

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

INTRODUCTION

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

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

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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.

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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 ≥ 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

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

functional B-cell reconstitution, and thus these patients do not produce functional antibody and should be treated as if they were agammaglobulinemic.

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 pneumonia¹⁷ 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 antibodies²⁶ 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 Φ X174, 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 jirovecii* (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 hematopoietic 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 controlled⁹⁶ and open-label⁹⁷ 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 cases¹¹³ and open-label studies¹¹⁴ 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-scleroderma¹¹⁶ or Still disease¹¹⁷ 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 FEV₁ 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 FEV₁ 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 lymphotropic 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 children¹⁵² 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 anti-myelin-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 study¹⁷⁶ 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 crises¹⁷⁹ and juvenile myasthenia¹⁸⁰ 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 studies¹⁸⁷⁻¹⁸⁹ 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 \pm 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 neuro-immunologic disorders and have been reviewed.^{147,203} Examples of positive reports include those describing IGIV treatment of patients with acute disseminated encephalomyelitis,²⁰⁴ demyelinating 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
	<i>Campylobacter</i> 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 (≤ 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-idiotypic 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 settings²⁴⁰

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 than 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 pneumonia²⁵⁷ or adenoviral pneumonitis²⁵⁸ 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 difficile* (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 foliaceus²⁹⁴ 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 report³⁰³ 9 of 10 patients with chronic urticaria were reported to benefit from IGIV therapy, and in another³⁰⁴ 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 levels³¹⁵ and autoimmune antibodies against neural antigens³¹⁶ 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 plasmapheresis 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 osmolality 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	Indications [§]
0.01 mEq/mL (3% solution)	6.6	720 µg/mL	Sucrose	PI, ITP
0.02 mEq/mL (6% solution)				
0.041 mEq/mL (12% solution)				
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)	6.6	720 µg/mL	Sucrose	PI, ITP
0.02 mEq/mL (6% solution)				
0.031 mEq/mL (9% solution)				
0.041 mEq/mL (12% solution) or none				
0.145 mEq/mL (5% solution)	6.8	<2.2 µg/mL	Glucose	PI, ITP, CLL, KD
0.28 mEq/mL (10% solution)				

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 osmolality 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 reported⁵; however, a mechanism is currently unknown. The transmission of infection has been reduced after manufacturing processes were altered after a hepatitis C virus outbreak³³⁸ 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 Berger³⁵⁴). 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-analysis³⁵⁶ 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 $>20,000/\text{mm}^3$ after 48 hours of therapy, and thus further substantiates the “definitely beneficial” recommendation made in Table IV.

REFERENCES

- Milgrom H. Shortage of intravenous immunoglobulin. *Ann Allergy Asthma Immunol* 1998;81:97-100.
- Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003;17:241-51.
- Wittstock M, Benecke R, Zetl UK. Therapy with intravenous immunoglobulins: complications and side-effects. *Eur Neurol* 2003;50:172-5.
- Hefer D, Jaloudi M. Thromboembolic events as an emerging adverse effect during high-dose intravenous immunoglobulin therapy in elderly patients: a case report and discussion of the relevant literature. *Ann Hematol* 2005;84:411-5.
- Ziegner UH, Kobayashi RH, Cunningham-Rundles C, Espanol T, Fasth A, Huttenlocher A, et al. Progressive neurodegeneration in patients with primary immunodeficiency disease on IVIG treatment. *Clin Immunol* 2002;102:19-24.
- Renal insufficiency and failure associated with immune globulin intravenous therapy—United States, 1985-1998. *MMWR Morb Mortal Wkly Rep* 1999;48:518-21.
- Ammann AJ, Ashman RF, Buckley RH, Hardie WR, Krantmann HJ, Nelson J, et al. Use of intravenous gamma-globulin in antibody immunodeficiency: results of a multicenter controlled trial. *Clin Immunol Immunopathol* 1982;22:60-7.
- Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med* 1991;325:110-7.
- Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine (Baltimore)* 1985;64:145-56.
- Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;134:589-96.
- Liese JG, Wintergerst U, Tymphner KD, Belohradsky BH. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992;146:335-9.
- Cunningham-Rundles C, Siegal FP, Smithwick EM, Lion-Boulet A, Cunningham-Rundles S, O'Malley J, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. *Ann Intern Med* 1984;101:435-9.
- Nolte MT, Pirofsky B, Gerritz GA, Golding B. Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol* 1979;36:237-43.
- Roifman CM, Lederman HM, Lavi S, Stein LD, Levison H, Gelfand EW. Benefit of intravenous IgG replacement in hypogammaglobulinemic patients with chronic sinopulmonary disease. *Am J Med* 1985;79:171-4.
- Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *QJM* 2002;95:655-62.
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34-48.
- Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2002;109:1001-4.
- de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol* 2004;4:745-53.
- Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)* 2003;82:373-84.
- Quartier P, Bustamante J, Sanal O, Plebani A, Debre M, Deville A, et al. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to activation-induced cytidine deaminase deficiency. *Clin Immunol* 2004;110:22-9.
- Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordignon P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr* 1997;131:47-54.
- Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol* 2005;94(suppl):S1-63.
- Wolpert J, Knutsen A. Natural history of selective antibody deficiency to bacterial polysaccharide antigens in children. *Pediatr Asthma Allergy Immunol* 1998;12:183-91.
- Ortigas AP, Leiva LE, Moore C, Bradford N, Sorensen RU. Natural history of specific antibody deficiency after IgG replacement therapy. *Ann Allergy Asthma Immunol* 1999;82:71.
- Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, et al. TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet* 2005;37:829-34.
- Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N Engl J Med* 1986;314:560-4.
- Bjorkander J, Hammarstrom L, Smith CI, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with

- antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol* 1987;7:8-15.
28. de Albuquerque Campos R, Sato MN, da Silva Duarte AJ. IgG anti-IgA subclasses in common variable immunodeficiency and association with severe adverse reactions to intravenous immunoglobulin therapy. *J Clin Immunol* 2000;20:77-82.
 29. Leung DY, Ambrosino DM, Arbeit RD, Newton JL, Geha RS. Impaired antibody responses in the hyperimmunoglobulinemia E syndrome. *J Allergy Clin Immunol* 1988;81:1082-97.
 30. Sheerin KA, Buckley RH. Antibody responses to protein, polysaccharide, and phiX174 antigens in the hypergammaglobulinemia E (hyper-IgE) syndrome. *J Allergy Clin Immunol* 1991;87:803-11.
 31. Bilora F, Petrobelli F, Boccioletti V, Pomerri F. Moderate-dose intravenous immunoglobulin treatment of Job's syndrome. Case report. *Minerva Med* 2000;91:113-6.
 32. Wakim M, Alazard M, Yajima A, Speights D, Saxon A, Stiehm ER. High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. *Ann Allergy Asthma Immunol* 1998;81:153-8.
 33. Ochs HD, Slichter SJ, Harker LA, Von Behrens WE, Clark RA, Wedgwood RJ. The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes, and platelets. *Blood* 1980;55:243-52.
 34. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. *J Pediatr* 1994;125:876-85.
 35. Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova JL. An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. *Clin Immunol* 2003;109:272-7.
 36. Litzman J, Jones A, Hann I, Chapel H, Strobel S, Morgan G. Intravenous immunoglobulin, splenectomy, and antibiotic prophylaxis in Wiskott-Aldrich syndrome. *Arch Dis Child* 1996;75:436-9.
 37. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. *N Engl J Med* 1988;319:902-7.
 38. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. *N Engl J Med* 1991;325:81-6.
 39. Chapel H, Dicato M, Gamm H, Brennan V, Ries F, Bunch C, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994;88:209-12.
 40. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991;325:73-80.
 41. Spector SA, Gelber RD, McGrath N, Wara D, Barzilai A, Abrams E, et al. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. *Pediatric AIDS Clinical Trials Group*. *N Engl J Med* 1994;331:1181-7.
 42. Mofenson LM, Moye J Jr, Korelitz J, Bethel J, Hirschhorn R, Nugent R. Crossover of placebo patients to intravenous immunoglobulin confirms efficacy for prophylaxis of bacterial infections and reduction of hospitalizations in human immunodeficiency virus-infected children. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *Pediatr Infect Dis J* 1994;13:477-84.
 43. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev* 2004;CD001239.
 44. Bussell JB. Intravenous gammaglobulin in the prophylaxis of late sepsis in very-low-birth-weight infants: preliminary results of a randomized, double-blind, placebo-controlled trial. *Rev Infect Dis* 1990;12(suppl 4):S457-62.
 45. Sandberg K, Fasth A, Berger A, Eibl M, Isacson K, Lischka A, et al. Preterm infants with low immunoglobulin G levels have increased risk of neonatal sepsis but do not benefit from prophylactic immunoglobulin G. *J Pediatr* 2000;137:623-8.
 46. Nelson RP Jr, Ballow M. Immunomodulation and immunotherapy: drugs, cytokines, cytokine receptors, and antibodies. *J Allergy Clin Immunol* 2003;111(suppl):S720-43.
 47. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;1:1075-7.
 48. Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. *Int Immunopharmacol* 2003;3:1325-33.
 49. Schiff RI, Rudd C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. *J Clin Immunol* 1986;6:256-64.
 50. Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med* 2001;135:165-74.
 51. Pruzanski W, Sussman G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. *Inflammation* 1996;20:353-9.
 52. Buckley RH. Long term use of intravenous immune globulin in patients with primary immunodeficiency diseases: inadequacy of current dosage practices and approaches to the problem. *J Clin Immunol* 1982;2(suppl):15S-21S.
 53. Bernatowska E, Madalinski K, Janowicz W, Weremowicz R, Gutkowski P, Wolf HM, et al. Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. *Clin Immunol Immunopathol* 1987;43:153-62.
 54. Gardulf A, Andersen V, Bjorkander J, Ericson D, Froland SS, Gustafson R, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet* 1995;345:365-9.
 55. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol* 2000;20:94-100.
 56. Sandoval C, Visintainer P, Ozkaynak MF, Tugal O, Jayabose S. Clinical features and treatment outcomes of 79 infants with immune thrombocytopenic purpura. *Pediatr Blood Cancer* 2004;42:109-12.
 57. Duru F, Fisgin T, Yarali N, Kara A. Clinical course of children with immune thrombocytopenic purpura treated with intravenous immunoglobulin G or megadose methylprednisolone or observed without therapy. *Pediatr Hematol Oncol* 2002;19:219-25.
 58. Tarantino MD. Acute immune (idiopathic) thrombocytopenic purpura in childhood. *Blood Rev* 2002;16:19-21.
 59. Godeau B, Chevret S, Varet B, Lefere F, Zini JM, Bassompierre F, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002;359:23-9.
 60. Hedlund-Treutiger I, Henter JI, Elinder G. Randomized study of IVIg and high-dose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. *J Pediatr Hematol Oncol* 2003;25:139-44.
 61. Tarantino MD. Treatment options for chronic immune (idiopathic) thrombocytopenia purpura in children. *Semin Hematol* 2000;37:35-41.
 62. Fujisawa K, Iyori H, Ohkawa H, Konishi S, Bessho F, Shirahata A, et al. A prospective, randomized trial of conventional, dose-accelerated corticosteroids and intravenous immunoglobulin in children with newly diagnosed idiopathic thrombocytopenic purpura. *Int J Hematol* 2000;72:376-83.
 63. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* 2001;291:484-6.
 64. Rayment R, Brunskill SJ, Stanworth S, Soothill PW, Roberts DJ, Murphy MF. Antenatal interventions for fetomaternal alloimmune thrombocytopenia. *Cochrane Database Syst Rev* 2005;CD004226.
 65. Ziman A, Klapper E, Pepkowitz S, Smith R, Garratty G, Goldfinger D. A second case of post-transfusion purpura caused by HPA-5a

- antibodies: successful treatment with intravenous immunoglobulin. *Vox Sang* 2002;83:165-6.
66. Evenson DA, Stroncek DF, Pulkrabek S, Perry EH, Radford J, Miller JS, et al. Posttransfusion purpura following bone marrow transplantation. *Transfusion* 1995;35:688-93.
67. Kroll H, Kiefel V, Mueller-Eckhardt C. Clinical and serologic studies in 34 patients with post-transfusion purpura. *Beitrage zur Infusionstherapie* 1992;30:403-7.
68. Song S, Crow AR, Freedman J, Lazarus AH. Monoclonal IgG can ameliorate immune thrombocytopenia in a murine model of ITP: an alternative to IVIG. *Blood* 2003;101:3708-13.
69. Kumar R, Ghali A, Ekaldious AW, Mahmoud OI, Al-Lumai AS. Post-transfusion purpura: case report. *Ann Hematol* 2001;80:488-91.
70. Mueller-Eckhardt C, Kiefel V. High-dose IgG for post-transfusion purpura-revisited. *Blut* 1988;57:163-7.
71. Bux J, Behrens G, Jaeger G, Welte K. Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. *Blood* 1998;91:181-6.
72. Christensen RD, Brown MS, Hall DC, Lassiter HA, Hill HR. Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991;118:606-14.
73. Kurtzberg J, Friedman HS, Chaffee S, Falletta JM, Kinney TR, Kurlander R, et al. Efficacy of intravenous gamma globulin in autoimmune-mediated pediatric blood dyscrasias. *Am J Med* 1987;83:4-9.
74. Bussel J, Lalezari P, Hilgartner M, Partin J, Fikrig S, O'Malley J, et al. Reversal of neutropenia with intravenous gammaglobulin in autoimmune neutropenia of infancy. *Blood* 1983;62:398-400.
75. Mascarin M, Ventura A. Anti-Rh(D) immunoglobulin for autoimmune neutropenia of infancy. *Acta Paediatr* 1993;82:142-4.
76. Khouri IF, Ippoliti C, Gajewski J, Przepiorka D, Champlin RE. Neutropenias following allogeneic bone marrow transplantation: response to therapy with high-dose intravenous immunoglobulin. *Am J Hematol* 1996;52:313-5.
77. Klumpp TR, Herman JH. Autoimmune neutropenia after bone marrow transplantation. *Blood* 1993;82:1035.
78. Besa EC. Rapid transient reversal of anemia and long-term effects of maintenance intravenous immunoglobulin for autoimmune hemolytic anemia in patients with lymphoproliferative disorders. *Am J Med* 1988;84:691-8.
79. Hilgartner MW, Bussel J. Use of intravenous gamma globulin for the treatment of autoimmune neutropenia of childhood and autoimmune hemolytic anemia. *Am J Med* 1987;83:25-9.
80. Flores G, Cunningham-Rundles C, Newland AC, Bussel JB. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. *Am J Hematol* 1993;44:237-42.
81. Alpay F. High-dose intravenous immunoglobulin therapy in neonatal immune haemolytic jaundice. *Acta Paediatr* 2000;89:371-2.
82. Dagoglu T, Ovali F, Samanci N, Bengisu E. High-dose intravenous immunoglobulin therapy for rhesus haemolytic disease. *J Int Med Res* 1995;23:264-71.
83. Rubo J, Albrecht K, Lasch P, Laufkotter E, Leititis J, Marsan D, et al. High-dose intravenous immune globulin therapy for hyperbilirubinemia caused by Rh hemolytic disease. *J Pediatr* 1992;121:93-7.
84. Alcock GS, Liley H. Immunoglobulin infusion for isoimmune haemolytic jaundice in neonates. *Cochrane Database Syst Rev* 2002;CD003313.
85. Scaradavou A, Bussel J. Evans syndrome. Results of a pilot study utilizing a multiagent treatment protocol. *J Pediatr Hematol Oncol* 1995;17:290-5.
86. Alliot C, Barrios M, Tabuteau S, Desablens B. Autoimmune cytopenias associated with malignancies and successfully treated with intravenous immune globulins: about two cases. *Therapie* 2000;55:371-4.
87. Larroche C, Mouthon L, Casadevall N, Le Roux G, Casassus P, Guillemin L. Successful treatment of thymoma-associated pure red cell aplasia with intravenous immunoglobulins. *Eur J Haematol* 2000;65:74-6.
88. Aharon A, Levy Y, Bar-Dayana Y, Afek A, Zandman-Goddard G, Skurnik Y, et al. Successful treatment of early secondary myelofibrosis in SLE with IVIG. *Lupus* 1997;6:408-11.
89. Blanchette VS, Kirby MA, Turner C. Role of intravenous immunoglobulin G in autoimmune hematologic disorders. *Semin Hematol* 1992;29:72-82.
90. Boggio LN, Green D. Acquired hemophilia. *Rev Clin Exp Hematol* 2001;5:389-404; quiz following 31.
91. Bossi P, Cabane J, Ninet J, Dhote R, Hanslik T, Chosidow O, et al. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *Am J Med* 1998;105:400-8.
92. Sultan Y. Acquired hemophilia and its treatment. *Blood Coagul Fibrinolysis* 1997;8(suppl 1):S15-8.
93. Gianella-Borradori A, Hirt A, Luthy A, Wagner HP, Imbach P. Haemophilia due to factor VIII inhibitors in a patient suffering from an autoimmune disease: treatment with intravenous immunoglobulin. A case report. *Blut* 1984;48:403-7.
94. Sultan Y, Kazatchkine MD, Maisonneuve P, Nydegger UE. Anti-idiotypic suppression of autoantibodies to factor VIII (antihaemophilic factor) by high-dose intravenous gammaglobulin. *Lancet* 1984;2:765-8.
95. Dalakas MC. Immunopathogenesis of inflammatory myopathies. *Ann Neurol* 1995;37(suppl 1):S74-86.
96. Dalakas MC. Update on the use of intravenous immune globulin in the treatment of patients with inflammatory muscle disease. *J Clin Immunol* 1995;15:70S-5S.
97. Cherin P, Piette JC, Wechsler B, Blety O, Ziza JM, Laraki R, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. *J Rheumatol* 1994;21:1092-7.
98. Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis—four year review of nine cases. *Arch Dis Child* 1995;72:25-8.
99. Amato AA, Barohn RJ, Jackson CE, Pappert EJ, Sahenk Z, Kissel JT. Inclusion body myositis: treatment with intravenous immunoglobulin. *Neurology* 1994;44:1516-8.
100. Moriya Y, Yamaji K, Kanai Y, Tsuda H. The effectiveness of intravenous human immunoglobulin treatment after plasmapheresis in restoring serum immunoglobulin levels: a preliminary study. *Ther Apher* 2002;6:154-8.
101. Savery F. Intravenous immunoglobulin treatment of rheumatoid arthritis-associated immunodeficiency. *Clin Ther* 1988;10:527-9.
102. Ballou M. Mechanisms of action of intravenous immunoglobulin therapy and potential use in autoimmune connective tissue diseases. *Cancer* 1991;68:1430-6.
103. Kanik KS, Yarboro CH, Naparstek Y, Plotz PH, Wilder RL. Failure of low-dose intravenous immunoglobulin therapy to suppress disease activity in patients with treatment-refractory rheumatoid arthritis. *Arthritis Rheum* 1996;39:1027-9.
104. Amal C, Piette JC, Leone J, Taillan B, Hachulla E, Roudot-Thoraval F, et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002;29:75-83.
105. Meissner M, Sherer Y, Levy Y, Chwalinska-Sadowska H, Langevitz P, Shoenfeld Y. Intravenous immunoglobulin therapy in a patient with lupus serositis and nephritis. *Rheumatol Int* 2000;19:199-201.
106. Silvestris F, D'Amore O, Cafforio P, Savino L, Dammacco F. Intravenous immune globulin therapy of lupus nephritis: use of pathogenic anti-DNA-reactive IgG. *Clin Exp Immunol* 1996;104(suppl 1):91-7.
107. Levy Y, Sherer Y, George J, Langevitz P, Ahmed A, Bar-Dayana Y, et al. Serologic and clinical response to treatment of systemic vasculitis and associated autoimmune disease with intravenous immunoglobulin. *Int Arch Allergy Immunol* 1999;119:231-8.
108. Lesprit P, Mouloud F, Bierling P, Schaeffer A, Cesaro P, Brun-Buisson C, et al. Prolonged remission of SLE-associated polyradiculoneuropathy after a single course of intravenous immunoglobulin. *Scand J Rheumatol* 1996;25:177-9.
109. Aharon A, Zandman-Goddard G, Shoenfeld Y. Autoimmune multiorgan involvement in elderly men is it SLE? *Clin Rheumatol* 1994;13:631-4.
110. Pasatiempo AM, Kroser JA, Rudnick M, Hoffman BI. Acute renal failure after intravenous immunoglobulin therapy. *J Rheumatol* 1994;21:347-9.
111. Galli M, Cortelazzo S, Barbui T. In vivo efficacy of intravenous gammaglobulins in patients with lupus anticoagulant is not mediated by an anti-idiotypic mechanism. *Am J Hematol* 1991;38:184-8.
112. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005;CD002859.

113. Jordan SC. Treatment of systemic and renal-limited vasculitic disorders with pooled human intravenous immune globulin. *J Clin Immunol* 1995;15:76S-85S.
114. Jayne DR, Esnault VL, Lockwood CM. ANCA anti-idiotype antibodies and the treatment of systemic vasculitis with intravenous immunoglobulin. *J Autoimmun* 1993;6:207-19.
115. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. *Ann Intern Med* 1999;131:522-30.
116. Rutter A, Luger TA. Intravenous immunoglobulin: an emerging treatment for immune-mediated skin diseases. *Curr Opin Investig Drugs* 2002;3:713-9.
117. Prieur AM. Intravenous immunoglobulins in Still's disease: still controversial, still unproven. *J Rheumatol* 1996;23:797-800.
118. Richter WO, Donner MG, Schwandt P. Elimination of islet cell antibodies and glutamic acid decarboxylase antibodies II in a patient with newly diagnosed insulin-dependent diabetes mellitus. *J Clin Apheresis* 1997;12:196-9.
119. Heinze E. Immunoglobulins in children with autoimmune diabetes mellitus. *Clin Exp Rheumatol* 1996;14(suppl):S99-102.
120. Colagiuri S, Leong GM, Thayer Z, Antony G, Dwyer JM, Kidson W, et al. Intravenous immunoglobulin therapy for autoimmune diabetes mellitus. *Clin Exp Rheumatol* 1996;14(suppl 15):S93-7.
121. Kahaly G, Pitz S, Muller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. *Clin Exp Immunol* 1996;106:197-202.
122. Philipsen EK, Larsen S, Helin P. A preliminary trial of high-dose intravenous immunoglobulin to a patient with euthyroid ophthalmopathy. *Thyroidology* 1989;1:93-5.
123. LeHoang P, Cassoux N, George F, Kullmann N, Kazatchkine MD. Intravenous immunoglobulin (IVIg) for the treatment of birdshot retinochoroidopathy. *Ocul Immunol Inflamm* 2000;8:49-57.
124. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. *Am J Ophthalmol* 1999;127:545-9.
125. Carmassi F, Morale M, Puccetti R, Pistelli F, Palla R, Bevilacqua G, et al. Efficacy of intravenous immunoglobulin therapy in a case of autoimmune-mediated chronic active hepatitis. *Clin Exp Rheumatol* 1992;10:13-7.
126. Hamilos DL, Young RM, Peter JB, Agopian MS, Ikle DN, Barka N. Hypogammaglobulinemia in asthmatic patients. *Ann Allergy* 1992;68:472-81.
127. Moss RB, Carmack MA, Esrig S. Deficiency of IgG4 in children: association of isolated IgG4 deficiency with recurrent respiratory tract infection. *J Pediatr* 1992;120:16-21.
128. Klaustermeier WB, Wong SC, Schoettler JJ, Gianos ME, Heiner DC. Quantitative immunoglobulins and IgG subclasses in patients with corticosteroid-dependent reversible airway obstruction. *Ann Allergy* 1989;63:327-30.
129. Barth J, Winkler I, Mollmann HW, Ulmer WT, Skvaril F. IgG-2 deficiency in asthmatic patients course of disease in four adults. *Agents Actions Suppl* 1989;28:245-8.
130. Loftus BG, Price JF, Lobo-Yeo A, Vergani D. IgG subclass deficiency in asthma. *Arch Dis Child* 1988;63:1434-7.
131. Hanson LA, Soderstrom R, Avanzini A, Bengtsson U, Bjorkander J, Soderstrom T. Immunoglobulin subclass deficiency. *Pediatr Infect Dis J* 1988;7(suppl):S17-21.
132. Oxelius VA, Hanson LA, Bjorkander J, Hammarstrom L, Sjolholm A. IgG3 deficiency: common in obstructive lung disease. Hereditary in families with immunodeficiency and autoimmune disease. *Monogr Allergy* 1986;20:106-15.
133. Page R, Friday G, Stillwagon P, Skoner D, Caliguiri L, Fireman P. Asthma and selective immunoglobulin subclass deficiency: improvement of asthma after immunoglobulin replacement therapy. *J Pediatr* 1988;112:127-31.
134. Schwartz HJ, Berger M. Intravenous gamma-globulin therapy in bronchial asthma. *Allergy Asthma Proc* 2002;23:15-8.
135. Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87:976-83.
136. Spahn JD, Leung DY, Chan MT, Szefer SJ, Gelfand EW. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 1999;103:421-6.
137. Sigman K, Ghibu F, Sommerville W, Toledano BJ, Bastein Y, Cameron L, et al. Intravenous immunoglobulin inhibits IgE production in human B lymphocytes. *J Allergy Clin Immunol* 1998;102:421-7.
138. Zhuang Q, Mazer B. Inhibition of IgE production in vitro by intact and fragmented intravenous immunoglobulin. *J Allergy Clin Immunol* 2001;108:229-34.
139. Basta M, Van Goor F, Luccioli S, Billings EM, Vortmeyer AO, Baranyi L, et al. F(ab)'2-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. *Nat Med* 2003;9:431-8.
140. Jakobsson T, Croner S, Kjellman NI, Pettersson A, Vassella C, Bjorksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma. *Allergy* 1994;49:413-20.
141. Landwehr LP, Jeppson JD, Katlan MG, Esterl B, McCormick D, Hamilos DL, et al. Benefits of high-dose i.v. immunoglobulin in patients with severe steroid-dependent asthma. *Chest* 1998;114:1349-56.
142. Haque S, Boyce N, Thien FC, O'Hehir RE, Douglass J. Role of intravenous immunoglobulin in severe steroid-dependent asthma. *Intern Med J* 2003;33:341-4.
143. Niggemann B, Leupold W, Schuster A, Schuster R, v Berg A, Grubl A, et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. *Clin Exp Allergy* 1998;28:205-10.
144. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999;91:126-33.
145. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. *J Allergy Clin Immunol* 1999;103:810-5.
146. Sacher RA. Intravenous immunoglobulin consensus statement. *J Allergy Clin Immunol* 2001;108(suppl):S139-46.
147. Latov N, Chaudhry V, Koski CL, Lisak RP, Apatoff BR, Hahn AF, et al. Use of intravenous gamma globulins in neuroimmunologic diseases. *J Allergy Clin Immunol* 2001;108(suppl):S126-32.
148. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004;291:2367-75.
149. van der Meche FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. *N Engl J Med* 1992;326:1123-9.
150. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. *Lancet* 1997;349:225-30.
151. van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial. *Lancet* 2004;363:192-6.
152. Gurses N, Uysal S, Cetinkaya F, Islek I, Kalayci AG. Intravenous immunoglobulin treatment in children with Guillain-Barre syndrome. *Scand J Infect Dis* 1995;27:241-3.
153. Bril V, Ilse WK, Pearce R, Dhanani A, Sutton D, Kong K. Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barre syndrome. *Neurology* 1996;46:100-3.
154. Hughes RA, Raphael JC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. *Cochrane Database Syst Rev* 2001; CD002063.
155. Kanra G, Ozon A, Vajsar J, Castagna L, Secmeer G, Topaloglu H. Intravenous immunoglobulin treatment in children with Guillain-Barre syndrome. *Eur J Paediatr Neurol* 1997;1:7-12.
156. Singhi SC, Jayshree M, Singhi P, Banerjee S, Prabhakar S. Intravenous immunoglobulin in very severe childhood Guillain-Barre syndrome. *Ann Trop Paediatr* 1999;19:167-74.
157. Shahar E, Leiderman M. Outcome of severe Guillain-Barre syndrome in children: comparison between untreated cases versus gamma-globulin therapy. *Clin Neuropharmacol* 2003;26:84-7.
158. Yata J, Nihei K, Ohya T, Hirano Y, Momoi M, Maekawa K, et al. High-dose immunoglobulin therapy for Guillain-Barre syndrome in Japanese children. *Pediatr Int* 2003;45:543-9.

159. Shanbag P, Amirtharaj C, Pathak A. Intravenous immunoglobulins in severe Guillian-Barre syndrome in childhood. *Indian J Pediatr* 2003; 70:541-3.
160. Hughes RAC. The spectrum of acquired demyelinating polyradiculoneuropathy. *Acta Neurol Belg* 1994;94:128-32.
161. van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, crossover study. *Neurology* 1990;40:209-12.
162. Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994;36:838-45.
163. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 1996; 119(suppl):1067-77.
164. Mendell JR, Barohn RJ, Freimer ML, Kissel JT, King W, Nagaraja HN, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2001;56: 445-9.
165. van Schaik IN, Winer JB, de Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. *Lancet Neurol* 2002;1:491-8.
166. Ropper AH. Current treatments for CIDP. *Neurology* 2003;60(suppl): S16-22.
167. Van Schaik IN, Winer JB, De Haan R, Vermeulen M. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2002;CD001797.
168. van Schaik IN, van den Berg LH, de Haan R, Vermeulen M. Intravenous immunoglobulin for multifocal motor neuropathy. *Cochrane Database Syst Rev* 2005;CD004429.
169. Azulay JP, Blin O, Pouget J, Boucraut J, Bille-Turc F, Carles G, et al. Intravenous immunoglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double-blind, placebo-controlled study. *Neurology* 1994;44:429-32.
170. Van den Berg LH, Kerkhoff H, Oey PL, Franssen H, Mollee I, Vermeulen M, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1995;59:248-52.
171. Federico P, Zochodne DW, Hahn AF, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology* 2000;55:1256-62.
172. Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001;124:145-53.
173. Van den Berg-Vos RM, Franssen H, Wokke JH, Van den Berg LH. Multifocal motor neuropathy: long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment. *Brain* 2002;125:1875-86.
174. van Doorn PA, van der Meche FG. IVIg treatment improves multifocal motor neuropathy: easy to start but difficult to stop. *Neurology* 2000;55: 1246-7.
175. Dalakas MC, Quarles RH, Farrer RG, Dambrosia J, Soueidan S, Stein DP, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgM gammopathy. *Ann Neurol* 1996;40:792-5.
176. Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Myasthenia Gravis Clinical Study Group*. *Ann Neurol* 1997;41:789-96.
177. Ronager J, Ravnborg M, Hermansen I, Vorstrup S. Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. *Artif Organs* 2001;25:967-73.
178. Wolfe GI, Barohn RJ, Foster BM, Jackson CE, Kissel JT, Day JW, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis. *Muscle Nerve* 2002;26:549-52.
179. Qureshi AI, Choudhry MA, Akbar MS, Mohammad Y, Chua HC, Yahia AM, et al. Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 1999;52:629-32.
180. Selcen D, Dabrowski ER, Michon AM, Nigro MA. High-dose intravenous immunoglobulin therapy in juvenile myasthenia gravis. *Pediatr Neurol* 2000;22:40-3.
181. Perez Nellar J, Dominguez AM, Llorens-Figueroa JA, Ferra-Betancourt A, Pardo A, Quiala M, et al. A comparative study of intravenous immunoglobulin and plasmapheresis preoperatively in myasthenia. *Rev Neurol* 2001;33:413-6.
182. Huang CS, Hsu HS, Kao KP, Huang MH, Huang BS. Intravenous immunoglobulin in the preparation of thymectomy for myasthenia gravis. *Acta Neurol Scand* 2003;108:136-8.
183. Bain PG, Motomura M, Newsom-Davis J, Misbah SA, Chapel HM, Lee ML, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. *Neurology* 1996;47:678-83.
184. Muchnik S, Losavio AS, Vidal A, Cura L, Mazia C. Long-term follow-up of Lambert-Eaton syndrome treated with intravenous immunoglobulin. *Muscle Nerve* 1997;20:674-8.
185. Peterlin BL, Flood W, Kothari MJ. Use of intravenous immunoglobulin in Lambert-Eaton myasthenic syndrome. *J Am Osteopath Assoc* 2002; 102:682-4.
186. Rich MM, Teener JW, Bird SJ. Treatment of Lambert-Eaton syndrome with intravenous immunoglobulin. *Muscle Nerve* 1997;20:614-5.
187. Fazekas F, Deisenhammer F, Strasser-Fuchs S, Nahler G, Mamoli B. Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing-remitting multiple sclerosis. *Austrian Immunoglobulin in Multiple Sclerosis Study Group*. *Lancet* 1997;349: 589-93.
188. Sorensen PS, Wanscher B, Schreiber K, Blinkenberg M, Jensen CV, Ravnborg M. A double-blind, cross-over trial of intravenous immunoglobulin G in multiple sclerosis: preliminary results. *Mult Scler* 1997;3:145-8.
189. Achiron A, Gabbay U, Gilad R, Hassin-Baer S, Barak Y, Gornish M, et al. Intravenous immunoglobulin treatment in multiple sclerosis. Effect on relapses. *Neurology* 1998;50:398-402.
190. Sorensen PS, Fazekas F, Lee M. Intravenous immunoglobulin G for the treatment of relapsing-remitting multiple sclerosis: a meta-analysis. *Eur J Neurol* 2002;9:557-63.
191. Sorensen PS, Wanscher B, Jensen CV, Schreiber K, Blinkenberg M, Ravnborg M, et al. Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* 1998;50:1273-81.
192. Sorensen PS. Treatment of multiple sclerosis with intravenous immunoglobulin: review of clinical trials. *Neurol Sci* 2003;24(suppl 4): S227-30.
193. Gray O, McDonnell G, Forbes R. Intravenous immunoglobulins for multiple sclerosis. *Cochrane Database Syst Rev* 2003;CD002936.
194. Gross-Tsur V, Shalev RS, Kazir E, Engelhard D, Amir N. Intravenous high-dose gammaglobulins for intractable childhood epilepsy. *Acta Neurol Scand* 1993;88:204-9.
195. van Engelen BG, Renier WO, Weemaes CM, Strengers PF, Bernsen PJ, Notermans SL. High-dose intravenous immunoglobulin treatment in cryptogenic West and Lennox-Gastaut syndrome; an add-on study. *Eur J Pediatr* 1994;153:762-9.
196. Espinosa Zacarias J, Gutierrez Moctezuma J, Villegas Pena H, Olmos GDA. Intravenous treatment with immunoglobulins in epileptic syndromes which are difficult to control. *Rev Neurol* 2002;34:816-9.
197. Deda G, Caksen H. Atypical benign partial epilepsy of childhood (pseudo-Lennox syndrome): report of two brothers. *Neurol India* 2002;50:337-9.
198. Illum N, Taudorf K, Heilmann C, Smith T, Wulff K, Mansa B, et al. Intravenous immunoglobulin: a single-blind trial in children with Lennox-Gastaut syndrome. *Neuropediatrics* 1990;21:87-90.
199. van Rijckevorsel-Harmant K, Delire M, Schmitz-Moorman W, Wieser HG. Treatment of refractory epilepsy with intravenous immunoglobulins. Results of the first double-blind/dose finding clinical study. *Int J Clin Lab Res* 1994;24:162-6.
200. Villani F, Spreafico R, Farina L, Giovagnoli AR, Bernasconi P, Granata T, et al. Positive response to immunomodulatory therapy in an adult patient with Rasmussen's encephalitis. *Neurology* 2001;56:248-50.
201. Granata T. Rasmussen's syndrome. *Neurol Sci* 2003;24(suppl 4): S239-43.
202. Hart YM, Cortez M, Andermann F, Hwang P, Fish DR, Dulac O, et al. Medical treatment of Rasmussen's syndrome (chronic encephalitis and epilepsy): effect of high-dose steroids or immunoglobulins in 19 patients. *Neurology* 1994;44:1030-6.
203. Ratko TA. Technology assessment: intravenous immunoglobulin preparations. Oak Brook (IL): University Health System Consortium; 1999.

204. Kleiman M, Brunquell P. Acute disseminated encephalomyelitis: response to intravenous immunoglobulin. *J Child Neurol* 1995;10:481-3.
205. Assa A, Waternberg N, Bujanover Y, Lerman-Sagie T. Demyelinative brainstem encephalitis responsive to intravenous immunoglobulin therapy. *Pediatrics* 1999;104:301-3.
206. Zivkovic SA, Heyman R, Pless M. Subacute rhombencephalitis optica responsive to intravenous immunoglobulins. *Eur J Neurol* 2003;10:83-6.
207. Mariette X, Chastang C, Clavelou P, Louboutin JP, Leger JM, Brouet JC. A randomized clinical trial comparing interferon-alpha and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. The IgM-associated Polyneuropathy Study Group. *J Neurol Neurosurg Psychiatry* 1997;63:28-34.
208. Winston DJ, Antin JH, Wolff SN, Bierer BE, Small T, Miller KB, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001;28:187-96.
209. Winston DJ, Ho WG, Rasmussen LE, Lin CH, Chu HL, Merigan TC, et al. Use of intravenous immune globulin in patients receiving bone marrow transplants. *J Clin Immunol* 1982;2(suppl):42S-7S.
210. Emanuel D, Cunningham I, Jules-Elysee K, Brochstein JA, Kernan NA, Laver J, et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. *Ann Intern Med* 1988;109:777-82.
211. Ljungman P, Engelhard D, Link H, Biron P, Brandt L, Brunet S, et al. Treatment of interstitial pneumonitis due to cytomegalovirus with ganciclovir and intravenous immune globulin: experience of European Bone Marrow Transplant Group. *Clin Infect Dis* 1992;14:831-5.
212. Kruger RM, Paranjothi S, Storch GA, Lynch JP, Trulock EP. Impact of prophylaxis with cytogram alone on the incidence of CMV viremia in CMV-seropositive lung transplant recipients. *J Heart Lung Transplant* 2003;22:754-63.
213. Cortez K, Murphy BR, Almeida KN, Beeler J, Levandowski RA, Gill VJ, et al. Immune-globulin prophylaxis of respiratory syncytial virus infection in patients undergoing stem-cell transplantation. *J Infect Dis* 2002;186:834-8.
214. Bass EB, Powe NR, Goodman SN, Graziano SL, Griffiths RI, Kickler TS, et al. Efficacy of immune globulin in preventing complications of bone marrow transplantation: a meta-analysis. *Bone Marrow Transplant* 1993;12:273-82.
215. Guglielmo BJ, Wong-Beringer A, Linker CA. Immune globulin therapy in allogeneic bone marrow transplant: a critical review. *Bone Marrow Transplant* 1994;13:499-510.
216. Sullivan KM, Storek J, Kopecky KJ, Jocom J, Longton G, Flowers M, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. *Biol Blood Marrow Transplant* 1996;2:44-53.
217. King SM, Superina R, Andrews W, Winston DJ, Dunn S, Busuttil RW, et al. Randomized comparison of ganciclovir plus intravenous immune globulin (IVIG) with IVIG alone for prevention of primary cytomegalovirus disease in children receiving liver transplants. *Clin Infect Dis* 1997;25:1173-9.
218. Sullivan KM, Kopecky KJ, Jocom J, Fisher L, Buckner CD, Meyers JD, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990;323:705-12.
219. Caccavelli L, Field AC, Betin V, Dreillard L, Belair MF, Bloch MF, et al. Normal IgG protects against acute graft-versus-host disease by targeting CD4(+)CD134(+) donor alloreactive T cells. *Eur J Immunol* 2001;31:2781-90.
220. Cordonnier C, Chevret S, Legrand M, Rafi H, Dhedin N, Lehmann B, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. *Ann Intern Med* 2003;139:8-18.
221. Jordan SC, Vo A, Bunnapradist S, Toyoda M, Peng A, Puliya D, et al. Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation* 2003;76:631-6.
222. Casadei DH, del CRM, Opelz G, Golberg JC, Argento JA, Greco G, et al. A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal antibodies for rescue of kidney grafts with steroid-resistant rejection. *Transplantation* 2001;71:53-8.
223. Montgomery RA, Zachary AA, Racusen LC, Leffell MS, King KE, Burdick J, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation* 2000;70:887-95.
224. Schweitzer EJ, Wilson JS, Fernandez-Vina M, Fox M, Gutierrez M, Wiland A, et al. A high panel-reactive antibody rescue protocol for cross-match-positive live donor kidney transplants. *Transplantation* 2000;70:1531-6.
225. Glotz D, Antoine C, Julia P, Suberbielle-Boissel C, Boudjeltia S, Fraoui R, et al. Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). *Am J Transplant* 2002;2:758-60.
226. Jordan S, Cunningham-Rundles C, McEwan R. Utility of intravenous immune globulin in kidney transplantation: efficacy, safety, and cost implications. *Am J Transplant* 2003;3:653-64.
227. Riechsteiner G, Speich R, Schanz U, Russi EW, Weder W, Boehler A. Haemolytic anaemia after lung transplantation: an immune-mediated phenomenon? *Swiss Med Wkly* 2003;133:143-7.
228. Lloyd AJ, Walker C, Wilkinso M. Kawasaki disease: is it caused by an infectious agent? *Br J Biomed Sci* 2001;58:122-8.
229. Sundel RP. Update on the treatment of Kawasaki disease in childhood. *Curr Rheumatol Rep* 2002;4:474-82.
230. Tse SM, Silverman ED, McCrindle BW, Yeung RS. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. *J Pediatr* 2002;140:450-5.
231. Muta H, Ishii M, Egami K, Furui J, Sugahara Y, Akagi T, et al. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. *J Pediatr* 2004;144:496-9.
232. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-9.
233. Oates-Whitehead R, Baumer J, Haines L, Love S, Maconochie I, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2003;4:CD004000.
234. Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995;96:1057-61.
235. Leung DY. Kawasaki syndrome: immunomodulatory benefit and potential toxin neutralization by intravenous immune globulin. *Clin Exp Immunol* 1996;104(suppl 1):49-54.
236. Leung DY. Superantigens related to Kawasaki syndrome. *Springer Semin Immunopathol* 1996;17:385-96.
237. Wolf HM, Eibl MM. Immunomodulatory effect of immunoglobulins. *Clin Exp Rheumatol* 1996;14(suppl 15):S17-25.
238. Xu C, Poirier B, Van Huyen JP, Lucchiari N, Michel O, Chevalier J, et al. Modulation of endothelial cell function by normal polyspecific human intravenous immunoglobulins: a possible mechanism of action in vascular diseases. *Am J Pathol* 1998;153:1257-66.
239. Church JA, Fox S, Gomperts E. Effects of high-dose intravenous immunoglobulin on virus load in HIV-infected children. *J Acquir Immune Defic Syndr* 1999;22:309-11.
240. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002;CD001090.
241. Werdan K. Pathophysiology of septic shock and multiple organ dysfunction syndrome and various therapeutic approaches with special emphasis on immunoglobulins. *Ther Apher* 2001;5:115-22.
242. Friedman CA, Wender DF, Temple DM, Rawson JE. Intravenous gamma globulin as adjunct therapy for severe group B streptococcal disease in the newborn. *Am J Perinatol* 1990;7:1-4.
243. Kaul R, McGeer A, Norrby-Teglund A, Kotb M, Schwartz B, O'Rourke K, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. The Canadian Streptococcal Study Group. *Clin Infect Dis* 1999;28:800-7.

244. Jackson MA, Colombo J, Boldrey A. Streptococcal fasciitis with toxic shock syndrome in the pediatric patient. *Orthop Nurs* 2003;22:4-8.
245. Perez CM, Kubak BM, Cryer HG, Salehmugodam S, Vespa P, Farmer D. Adjunctive treatment of streptococcal toxic shock syndrome using intravenous immunoglobulin: case report and review. *Am J Med* 1997; 102:111-3.
246. Yong JM. Necrotising fasciitis. *Lancet* 1994;343:1427.
247. Barry W, Hudgins L, Donta ST, Pesanti EL. Intravenous immunoglobulin therapy for toxic shock syndrome. *JAMA* 1992;267:3315-6.
248. Werdan K, Pilz G. Supplemental immune globulins in sepsis: a critical appraisal. *Clin Exp Immunol* 1996;104(suppl 1):83-90.
249. Douzinas EE, Pitaridis MT, Louris G, Andrianakis I, Katsouyanni K, Karpaliotis D, et al. Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins. *Crit Care Med* 2000;28:8-15.
250. Jensen HB, Pollock BH. The role of intravenous immunoglobulin for the prevention and treatment of neonatal sepsis. *Semin Perinatol* 1998;22:50-63.
251. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev* 2001;CD001239.
252. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. *Ann Intern Med* 1988;109:783-8.
253. Whimby E, Champlin RE, Englund JA, Mirza NQ, Piedra PA, Goodrich JM, et al. Combination therapy with aerosolized ribavirin and intravenous immunoglobulin for respiratory syncytial virus disease in adult bone marrow transplant recipients. *Bone Marrow Transplant* 1995;16:393-9.
254. Ghosh S, Champlin RE, Englund J, Giral SA, Rolston K, Raad I, et al. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant* 2000;25:751-5.
255. DeVincenzo JP, Hirsch RL, Fuentes RJ, Top FH Jr. Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation—a compassionate use experience. *Bone Marrow Transplant* 2000;25:161-5.
256. Wang EE, Tang NK. Immunoglobulin for preventing respiratory syncytial virus infection. *Cochrane Database Syst Rev* 2000;CD001725.
257. Tokat O, Kelebek N, Turker G, Kahveci SF, Ozcan B. Intravenous immunoglobulin in adult varicella pneumonia complicated by acute respiratory distress syndrome. *J Int Med Res* 2001;29:252-5.
258. Sabroe I, McHale J, Tait DR, Lynn WA, Ward KN, Shaunak S. Treatment of adenoviral pneumonitis with intravenous ribavirin and immunoglobulin. *Thorax* 1995;50:1219-20.
259. Ramisse F, Szatanik M, Binder P, Alonso JM. Passive local immunotherapy of experimental staphylococcal pneumonia with human intravenous immunoglobulin. *J Infect Dis* 1993;168:1030-3.
260. De Hennezel L, Ramisse F, Binder P, Marchal G, Alonso JM. Effective combination therapy for invasive pneumococcal pneumonia with ampicillin and intravenous immunoglobulins in a mouse model. *Antimicrob Agents Chemother* 2001;45:316-8.
261. Guarino A, Canani RB, Russo S, Albano F, Canani MB, Ruggeri FM, et al. Oral immunoglobulins for treatment of acute rotaviral gastroenteritis. *Pediatrics* 1994;93:12-6.
262. Melamed I, Griffiths AM, Roifman CM. Benefit of oral immune globulin therapy in patients with immunodeficiency and chronic diarrhea. *J Pediatr* 1991;119:486-9.
263. Losonsky GA, Johnson JP, Winkelstein JA, Yolken RH. Oral administration of human serum immunoglobulin in immunodeficient patients with viral gastroenteritis. A pharmacokinetic and functional analysis. *J Clin Invest* 1985;76:2362-7.
264. Kanfer EJ, Abrahamson G, Taylor J, Coleman JC, Samson DM. Severe rotavirus-associated diarrhoea following bone marrow transplantation: treatment with oral immunoglobulin. *Bone Marrow Transplant* 1994; 14:651-2.
265. Guarino A, Guandalini S, Albano F, Mascia A, De Ritis G, Rubino A. Enteral immunoglobulins for treatment of protracted rotaviral diarrhea. *Pediatr Infect Dis J* 1991;10:612-4.
266. Hammarstrom V, Smith CI, Hammarstrom L. Oral immunoglobulin treatment in *Campylobacter jejuni* enteritis. *Lancet* 1993;341:1036.
267. Salcedo J, Keates S, Pothoulakis C, Warny M, Castagliuolo I, LaMont JT, et al. Intravenous immunoglobulin therapy for severe *Clostridium difficile* colitis. *Gut* 1997;41:366-70.
268. Leung DY, Kelly CP, Boguniewicz M, Pothoulakis C, LaMont JT, Flores A. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by *Clostridium difficile* toxin. *J Pediatr* 1991;118:633-7.
269. Ljungman P, Cordonnier C, Einsele H, Bender-Gotze C, Bosi A, Dekker A, et al. Use of intravenous immune globulin in addition to antiviral therapy in the treatment of CMV gastrointestinal disease in allogeneic bone marrow transplant patients: a report from the European Group for Blood and Marrow Transplantation (EBMT). *Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant* 1998;21:473-6.
270. Dwyer JM, Erlendsson K. Intraventricular gamma-globulin for the management of enterovirus encephalitis. *Pediatr Infect Dis J* 1988;7:S30-3.
271. Erlendsson K, Swartz T, Dwyer JM. Successful reversal of echovirus encephalitis in X-linked hypogammaglobulinemia by intraventricular administration of immunoglobulin. *N Engl J Med* 1985;312:351-3.
272. Mease PJ, Ochs HD, Wedgwood RJ. Successful treatment of echovirus meningoencephalitis and myositis-fasciitis with intravenous immune globulin therapy in a patient with X-linked agammaglobulinemia. *N Engl J Med* 1981;304:1278-81.
273. Mease PJ, Ochs HD, Corey L, Dragavon J, Wedgwood RJ. Echovirus encephalitis/myositis in X-linked agammaglobulinemia. *N Engl J Med* 1985;313:758.
274. Misbah SA, Spickett GP, Ryba PC, Hockaday JM, Kroll JS, Sherwood C, et al. Chronic enteroviral meningoencephalitis in agammaglobulinemia: case report and literature review. *J Clin Immunol* 1992; 12:266-70.
275. Quartier P, Foray S, Casanova JL, Hau-Rainsard I, Blanche S, Fischer A. Enteroviral meningoencephalitis in X-linked agammaglobulinemia: intensive immunoglobulin therapy and sequential viral detection in cerebrospinal fluid by polymerase chain reaction. *Pediatr Infect Dis J* 2000; 19:1106-8.
276. Rotbart HA, Kinsella JP, Wasserman RL. Persistent enterovirus infection in culture-negative meningoencephalitis: demonstration by enzymatic RNA amplification. *J Infect Dis* 1990;161:787-91.
277. von der Wense A, Herrmann B, Deppermann R, Harms F, Wehinger H. Intrathecal interferon therapy in chronic echovirus meningoencephalitis in Bruton type agammaglobulinemia. *Klin Padiatr* 1998;210:51-5.
278. Rotbart HA, Webster AD. Treatment of potentially life-threatening enterovirus infections with pleconaril. *Clin Infect Dis* 2001;32:228-35.
279. Schmugge M, Lauener R, Bossart W, Seger RA, Gungor T. Chronic enteroviral meningo-encephalitis in X-linked agammaglobulinemia: favourable response to anti-enteroviral treatment. *Eur J Pediatr* 1999; 158:1010-1.
280. Koduri PR, Kumapley R, Valladares J, Teter C. Chronic pure red cell aplasia caused by parvovirus B19 in AIDS: use of intravenous immunoglobulin—a report of eight patients. *Am J Hematol* 1999;61: 16-20.
281. Mareschal-Desandes R, Andre JL, Lesesve JF, Krier MJ, Bordigoni P, Humbert JC. Successful treatment of chronic parvovirus B19 infection by high-dose immunoglobulin. *Clin Nephrol* 2003;59:311-2.
282. Rugolotto S, Padovani EM, Sanna A, Chiaffoni GP, Marradi PL, Borgna-Pignatti C. Intrauterine anemia due to parvovirus B19: successful treatment with intravenous immunoglobulins. *Haematologica* 1999;84:668-9.
283. Kerr JR, Cuniffe VS, Kelleher P, Bernstein RM, Bruce IN. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003;36: e100-6.
284. Voss LM, Wilson NJ, Neutze JM, Whitlock RM, Ameratunga RV, Cairns LM, et al. Intravenous immunoglobulin in acute rheumatic fever: a randomized controlled trial. *Circulation* 2001;103:401-6.
285. Prins C, Vittorio C, Padilla RS, Hunziker T, Itin P, Forster J, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology* 2003;207:96-9.
286. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003;139:33-6.

287. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami Experience. *Arch Dermatol* 2003;139:39-43.
288. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3.
289. Fontaine J, Joly P, Roujeau JC. Treatment of bullous pemphigoid. *J Dermatol* 2003;30:83-90.
290. Scully C, Challacombe SJ. Pemphigus vulgaris: update on etiopathogenesis, oral manifestations, and management. *Crit Rev Oral Biol Med* 2002;13:397-408.
291. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001;45:825-35.
292. Ahmed AR. Intravenous immunoglobulin therapy in the treatment of patients with pemphigus vulgaris unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001;45:679-90.
293. Sami N, Bhol KC, Ahmed AR. Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human alpha6 integrin. *Clin Exp Immunol* 2002;129:533-40.
294. Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. *J Am Acad Dermatol* 2002;46:42-9.
295. Sami N, Qureshi A, Ruocco E, Ahmed AR. Corticosteroid-sparing effect of intravenous immunoglobulin therapy in patients with pemphigus vulgaris. *Arch Dermatol* 2002;138:1158-62.
296. Bystryn JC, Jiao D, Natow S. Treatment of pemphigus with intravenous immunoglobulin. *J Am Acad Dermatol* 2002;47:358-63.
297. Jolles S. A review of high-dose intravenous immunoglobulin (hdIVIg) in the treatment of the autoimmune blistering disorders. *Clin Exp Dermatol* 2001;26:127-31.
298. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003;139:1051-9.
299. Greaves MW. Pathophysiology of chronic urticaria. *Int Arch Allergy Immunol* 2002;127:3-9.
300. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woitschlag M, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; 96:2606-12.
301. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001;107:1056-62.
302. Altschul A, Cunningham-Rundles C. Chronic urticaria and angioedema as the first presentations of common variable immunodeficiency. *J Allergy Clin Immunol* 2002;110:664-5.
303. O'Donnell BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998;138:101-6.
304. Asero R. Are IVIG for chronic unremitting urticaria effective? *Allergy* 2000;55:1099-101.
305. Dawn G, Urcelay M, Ah-Weng A, O'Neill SM, Douglas WS. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. *Br J Dermatol* 2003;149:836-40.
306. Jolles S, Sewell C, Webster D, Ryan A, Heelan B, Waite A, et al. Adjunctive high-dose intravenous immunoglobulin treatment for resistant atopic dermatitis: efficacy and effects on intracellular cytokine levels and CD4 counts. *Acta Derm Venereol* 2003;83:433-7.
307. Jolles S, Hughes J, Rustin M. The treatment of atopic dermatitis with adjunctive high-dose intravenous immunoglobulin: a report of three patients and review of the literature. *Br J Dermatol* 2000;142:551-4.
308. Kimata H. High dose gammaglobulin treatment for atopic dermatitis. *Arch Dis Child* 1994;70:335-6.
309. Paul C, Lahfa M, Bachelez H, Chevrete S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002;147: 518-22.
310. Gurmin V, Mediawake R, Fernando M, Whittaker S, Rustin MH, Beynon HL. Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *Br J Dermatol* 2002;147:554-7.
311. Bulletti C, Flamigni C, Giacomucci E. Reproductive failure due to spontaneous abortion and recurrent miscarriage. *Hum Reprod Update* 1996;2:118-36.
312. Carp HJ, Ahiron R, Mashiach S, Schonfeld Y, Gazit E, Toder V. Intravenous immunoglobulin in women with five or more abortions. *Am J Reprod Immunol* 1996;35:360-2.
313. Daya S, Gunby J, Porter F, Scott J, Clark DA. Critical analysis of intravenous immunoglobulin therapy for recurrent miscarriage. *Hum Reprod Update* 1999;5:475-82.
314. Scott JR. Immunotherapy for recurrent miscarriage. *Cochrane Database Syst Rev* 2003;CD000112.
315. Croonenberghs J, Wauters A, Devreese K, Verkerk R, Scharpe S, Bosmans E, et al. Increased serum albumin, gamma globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. *Psychol Med* 2002;32: 1457-63.
316. Vojdani A, Campbell AW, Anyanwu E, Kashanian A, Bock K, Vojdani E. Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, *Chlamydia pneumoniae* and streptococcus group A. *J Neuroimmunol* 2002; 129:168-77.
317. Plioplys AV. Intravenous immunoglobulin treatment of children with autism. *J Child Neurol* 1998;13:79-82.
318. DeGiudice-Asch G, Simon L, Schmeidler J, Cunningham-Rundles C, Hollander E. Brief report: a pilot open clinical trial of intravenous immunoglobulin in childhood autism. *J Autism Dev Disord* 1999;29: 157-60.
319. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264-71.
320. Snider LA, Swedo SE. Childhood-onset obsessive-compulsive disorder and tic disorders: case report and literature review. *J Child Adolesc Psychopharmacol* 2003;13(suppl 1):S81-8.
321. Nicolson R, Swedo SE, Lenane M, Bedwell J, Wudarsky M, Gochman P, et al. An open trial of plasma exchange in childhood-onset obsessive-compulsive disorder without poststreptococcal exacerbations. *J Am Acad Child Adolesc Psychiatry* 2000;39:1313-5.
322. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999;354:1153-8.
323. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, Tymms K, Wakefield D, Dwyer J, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med* 1997;103:38-43.
324. Winnie GB, Cowan RG, Wade NA, Cairo MS. Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. *J Pediatr* 1989;114:309-14.
325. Garside JP, Kerrin DP, Brownlee KG, Gooi HC, Taylor JM, Conway SP. Immunoglobulin and IgG subclass levels in a regional pediatric cystic fibrosis clinic. *Pediatr Pulmonol* 2005;39:135-40.
326. Bentur L, McKlusky I, Levison H, Roifman CM. Advanced lung disease in a patient with cystic fibrosis and hypogammaglobulinemia: response to intravenous immune globulin therapy. *J Pediatr* 1990;117:741-3.
327. Matthews WJ Jr, Williams M, Oliphant B, Geha R, Colten HR. Hypogammaglobulinemia in patients with cystic fibrosis. *N Engl J Med* 1980;302:245-9.
328. Drucker NA, Colan SD, Lewis AB, Beiser AS, Wessel DL, Takahashi M, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. *Circulation* 1994;89:252-7.
329. Briassoulis G, Papadopoulos G, Zavras N, Pailopoulos V, Hatzis T, Thanopoulos V. Cardiac troponin I in fulminant adenovirus myocarditis treated with a 24-hour infusion of high-dose intravenous immunoglobulin. *Pediatr Cardiol* 2000;21:391-4.
330. Takeda Y, Yasuda S, Miyazaki S, Daikoku S, Nakatani S, Nonogi H. High-dose immunoglobulin G therapy for fulminant myocarditis. *Jpn Circ J* 1998;62:871-2.
331. Tedeschi A, Airaghi L, Giannini S, Ciceri L, Massari FM. High-dose intravenous immunoglobulin in the treatment of acute myocarditis. A case report and review of the literature. *J Intern Med* 2002;251:169-73.
332. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation* 2001;103:2254-9.

333. 2002 Immune Deficiency Foundation patient survey. Available at: <http://www.primaryimmune.org/pid/survey.htm>. Accessed November 1, 2005.
334. Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. *Haematologica* 1993;78:35-40.
335. Stangel M, Hartung HP, Marx P, Gold R. Side effects of high-dose intravenous immunoglobulins. *Clin Neuropharmacol* 1997;20:385-93.
336. Eibl MM. Intravenous immunoglobulins in neurological disorders: safety issues. *Neurol Sci* 2003;24(suppl 4):S222-6.
337. Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile. *Pharmacol Ther* 2004;102:177-93.
338. Razvi S, Schneider L, Jonas MM, Cunningham-Rundles C. Outcome of intravenous immunoglobulin-transmitted hepatitis C virus infection in primary immunodeficiency. *Clin Immunol* 2001;101:284-8.
339. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. *Ann Intern Med* 1980;93:55-6.
340. Berger M, Cupps TR, Fauci AS. High-dose immunoglobulin replacement therapy by slow subcutaneous infusion during pregnancy. *JAMA* 1982;247:2824-5.
341. Welch MJ, Stiehm ER. Slow subcutaneous immunoglobulin therapy in a patient with reactions to intramuscular immunoglobulin. *J Clin Immunol* 1983;3:285-6.
342. Leahy MF. Subcutaneous immunoglobulin home treatment in hypogammaglobulinaemia. *Lancet* 1986;2:48.
343. Smith GN, Griffiths B, Mollison D, Mollison PL. Uptake of IgG after intramuscular and subcutaneous injection. *Lancet* 1972;1:1208-12.
344. Weiler CR. Immunoglobulin therapy: history, indications, and routes of administration. *Int J Dermatol* 2004;43:163-6.
345. Thomas MJ, Brennan VM, Chapel HH. Rapid subcutaneous immunoglobulin infusions in children. *Lancet* 1993;342:1432-3.
346. Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. *Arch Dis Child* 1998;79:48-51.
347. Gardulf A, Bjorvell H, Gustafson R, Hammarstrom L, Smith CI. The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions. *Clin Exp Immunol* 1993;92:200-4.
348. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics* 1996;98:1127-31.
349. Dams ET, van der Meer JW. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies. *Lancet* 1995;345:864.
350. Grunebaum E, Levy Y, Shoenfeld Y. Novel aspects of hypogammaglobulinemic states: subcutaneous immunoglobulin treatment. *Isr Med Assoc J* 2002;4:288-9.
351. Gardulf A, Bjorvell H, Gustafson R, Hammarstrom L, Smith CI. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. *Immunodeficiency* 1993;4:81-4.
352. Sundin U, Nava S, Hammarstrom L. Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy. *Clin Exp Immunol* 1998;112:341-6.
353. Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Bock A, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol* 2004;114:936-42.
354. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004;112:1-7.
355. Christiansen OB, Nielsen HS. Intravenous immunoglobulin in the prevention of recurrent miscarriage: does it work? *Chem Immunol Allergy* 2005;88:117-27.
356. Clark DA, Coulam CB, Stricker RB. Is intravenous immunoglobulin (IVIG) efficacious in early pregnancy failure? A critical review and meta-analysis for patients who fail in vitro fertilization and embryo transfer (IVF). *J Assist Reprod Genet* 2006 Jan 19;1-13 [E-pub ahead of print].
357. Beck CE, Nathan PC, Parkin PC, Blanchette VS, Macarthur C. Corticosteroids versus intravenous immune globulin for the treatment of acute immune thrombocytopenic purpura in children: a systematic review and meta-analysis of randomized controlled trials. *J Pediatr* 2005;147:521-7.