 patients.[151] Several other studies that have compared IGIV with supportive measures or PE in children[152] or adults[153,154] showed similar findings, but patients were not always randomized, and investigators were not blinded to the treatments.[155-159] IGIV is thus considered equivalent to PE in the treatment of GBS but is used more frequently because of reduced availability of PE, vascular access, and safety issues, particularly in children or patients with autonomic instability.

Chronic inflammatory demyelinating polyneuropathy. Chronic inflammatory demyelinating polyneuropathy is characterized by progressive symmetric weakness, sensory loss, and areflexia. Contrary to the acute nature of GBS, signs of progression occur over months, with immunologic damage targeting the myelin sheaths of the peripheral nerves.[147,160] It has been traditionally treated with corticosteroids, PE, or, in more resistant cases, cytotoxic immunosuppressant drugs. Rigorously controlled randomized trials showed that IGIV improved disability within 2 to 6 weeks compared with placebo and had similar efficacy to PE and prednisolone, although with

increased quality of life.[161-165] The standard dose is 0.4 g/kg per day for 5 days, but this dose might need to be repeated in some patients every 2 to 8 weeks to maintain improvement.[166] IGIV is considered the preferred treatment for chronic inflammatory demyelinating polyneuropathy, particularly in children, in patients whose poor venous access precludes the use of PE, and in those susceptible to the complications of long-term corticosteroid therapy.[147] A meta-analysis comparing the efficacy of IGIV, PE, and oral glucocorticosteroids found equivalence between all 3, at least within the first 6 weeks of therapy.[167]

Multifocal motor neuropathy. Several randomized, double-blind, placebo-controlled, crossover clinical trials have shown IGIV to provide efficacy in treating multifocal motor neuropathy (MMN), a chronic inflammatory condition that selectively affects the motor nerves (especially the radial, ulnar, median, and common peroneal nerves).[168] By using a dose of 0.4 to 0.5 g/kg per day for 5 consecutive days, more than 80% of patients reported improvement, as assessed on the basis of self-evaluation scores. IGIV had no consistent effect on IgM anti-GM1 antibody titers nor was it invariably accompanied by improvement of motor conduction block or Medical Research Council scores.[169-172] A follow-up study of 11 patients with MMN for 4 to 8 years demonstrated a long-term beneficial effect of maintenance IGIV therapy on muscle strength and upper limb disability. IGIV influenced remyelination or reinnervation, but axon loss could not be prevented.[173] Considering that MMN is unresponsive to PE therapy and might even be exacerbated by corticosteroids, IGIV might be the safest treatment, alone or in combination with cytotoxic immunosuppressant drugs.[147,174]

IgM antimyelin-associated glycoprotein paraprotein–associated peripheral neuropathy. One randomized controlled trial has demonstrated significant clinical benefit for high-dose (2 g/kg) IGIV therapy for this disorder.[175]

Neuromuscular junction syndromes

IGIV therapy has been evaluated in myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS). The benefit in MG (0.4 g/kg per day for 3-5 days) was comparable with that of PE in 2 randomized comparative studies, with a decrease in titer of acetylcholine receptor antibody in one study[176] and the quantified MG clinical score in another.[177] Patient tolerance of IGIV was generally better than that of PE. A third randomized placebo-controlled study failed to demonstrate a significant effect after 6 weeks.[178] IGIV was considered of possible benefit in myasthenic crises[179] and juvenile myasthenia[180] and in preparing myasthenic patients for surgery.[181,182] These studies, however, were not blinded, and the groups were not necessarily equivalent. Furthermore, because the optimum dosage is not established and the need for maintenance is not well identified, more rigorous clinical trials are needed before recommending the routine use of IGIV in MG.

LEMS is identified by decreased or absent reflexes, frequent autonomic changes, incremental responses on repetitive nerve stimulation, and the presence of antibodies to the presynaptic calcium channels at the motor end plates. In a randomized, double-blind, placebo-controlled crossover trial, 8 of 9 patients exhibited clinical improvement within 2 to 4 weeks of IGIV infusion (1 g/kg per day for 2 consecutive days), although it decreased after 8 weeks, correlating with a rebound of serum calcium-channel antibody titers.[183] A similar response and lack of serious adverse effects have been reported in additional case reports and uncontrolled trials.[184-186] IGIV might thus be used as an alternative treatment in patients who do not respond to or tolerate other treatments of LEMS.

Multiple sclerosis

At least 3 randomized, double-blind, placebo-controlled studies[187-189] demonstrate some benefit of IGIV treatment in reducing exacerbations of multiple sclerosis (MS). Combining the data from these studies showed that 34% of IGIV recipients had reduced exacerbations versus 15% of placebo recipients. The largest study (148 patients) revealed that IGIV (0.15-0.2 g/kg monthly for 2 years) was associated with reduced clinical disability.[187] When larger doses were tried (1 g/kg per day for 2 days at 4-week intervals), 65% (of 25 patients) had no exacerbations in 6 months versus 35% of the control group.[188] The mechanism of action has been proposed to occur through promotion of remyelination, as well as anti-inflammatory and macrophage inhibitory effects.[190] Although reduction in the number and volume of gadolinium-enhanced magnetic resonance imaging (MRI) lesions was reported,[191] this finding was insignificant in another 2-year follow-up study.[189] A meta-analysis of 265 patients revealed significant reduction in the disability score (Expanded Disability Status Scale), annual relapse rate, proportion of patients who deteriorated, and new MRI lesions.[190] IGIV does not seem to be of any benefit in ameliorating chronic visual symptoms or established weakness and has not shown a significant effect on the course of illness in secondary progressive MS.[192] Thus IGIV should be considered a potentially effective second-line treatment in relapsing-remitting MS, but the optimal dosage still needs to be established. In addition, more studies with MRI scores for efficacy assessment are needed.[192,193]

Other neurologic syndromes

There is some evidence that an aberrant immune response is involved in the pathogenesis of some forms of intractable childhood epilepsy, including the Lennox-Gastaut syndrome, West syndrome, and early myoclonic encephalopathy. The available data regarding a benefit for IGIV treatment comes mostly from uncontrolled open series or case reports.[194-197] However, there are 2 randomized placebo-controlled trials that have been performed for Lennox-Gastaut syndrome. One was a small (n = 10) single-blind crossover study.[198] Two doses of IGIV at 0.4 g/kg or placebo were given with an interval of 2 weeks. Two of the children noted a reduction of their seizures of 42% and 100%. The other 8 children showed no change over an observation period of 14 weeks. The other study

was double-blind and found that IGIV therapy (0.1-0.4 g/kg per day for 4 days then once in the second, third, and sixth weeks ± the sixth month) reduced clinical seizure frequency by half in 52% of the recipients (n = 40) compared with 28% of the placebo recipients (n = 18).[199] In Rasmussen syndrome (focal seizures, progressive neurologic and intellectual deterioration, chronic encephalitis, and hemispheric atrophy), the possible role of serum antibodies against the glutamate receptor GluR3 supports an immune component in the pathogenesis and provides a rational basis for immunomodulatory treatment in resistant cases. The use of IGIV has produced encouraging results in childhood, as well as in adult-onset, disease.[200,201] It has led to reduction in seizure frequency in 8 of 9 recipients compared with that seen in 10 of 17 high-dose steroid recipients in a retrospective case series.[202] Because of the paucity of reliable studies that demonstrate substantial efficacy of IGIV in these syndromes, its routine use cannot be recommended. However, the poor prognosis and quality of life of children whose symptoms do not improve with antiepileptic drugs and corticosteroids would justify a trial of IGIV therapy, especially in patients who are otherwise candidates for surgical resection.

Abundant case reports and smaller trials document variable clinical successes of IGIV therapy in other neuroimmunologic disorders and have been reviewed.[147,203] Examples of positive reports include those describing IGIV treatment of patients with acute disseminated encephalomyelitis,[204] demyelinative brain stem encephalitis,[205] or subacute rhombencephalitis optica.[206] An example of a report in a disease in which IGIV was ineffective or even had negative effects was IgM monoclonal gammopathy.[207] The evidence categories and recommendation levels regarding these diseases are summarized in Table V.

TRANSPLANTATION

IGIV has been used for more than 2 decades as part of the supportive treatment of bone marrow transplant recipients and is approved by the FDA for this indication.[208] There is also emerging evidence that IGIV might have utility in the treatment of certain complications of solid organ, most notably renal, transplantation.

Transplantation-related infection

Part of the rationale for using IGIV in the setting of transplantation is that the provision of passive antibody might prevent infections in these iatrogenically immunocompromised patients, particularly infections caused by cytomegalovirus (CMV).[209] IGIV reduced the incidence of CMV infection and interstitial pneumonia in allogeneic bone marrow transplant recipients in the era before ganciclovir.[209] Subsequent studies suggest that a combination of high-dose IGIV and ganciclovir is better than either alone for the treatment of interstitial pneumonitis.[210,211] The development of hyperimmune anti-CMV IGIV preparations provides an alternative to polyclonal IGIV preparations; however, anti-CMV IGIV alone did not prevent CMV-induced viremia or interstitial pneumonitis or deaths at 1 year in a series of seropositive lung transplant recipients.[212] This is unfortunate, considering the increasing incidence of ganciclovir-resistant CMV in some bone marrow and organ transplant centers.

IGIV is believed to decrease the high mortality rate of respiratory syncytial virus (RSV) pneumonia after allogeneic bone marrow transplantation. RSV immune globulin had historically been used for this purpose because it contains high titers of antibodies to several respiratory viruses, including RSV, parainfluenza 3, and the influenza viruses. A non–placebo-controlled study showed that RSV immune globulin significantly increased antiviral titers in patients undergoing transplantation but did not show efficacy in preventing RSV infections because of the low incidence of these infections in the study population.[213] The recent discontinuation of RSV immune globulin manufacturing, however, obviates the need for further debate over the use of RSV immune globulin versus IGIV.

Although the above-cited reports have supported the use of IGIV for infection control in bone marrow transplant recipients, there are doubts regarding efficacy. Two recent large meta-analyses demonstrated divergent conclusions, with one supporting its use and the other not.[214,215] None of the trials reviewed were placebo controlled, and most were carried out before effective drugs for CMV infection were available. No benefit was seen for IGIV infusions in the prevention of late infections after bone marrow transplantation in a nonimmunodeficient patient population.[216] In a small randomized trial the combination of ganciclovir and IGIV might have provided some benefit in preventing CMV-induced disease, but results were not statistically significant.[217]

Graft-versus-host disease

IGIV might exert an immunomodulatory effect, lessening the occurrence and severity of acute graft-versus-host disease (GVHD).[218] This is not the case for chronic GVHD.[216] Intact IgG molecules and $F(ab)_2$ fragments of IgG protect against acute GVHD in a rat model of the disease.[219] Protection was associated with decreased lymphocyte proliferation and decreased nitrous oxide and IFN-γ production *in vitro* in the absence of increased production of IL-10. A recent US multicenter, randomized, double-blind comparison of 3 different doses of IGIV (0.1, 0.25, and 0.5 g/kg), however, showed no differences in the rates of acute or chronic GVHD or infection after unrelated allogeneic bone marrow transplantation.[208] There was less GVHD in patients with unrelated marrow donors who were treated with the higher dose, but the difference was not statistically significant ($P < .07$). The first randomized, double-blind, dose-effect, placebo-controlled, multicenter trial of IGIV in related allogeneic marrow transplantation was recently reported. The 200 patients studied were from 19 different centers; all received HLA-identical sibling marrow. Surprisingly, IGIV-treated patients experienced no benefit over those receiving

TABLE VI. Uses of IGIV in infectious and infection-related diseases

	Indication	Evidence category	Recommendation
Definitely beneficial	Kawasaki disease	Ia	A
	CMV-induced pneumonitis in solid organ transplants	Ib	A
Probably beneficial	Neonatal sepsis	Ia	A
	Rotaviral enterocolitis	Ib	A
	Bacterial infections in lymphoproliferative diseases	Ib	B
	Staphylococcal toxic shock	III	C
	Enteroviral meningoencephalitis	III	C
Might provide benefit	Postoperative sepsis	III	C
	RSV lower respiratory tract infection	III	C
	Pseudomembranous colitis	III	C
	Campylobacter species–induced enteritis	III	C
Unlikely to be beneficial	Chronic fatigue syndrome	Ib	A
	Acute rheumatic fever	IIa	B
	Viral load in HIV infection	IIb	B

placebo in terms of incidence of infection,[220] interstitial pneumonia, GVHD, transplantation-related mortality, or overall survival. There was a statistically higher incidence of grade 3 (severe) veno-occlusive disease associated with high-dose IGIV, and patients given higher doses of IGIV had more side effects, such as fever and chills. The data provide no basis to recommend IGIV for HLA-identical sibling bone marrow transplants.[220]

There is a clear perceived benefit in the administration to infants with severe combined immunodeficiency disease and to those with other primary immunodeficiency diseases who are undergoing bone marrow transplantation. The effect of IGIV in these children, however, is difficult to study because they are generally receiving IGIV for their primary diagnosis. Routine use of IGIV appears to offer little benefit to patients with malignancies undergoing HLA-identical sibling bone marrow transplants. Moreover, high doses of IGIV might increase the risk of severe veno-occlusive disease in some patients. More studies are needed to determine whether IGIV is beneficial in the case of HLA-matched unrelated donor bone marrow or cord blood transplants.

Solid organ transplantation

There appears to be a role for the use of IGIV in solid organ transplant recipients who experience acute humoral rejection. Encouraging results have been obtained with plasmapheresis followed by IGIV administration in patients who are presensitized (having reactive antibodies), who are in the midst of an acute antibody-mediated kidney rejection, or both.[221-225] These studies included randomized controlled trials, but the numbers of patients evaluated in this manner are not yet large enough to justify a generalized indication for treatment. Economic analyses, however, have demonstrated that the use of IGIV in these settings might be financially advantageous, and therefore broader application warrants consideration.[226]

IGIV might also be useful in solid organ transplant recipients who experience autoimmune cytopenias after transplantation, but currently available evidence is limited to case reports and retrospective analyses.[227]

USES OF IGIV IN INFECTIOUS AND INFECTION-RELATED DISEASES

Despite improvements in antimicrobial therapies, there are a large number of pathogens that remain difficult to control and others for which no specific chemotherapy exists. Thus polyclonal IGIV continues to be used in the treatment of a variety of infectious diseases and infection-related disorders (Table VI). Although there is significant anecdotal experience in a number of settings, the cumulative evidence, along with the cost-effectiveness and risk of complications, must be considered when using IGIV to treat infection. Of the conditions described in this section, only KD is an FDA-approved indication for IGIV.

Kawasaki disease

KD is an acute febrile childhood vasculitis of medium-sized vessels commonly affecting the coronary arteries. The cause of illness remains unknown, but several clinical, laboratory, and epidemiologic features strongly support an infectious or postinfectious origin.[228] IGIV in conjunction with aspirin is the standard of care for children during the first 10 days of the syndrome to prevent the development

of coronary aneurysms.[229] Limited evidence suggests that treatment by the fifth day of illness might be associated with even better outcomes,[230] but these data have been challenged.[231] All patients should be given a single dose of IGIV (2 g/kg) as soon as the diagnosis is established.[232] Reductions in fever, neutrophil counts, and acute-phase reactants typically occur within 24 hours after treatment. Although alternative IGIV regimens have been described, including 4 daily infusions (0.4 g/kg), they are less efficacious, as demonstrated in a prospective multicenter trial.[232] The frequency of coronary artery abnormalities and duration of fever were significantly greater with the multidose regimen. A meta-analysis of randomized controlled trials of IGIV in KD also supported the use of a single 2 g/kg dose of IGIV and found that this regimen resulted in a significant decrease in new coronary artery abnormalities 30 days after diagnosis.[233] There were no distinctions among different IGIV products. Another meta-analysis including more than 3400 patients also demonstrated that a single high dose of IGIV was superior to other IGIV regimens in preventing coronary aneurysms.[234] This analysis also found that low-dose aspirin ($\leq$80 mg/kg) was comparable with high-dose aspirin (>80 mg/kg) in preventing coronary aneurysms when combined with high-dose IGIV. Although the exact mechanism of action of IGIV in KD is not clear, it could involve neutralization of bacterial superantigen toxins that lead to vascular endothelial inflammation and damage that have been associated with KD.[235,236] Other proposed mechanisms include anti-idiotype inhibition of antiendothelial antibodies, effects on the cytokine milieu, inhibition of vascular endothelial activation, and inhibition of complement-mediated tissue damage.[237,238]

HIV infection

Although IGIV is efficacious and approved for reducing the incidence of secondary infection in HIV-infected children (discussed above),[40] its use in treating HIV infection per se has not been as widely evaluated. A single study that examined the effect of a 2 g/kg IGIV dose on viral load found that p24 antigen levels and numbers of HIV RNA copies were significantly increased after treatment.[239] Thus IGIV might be useful for preventing bacterial infections but should not be considered an antiviral therapy in the HIV-infected patient.

Sepsis, septic shock, and toxic shock syndromes

Adjuvant treatment of bacterial sepsis or septic shock with IGIV was reported to significantly reduce mortality, as demonstrated by a meta-analysis of 8 trials including 492 patients.[240] Likely beneficial mechanisms of IGIV include improvement of serum bactericidal activity caused by neutralizing and opsonizing IgG and IgM antibodies, as well as stimulation of phagocytosis and neutralization of bacterial toxins.[72] IGIV might also suppress proinflammatory cytokine release from endotoxin- or superantigen-activated blood cells.[241] There might be a benefit to IgM-containing IGIV preparations in these settings[240] because IgM can better use and activate complement, but these preparations are not available in the United States. Specific uses for which IGIV preparations have been evaluated and might be useful include group B streptococcal disease in newborns,[242] streptococcal toxic shock and invasive streptococcal syndromes,[243-247] postoperative sepsis,[248] trauma-associated sepsis,[249] and neonatal sepsis.[250] Of these, neonatal sepsis has been the most extensively evaluated, and a meta-analysis of trials found a 6-fold decrease in mortality when IGIV was added to conventional therapies.[250] This benefit was far greater that that derived from the prophylactic use of IGIV in preventing neonatal sepsis. The use of IGIV in treating streptococcal toxic shock has also been more rigorously evaluated and provides an odds ratio for survival of 8:1, which was demonstrated in a case-control series.[243] Thus polyclonal IGIV might represent a promising adjuvant in the treatment of neonatal sepsis and infections with toxin-producing bacteria. However, indications for IGIV therapy in this setting require more precise definition. For example, one study found no improvement in outcome when IGIV therapy was initiated early for suspected sepsis before obtaining results of cultures.[251]

Organ-specific infections

Pneumonia-pneumonitis. Treatment of pneumonitis caused by CMV has been reported in several small series of immunodeficient patients using high-dose IGIV[210,211] or high-titer anti-CMV polyclonal IGIV (CMV-IGIV).[252] High-dose IGIV combined with ganciclovir improved survival of patients, whereas either treatment alone did not.[210] Similarly, the combination of CMV-IGIV with ganciclovir resulted in better survival in treatment of CMV-induced pneumonitis than would be expected from other treatment regimens.[252]

The treatment of RSV-induced pneumonitis in a small series of immunodeficient patients has also been reported with IGIV[253,254] or high-titer anti-RSV polyclonal IGIV (RSV-IGIV)[255] combined with ribavirin. Survival rates in these series compared with those expected on the basis of historical cohorts were encouraging and suggest that IGIV or RSV-IGIV might be of benefit as an adjunct therapy to ribavirin.

RSV-IGIV has been extensively studied as a prophylactic agent for prevention of acute RSV infection in populations considered to be at high risk of serious morbidity or mortality, including prematurity with or without bronchopulmonary dysplasia and congenital heart disease. A meta-analysis of these studies indicated the effectiveness of RSV-IGIV for the prevention of hospital and intensive care unit admission, although there was a nonstatistically significant trend toward increased mortality in the treated infants.[256] The need for this hyperimmune IGIV preparation, however, has been reduced by the advent of palivizumab, an mAb therapy specific for RSV.

The anecdotal use of IGIV as adjunct therapy of varicella pneumonia[257] or adenoviral pneumonitis[258] has also been described. Although there are encouraging

animal data regarding the use of topically applied IGIV in the treatment of bacterial pneumonia,[259,260] there are no human data that suggest IGIV is of any benefit in the treatment of established bacterial pneumonia.

Infectious gastroenterocolitis and diarrhea. Orally administered IGIV was evaluated in a double-blind, placebo-controlled study in 98 children with acute rotaviral gastroenteritis. A single dose of 0.3 g/kg was found to significantly reduce the duration of diarrhea, viral shedding, and hospitalization.[261] The benefit of orally administered IGIV in immunodeficient patients with rotavirus or those with otherwise prolonged diarrhea has been presented anecdotally but has not been rigorously evaluated.[262-265] The value of immunoglobulin therapy has also been anecdotally described in *Campylobacter jejuni* infection (administered orally)[266] and in pseudomembranous colitis caused by *Clostridium difficle* (administered intravenously).[267,268] IGIV (administered intravenously) is probably not an effective adjunct therapy in the treatment of gastrointestinal disease caused by CMV in immunosuppressed patients.[269]

Enteroviral meningoencephalitis. Meningoencephalitis caused by enteroviral infection has been a particularly feared complication in patients with agammaglobulinemia and can occur despite IGIV therapy. Two methods for treating enteroviral meningoencephalitis in small numbers of patients with agammaglobulinemia using IGIV have been described: daily or frequent high-dose intravenous administration and intrathecal administration.[270-277] Relapses after either treatment are common,[272,273,276,277] and treatment failures do occur,[274] but the latter approach has been associated with long-term eradication of enterovirus in several patients.[270,275] Although antienteroviral drugs are under development,[278] their anecdotal utility in this particular setting has been variable,[275,279] and IGIV remains a therapeutic option in this rare but desperate clinical scenario.

Erythrovirus-associated syndromes. Several case reports describe the successful use of IGIV in the treatment of anemia caused by chronic erythrovirus (formerly parvovirus) B-19 infection.[280-282] IGIV therapy was also shown to clear viremia and improve symptoms and cytokine dysregulation in the erythrovirus B-19–associated chronic fatigue syndrome.[283] Because this viral infection is prevalent in the general population, IGIV contains a significant antierythrovirus titer and was considered the only specific treatment for infection.

Carditis in rheumatic fever. A single randomized trial did not demonstrate benefit of IGIV for the prevention of cardiac sequelae of acute rheumatic fever.[284]

MISCELLANEOUS USES

IGIV has been evaluated in a number of other conditions that have been proposed to result from an aberrant immunologic response (Table VII). Some of the reports are purely anecdotal, but others have been well designed and make a definitive statement regarding the use of IGIV in these conditions. Many of these diseases have few or no therapeutic alternatives and warrant consideration of IGIV therapy on the basis of the available evidence.

Dermatologic disorders

Toxic epidermal necrolysis and Stevens-Johnson syndrome. Toxic epidermal necrolysis and Stevens-Johnson syndrome are potentially fatal disorders. Sporadic case reports, as well as prospective and retrospective multicenter studies, showed that early administration of high-dose IGIV helps to resolve the disease and reduce fatality,[285] but conflicting reports exist.[286] The majority of evidence, however, supports the use of high-dose IGIV as an early therapeutic intervention given the risk of mortality.[287] To this end, a potential immunologic mechanism for IGIV action in these disorders has been proposed to involve the blockade of CD95, promoting cell survival.[288]

Autoimmune blistering diseases. Autoimmune blistering disorders of the skin include a number of distinct entities. Pemphigoid is an autoimmune, vesiculobullous, erosive disease that can affect the mucosa. Treatment regimens include prolonged courses of immunosuppressive therapies. An estimated 25% of patients with bullous pemphigoid do not respond to standard treatment.[289] Pemphigus is a group of autoimmune blistering diseases that involve the skin and mucous membranes. The pathognomonic feature of these is acantholysis, which likely results from an autoimmune response to desmoglein. Conventional therapy of pemphigus is immune suppression,[290] although not all patients respond.

Open uncontrolled trials in which IGIV was used as a last resort for the treatment of bullous pemphigoid showed some benefit.[289,291-293] IGIV therapy was also found to provide therapeutic benefit for both pemphigus foliaceus[294] and pemphigus vulgaris.[295,296] Other autoimmune blistering diseases reported to benefit from IGIV therapy are epidermolysis bullosa acquisita and linear IgA disease.[297] All the publications related to the subject are prospective open-label studies or case reports. No controlled studies have yet been conducted to substantiate its benefits compared with other therapeutic modalities. IGIV therapy should be considered only as a last resort in the treatment of patients with this category of disorders. Guidelines for IGIV treatment in this setting were outlined in a consensus statement published for the consensus development group of the American Academy of Dermatology.[298] Additional studies, however, are still needed.

Chronic urticaria. Chronic urticaria is a disorder that is often difficult to treat. One third of patients with chronic urticaria appear to have an autoimmune disease.[299-301] A single report of 5 patients with CVID with chronic urticaria documents amelioration of the urticaria in response to IGIV therapy.[302] Delayed-pressure urticaria is a variant of chronic urticaria that is also difficult to treat. In one report[303] 9 of 10 patients with chronic urticaria were reported to benefit from IGIV therapy, and in another[304] no benefit was observed. The use of IGIV in patients with delayed-pressure urticaria was conducted as an

TABLE VII. Miscellaneous uses of IGIV

	Indication	Evidence category	Recommendation
Definitely beneficial	None		
Probably beneficial	Toxic epidermal necrolysis and Stevens-Johnson syndrome	IIa	B
Might provide benefit	Severe, persistent, high-dose, steroid-dependent asthma	Ib	A
	Prevention of infection and acute GVHD after bone marrow transplantation	Ib	A
	Prevention of acute humoral rejection in renal transplantation	Ib	A
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	IIb	B
	Delayed-pressure urticaria	IIb	B
	Treatment of acute humoral rejection in renal transplantation	III	C
	Autoimmune blistering skin diseases and manifestation of systemic diseases	III	C
	Chronic urticaria	III	C
	Autoimmune liver disease	III	D
	Acute myocarditis	III	C
Unlikely to be beneficial	Prevention of spontaneous recurrent abortions	Ia	A
	Non–steroid-dependent asthma	Ib	A
	Dilated Cardiomyopathy	Ib	A
	Chronic fatigue syndrome	Ib	A
	Prevention of chronic GVHD after bone marrow transplantation	Ib	A
	Atopic dermatitis	IIa	B
	Autistic disorders	III	C

open trial; one third of the enrolled patients underwent a remission, another third experienced some benefit, and the rest did not respond.[305] Because there is not clear evidence that the use of IGIV benefits patients with chronic urticaria, additional studies are needed. Patients with pressure urticaria who fail other therapeutic modalities, however, might benefit from high-dose IGIV.

Atopic dermatitis. A small percentage of patients with atopic dermatitis fail standard therapeutic intervention regimens. IGIV treatment has been tried in those patients and had success in small, open uncontrolled trials.[306-308] A single small, randomized, evaluator-blinded trial (n = 10) did not support the routine use of IGIV in patients with atopic dermatitis.[309]

Other skin diseases. There is only a single case report of benefit from IGIV therapy for psoriasis.[310]

Recurrent spontaneous abortion

The underlying cause of recurrent miscarriage in some cases might be immune mediated. Prospective studies[311,312] have suggested that the use of IGIV in pregnant women with a history of recurrent abortions imparted a protective benefit. Other studies suggested no benefit.[313] To address this potential benefit, the publications reporting a number of high-quality randomized, placebo-controlled, multicenter studies were reviewed, and these found that IGIV did not provide benefit.[314] This indication, however, remains very controversial because of the existing studies that claim benefits in combination with the paucity of effective therapies available to patients affected by recurrent spontaneous abortion. Given the review of randomized trials,[314] however, cumulative current evidence does not presently support the widespread use of IGIV for the prevention of recurrent spontaneous abortions.

Neurocognitive disorders

Autism. Autistic children reportedly can have mild abnormalities in their immune systems, suggesting immunologic involvement in the pathophysiology of the disease. Increased immunoglobulin levels[315] and autoimmune antibodies against neural antigens[316] might be found in subsets of these patients. There are no formal randomized studies to evaluate the use of IGIV in autism. Two reports of open trials including a total of 15 autistic children placed on IGIV for 6 months showed no benefit from the infusions.[317,318]

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Streptococcal infections induce exacerbation of symptoms in some children with obsessive-compulsive and tic disorders,[319] possibly on an autoimmune basis. The syndrome of pediatric autoimmune neuropsychiatric disorders associated

TABLE VIII. Practical considerations in the use of IGIV

	Indication	Evidence category	Recommendation
Definitely beneficial	Subcutaneous therapy can reduce the occurrence of systemic adverse events in selected patients.	IIa	B
	Maintenance of IgG trough levels >500 in hypogammaglobulinemic patients reduces infectious consequences.	IIb	B
	Expert monitoring of patients receiving IGIV infusions to facilitate management of adverse events	IV	D
Probably beneficial	Providing home-based IGIV therapy for patients who are at low risk for adverse events can improve patient quality of life.	IIa	B
	Use of a low IgA content IGIV product for IgA-deficient patients having IgG–anti-IgA antibodies	III	C
	Product changes might improve adverse event profiles.	IV	D
	Premedication can improve mild adverse events.	IV	D
	Matching particular IGIV products to specific patient characteristics to reduce adverse events	IV	D
	Stopping infusion or slowing infusion rate to facilitate management of adverse events	IV	D
Might provide benefit	Subcutaneous therapy can improve quality of life for patients receiving IGIV intravenously.	III	C
	Maintenance of IgG trough >800 in hypogammaglobulinemic patients reduces infectious consequences.	III	D
Unlikely to be beneficial	Placement of indwelling catheters or ports for IGIV administration	IV	D
	Making IGIV dosing and treatment decisions for antibody replacement therapy in primary immunodeficiency solely upon IgG trough levels	IV	D
	Routinely testing IgG trough levels more frequently than every 6 months	IV	D

with streptococcal infection is referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.[320] Those children who do not have the autoimmune feature do not benefit from IGIV.[321] Only one case-controlled study showed benefit from plasmapharesis and IGIV therapy (one dose only).[322] Additional double-blind, placebo-controlled studies are needed before this becomes a standard of therapy.

Chronic fatigue syndrome. Chronic fatigue syndrome is a clinically defined disorder that has often been associated with mild immune dysfunction. There have been numerous anecdotal reports of IGIV use having subjective benefits; however, IGIV is not effective in the treatment of typical chronic fatigue syndrome, as demonstrated in a double-blind, placebo-controlled trial.[323]

Other organ-specific disease

Cystic fibrosis. Randomized controlled trials comparing the benefit of IGIV with that of placebo showed no added benefit for the use of IGIV.[324] Patients with cystic fibrosis and normal immune systems do not benefit from the addition of IGIV to therapy. Between 2% and 10% of patients with cystic fibrosis have hypogammaglobulinemia.[325] Some studies do not suggest any associated additional morbidity because of this,[325] whereas some anecdotal reports indicate benefit of IGIV in cystic fibrosis with hypogammaglobulinemia.[326,327] This question has not been subjected to a randomized trial.

Acute myocarditis and dilated cardiomyopathy. Treatment for acute myocarditis and dilated cardiomyopathy is not readily available. Case reports suggest that patients with acute myocarditis benefit from high-dose IGIV.[328-331] Placebo-controlled trials evaluating the benefit of IGIV use in recent-onset cardiomyopathy showed no benefit over placebo.[332] High-dose IGIV might provide help to patients with acute myocarditis but has no therapeutic role in recent-onset dilated cardiomyopathy.

IMMUNE GLOBULIN PRODUCTS, INFUSIONS, AND PRACTICAL CONSIDERATIONS

A number of practical considerations in the use of IGIV (Table VIII) are central in facilitating patient therapy and improving the life experience of patients receiving IGIV.

TABLE IX. Currently available IGIV products and their properties

Product	Dosage form	Diluent	Refrigeration	Filter required	Osmolality (mOsm/L)
Carimune NF	Lyophilized powder	0.9% Sodium chloride	No	No	498 (3%) 690 (6%) 1074 (12%)
Carimune NF	Lyophilized powder	Sterile water for injection	No	No	192 (3%) 384 (6%) 576 (9%) 768 (12%)
Flebogamma	5% Liquid	NA	No‡	Optional	240-350
Gamimune N 10%*	10% Liquid	NA incompatible with saline	Yes	No	274
Gammagard 5% S/D	Lyophilized powder	Sterile water for injection	No	Yes	636 (5%)
Gammagard 10% S/D	Lyophilized powder	Sterile water for injection	No	Yes	1250 (10%)
Gammagard liquid	10% Liquid	NA	No	No	240-300
Gammar-P	Lyophilized powder	Sterile water for injection	No	No	309 (5%) 600 (10%)
Gamunex	10% Liquid	NA incompatible with saline	No†	No	258
Iveegam EN†	Lyophilized powder	Sterile water for injection	Yes	Yes	≥240
Octagam	5% liquid	NA	No‡	No	310-380
Panglobulin NF	Lyophilized powder	(0.9% sodium chloride, 5% dextrose,) Sterile water for injection	No	No	With water: 192 (3%)* 384 (6%)* 576 (9%)* 768 (12%)*
Polygam S/D	Lyophilized powder	Sterile water for injection	No	Yes	636 (5%) 1250 (10%)

For specifics of each indication, please see the text and the manufacturer's product information.
PI, Primary immunodeficiency; *ITP*, immune thrombocytopenic purpura; *NA*, not applicable; *BMT*, bone marrow transplantation; *HIV*, pediatric HIV infection; *CLL*, B-cell chronic lymphocytic leukemia.
*Gamimune N has been discontinued but might still be offered by suppliers because inventories might still exist.
†Iveegam EN is currently only available for patients who have been maintained on this product.
‡Not required.
§FDA-licensed indications for the specific product.

The safe and effective use of IGIV requires attention to numerous issues that relate to both the product and the patient. The safe and effective administration of IGIV and the diagnosis and management of adverse events are complex and demand expert practice. It is critical for the prescribing physician to carefully assess and monitor patients receiving IGIV so that treatment can be optimized.

Products

There are currently a number of products that provide chemically unmodified lyophilized powders or liquid concentrates of polyclonal IgG (Table IX), and additional products will be licensed in the next several years. These products are produced from plasma recovered from whole blood donations or more commonly from a large number of paid plasmapheresis donors. The number of donors contributing to a pool that will be processed to yield IGIV has been recommended by the FDA (Center for Biologics Evaluation and Research) and Plasma Protein Therapeutics Association to be greater than 15,000 but not to exceed 60,000 donors. As for all blood products, tests for hepatitis B surface antigen, HIV-p24 antigen, and antibodies to syphilis, HIV-1, HIV-2, and hepatitis C are conducted. The plasma is separated by using alcohol-based fractionation procedures to precipitate the immunoglobulin-containing fraction and treated with solvent, detergent, caprylate, acid, or pepsin to inactivate any residual pathogens. The resulting intravenous solutions contain sodium in various amounts, as well as stabilizing agents, such as albumin, glycine, polyethylene glycol, D-mannitol, D-sorbitol, sucrose, glucose, or maltose, to prevent aggregation of IgG molecules. IGIV is supplied in lyophilized powder or as a premixed solution, with final concentrations of IgG of 3%, 5%, 6%, 10%, or 12% depending on the product. The final osmolarity of the reconstituted IgG solutions ranges from 253 mOsm/L for a 5% IgG product to 1250 mOsm/L for a 10% product (Table VIII). The IgA content of the different brands varies between less than 0.4 μg/mL and 720 μg/mL (Table VIII).

Sodium content	pH after reconstitution	IgA content	Stabilizer or added regulator	Indication§
0.01 mEq/mL (3% solution) 0.02 mEq/mL (6% solution) 0.041 mEq/mL (12% solution)	6.6	720 μg/mL	Sucrose	PI, ITP
None	6.6	720 μg/mL	Sucrose	PI, ITP
<0.032 mEq/ml	5-6	<50 μg/mL	D-sorbitol	PI
Trace	4.25	Traces	Glycine	PI, ITP, BMT, HIV
0.145 mEq/mL	6.8	<2.2 μg/mL	2% Glucose	PI, ITP, CLL, KD
0.145 mEq/mL	6.8	270 μg/mL	4% Glucose	PI, ITP, CLL, KD
None added	4.6-5.1	37 μg/mL	Glycine	PI
0.085 mEq/mL	6.8	<25 μg/mL	Sucrose	PI
None added	4-4.5	46 μg/mL	Glycine	PI
0.05 mEq/mL	6.4-7.2	<10 μg/mL	Glucose	PI, KD
0.03 mEq/ml	5.1-6.0	<100 μg/mL	Maltose	PI
0.01 mEq/mL (3% solution) 0.02 mEq/mL (6% solution) 0.031 mEq/mL (9% solution) 0.041 mEq/mL (12% solution) or none	6.6	720 μg/mL	Sucrose	PI, ITP
0.145 mEq/mL (5% solution) 0.28 mEq/mL (10% solution)	6.8	<2.2 μg/mL	Glucose	PI, ITP, CLL, KD

Particular care must be exercised when using maltose-containing products in patients using glucose meters to adjust doses of insulin or other hypoglycemic agents because some meters might falsely report high blood glucose readings because of interference by the maltose.

Dose

The usual dose of IGIV for antibody replacement is between 0.3 and 0.6 g/kg per month, delivered every 2 to 4 weeks through the intravenous route (in most cases), as discussed in the ''Primary and secondary immunodeficiency'' section. For other uses, the doses range between 0.4 g/kg per day for 5 days or a more rapid course of 1 or 2 g/kg administered in 1 or 2 days. The first infusion of a hypogammaglobulinemic patient not previously treated is given slowly as a 3% or 5% solution, starting with a rate of 0.5 to 1.0 mg/kg per minute. After 15 to 30 minutes, the rate is increased to 1.5 to 2.5 mg/kg per minute and increased further as tolerated. For subsequent infusions or when higher doses are to be administered, IGIV concentrations of 10% and 12% have been used, with rates as high as 4 mg/kg per minute. Considerations of the solute content, total volume to be administered, and the osmolarity of the product are important in some patients.[2]

Adverse reactions

IGIV is a complex therapy and can lead to adverse effects.[2] The incidence of these reactions is surprisingly high, as documented in licensing studies described in the information for prescribers that accompany the products. Similarly, a survey of more than 1000 patients with primary immunodeficiency conducted by the Immune Deficiency Foundation (IDF) found that 44% report experiencing adverse reactions that were not related to rate of infusion.[333] Although this suggests a rate of reaction greater than those observed in licensing studies, it highlights the complexity of routine IGIV treatment.

Fortunately, most IGIV reactions are mild and non-anaphylactic. They are typically characterized by back or abdominal aching or pain, nausea, rhinitis, asthma, chills,

low grade fever, myalgias, and/or headache. Slowing or stopping the infusion for 15 to 30 minutes will reverse many reactions. Diphenhydramine, acetaminophen, aspirin, or ibuprofen might also be helpful. More recalcitrant reactions can be treated with 50 to 100 mg of hydrocortisone (for adults), hydration with normal saline administered intravenously, or both. For patients who seem predisposed to reactions, pretreatment with diphenhydramine, acetaminophen, ibuprofen, hydrocortisone, or intravenous hydration can be helpful. Adverse reactions are particularly likely in a patient who has not received IGIV previously and who has or recently has had a bacterial infection. The IDF survey found that 34% of reactions occurred during the first infusion of an IGIV product.[333] After 2 or 3 immunoglobulin treatments with the same product, however, additional infusion reactions become less likely. There is an element of unpredictability to reactions to IGIV because the IDF survey identified 23% of patients who experienced a reaction to products that they had been receiving without issue.[333] Thus vigilance needs to be maintained for detecting and managing reactions, irrespective of an individual patient's personal experience with IGIV.

Unfortunately, there are a number of IGIV reactions that are more serious adverse events and can occur during or soon after infusion. They have been reviewed elsewhere[2,334-337] but include anaphylaxis, Stevens-Johnson syndrome, hypotension, myocardial infarction, thrombosis, cytopenia, hemolysis, stroke, seizure, loss of consciousness, acute respiratory distress syndrome, pulmonary edema, acute bronchospasm, and transfusion-associated lung injury. Expert monitoring of the patient receiving IGIV infusion therefore is necessary for consideration of these complications. Prompt diagnosis and treatment of these events is required to ensure patient safety. There are also several adverse events that can be associated with IGIV infusion but are not temporally related to infusion. These include acute renal failure, neurodegeneration, and the theoretic risk of transmitted infection. The acute renal failure is more commonly found in patients receiving IGIV products that contain sucrose as a stabilizing agent. The association with neurodegeneration has been reported[5]; however, a mechanism is currently unknown. The transmission of infection has been reduced after manufacturing processes were altered after a hepatitis C virus outbreak[338] but remains a theoretic possibility.

The placement and use of indwelling venous access for IGIV administration should be carefully weighed against the thrombotic and infectious risks inherent to these devices that might be further amplified in immunodeficient or autoimmune patients or by administration of IGIV. Because these devices have the potential to cause additional adverse events, their use for the sole purpose of providing IGIV is discouraged by the authors and others.[22]

Route of administration

Although subcutaneous infusions of immunoglobulin preparations were originally proposed as an alternative to intramuscular injections,[339-343] more recently, this method has been investigated as a safe and convenient method by using a variety of products and regimens of infusion.[54,55,344-351] Subcutaneous administration might have some clinical advantages over intravenous infusions, including a more benign side effect profile, better sustained levels of IgG in the blood,[346] and possibly reduced occurrence of adverse reactions in IgA-deficient patients who have anti-IgA antibodies.[352] An additional benefit is improvement in quality of life, which is in part secondary to the ability of patients to administer it themselves at home.[346,353] With subcutaneous infusions, the most common side effects are local and include swelling, itching, and erythema at the site of the infusion.[348] Local reactions usually resolve in 12 to 24 hours. Systemic reactions are similar to those seen with intravenous administration but occur less frequently.[54] The immunoglobulin dose used for subcutaneous replacement therapy for treatment of primary immunodeficiency is usually 0.1 g/kg body weight per week (0.4 g/kg per 28 days) but might be individualized as described for intravenous dosing in the ''Primary and secondary immunodeficiency'' section (and as outlined by Berger[354]). The rate of infusion, number of sites used, and volume per site will vary with the individual patient's size, tolerance, and preferences, but a starting point for adults might be 10 to 40 mL/h, with a maximum volume per site of 20 to 30 mL. Multiple infusion sites can be used simultaneously, and greater volumes can be administered in any given site if the infusion is given more slowly. The volume of given product required by a patient can be minimized by the use of a higher concentration of IGIV or intramuscular immunoglobulin preparations. Limited experience currently exists in using subcutaneous infusions for indications other than primary immunodeficiency. Thus this method should be limited to administration for these diagnoses. In particular, it is unclear whether subcutaneous infusions will be effective for disorders that presumably benefit from immunomodulatory effects of high peak serum IgG concentrations that result after intravenous infusion.

Supply and economic considerations

As physicians, it is difficult to consider the economic ramifications of offering a potentially life-saving therapy. The reimbursement, manufacturing, and supply environments for IGIV, however, exist in an increasingly fragile balance. For this reason, the appropriate use of IGIV for indications supported by rigorous scientific clinical evidence is essential. This is required to ensure that the patients who will benefit most from IGIV will have access to treatment. IGIV must be respected as a scarce resource, and its judicious use must be promoted and practiced within the medical community.

NOTE ADDED IN PROOF

Since completion of this manuscript several important developments have occurred that affect the IGIV community.

The first is that in January 2006 a polyclonal immunoglobulin product was licensed by the FDA specifically for subcutaneous administration for the treatment of patients with primary immunodeficiency (Vivaglobin; ZLB Behring, Melbourne, Australia). This further legitimizes this mode of therapy in the US for patients with primary immunodeficiencies. Importantly, the reader is referred to the prescribing information for this product because there are numerous differences in the way that it is recommended for use compared to methods published elsewhere and the experience discussed in this review. One important difference regards the recommended dosing regimen and protocol for converting a patient already receiving IGIV therapy to subcutaneous therapy. Furthermore, this product was only studied in patients who were already receiving IGIV and not patients who were naive to IGIV therapy. Finally, the availability of an FDA-approved product presents new challenges in deciding which patients will be appropriate candidates for the subcutaneous mode of therapy because it is certainly not appropriate for all primary immunodeficiency patients who require immunoglobulin replacement therapy.

A second development involves a more recent meta-analysis reviewing patients treated with IGIV for recurrent spontaneous abortion.[355] This review also evaluated specific subsets of patients treated with IGIV for this indication and found that women with repeated second trimester intrauterine fetal deaths were benefited by IGIV therapy as compared to placebo ($P < .01$). The authors concluded by recommending a new large and carefully designed placebo-controlled trial to study IGIV for patients affected by recurrent spontaneous abortion with particular attention to women who have experienced second trimester intrauterine fetal deaths. An additional recent meta-analysis[356] also suggests efficacy in certain selected subpopulations and thus supports the need for further study. We also support the call for additional study of IGIV for this indication.

A third development was the publication of a review and meta-analysis of randomized controlled trials comparing corticosteroids versus IGIV therapy for the treatment of acute immune thrombocytopenic purpura in children.[357] This analysis concluded that IGIV was more effective than corticosteroids in achieving a platelet count >20,000/mm^3 after 48 hours of therapy, and thus further substantiates the ''definitely beneficial'' recommendation made in Table IV.

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