Work Group Report of the American Academy of Allergy, Asthma & Immunology

Update on the use of immunoglobulin in human disease: A review of evidence

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Human immunoglobulin preparations for intravenous or subcutaneous administration are the cornerstone of treatment in patients with primary immunodeficiency diseases affecting the humoral immune system. Intravenous preparations have a number of important uses in the treatment of other diseases in humans as well, some for which acceptable treatment alternatives do not exist. We provide an update of the evidence-based guideline on immunoglobulin therapy, last published in 2006. Given the potential risks and inherent scarcity of human immunoglobulin, careful consideration of its indications and administration is warranted. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

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Immunoglobulin is increasingly recognized as a treatment of a variety of medical conditions, not only for its ability to fight infection as a replacement therapy but also for its anti-inflammatory and immunomodulating effects. The appropriate use of immunoglobulin can be life-saving. However, its administration can lead to numerous adverse events and potential additional adverse consequences.[1] Due to finite supply, possible adverse events, and the need for further research in some applications of therapeutic immunoglobulin, it is important for clinicians prescribing immunoglobulin to be familiar with current clinical indications and levels of evidence in support of its use in these conditions. This document is intended as an update of the 2006 American Academy of Allergy, Asthma & Immunology guideline[2] and centers on the use of standard immunoglobulin preparations specifically manufactured for intravenous (IV) or subcutaneous (SC) administration. The SC route of administration has become more utilized in the United States, so we include an expanded section to cover practical considerations surrounding the administration of immunoglobulin subcutaneously. Clinical indications for which IV immunoglobulin (IVIG) have been licensed by the US Food and Drug Administration (FDA) include (Table I): (1) treatment of primary immunodeficiencies (PIs); (2) prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent bacterial infection due to B-cell chronic lymphocytic leukemia (CLL); (3) prevention of coronary artery aneurysms in Kawasaki disease (KD); (4) prevention of infections, pneumonitis, and acute graft-versus-host disease (GVHD) following bone marrow transplantation; (5) reduction of serious bacterial infection in children infected with HIV; (6) increasing platelet count in idiopathic thrombocytopenic purpura

Abbreviations used

AD:	Atopic dermatitis
APS:	Anti–phospholipid antibody syndrome
AT:	Ataxia telangiectasia
BMI:	Body mass index
CIDP:	Chronic inflammatory demyelinating polyneuropathy
CLL:	Chronic lymphocytic leukemia
CVID:	Common variable immunodeficiency
DSA:	Donor-specific HLA antigen
FDA:	US Food and Drug Administration
GBS:	Guillain-Barré syndrome
GVHD:	Graft-versus-host disease
HAART:	Highly active antiretroviral treatment
ISR:	Infusion site reaction
ITP:	Immune thrombocytopenic purpura
IV:	Intravenous
IVIG:	Intravenous immunoglobulin
JIA:	Juvenile idiopathic arthritis
KD:	Kawasaki disease
LEMS:	Lambert-Eaton myasthenic syndrome
MG:	Myasthenia gravis
MM:	Multiple myeloma
MMN:	Multifocal motor neuropathy
MS:	Multiple sclerosis
PAN:	Polyarteritis nodosa
PE:	Plasma exchange
PI:	Primary immunodeficiency
RA:	Rheumatoid arthritis
RCT:	Randomized controlled trial
RSV:	Respiratory syncytial virus
SC:	Subcutaneous
SCID:	Severe combined immunodeficiency
SCIG:	Subcutaneous immunoglobulin
SCORAD:	Severity scoring of Alzheimer disease
THI:	Transient hypogammaglobulinemia
VOD:	Veno-occlusive disease
WAS:	Wiskott-Aldrich syndrome
XLA:	X-linked agammaglobulinemia

to prevent or control bleeding; and (7) treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) and, more recently, multifocal motor neuropathy (MMN).[3,4] Despite these indications, none of the original immunoglobulin products that were specifically licensed for use in pediatric HIV or post–bone marrow transplantation are still available in the US market. The only licensed indication of SC immunoglobulin (SCIG) to date is PI disease.

This document reviews the basis for the FDA-approved indications and discusses other disease states in which immunoglobulin therapy has been used. Some of these other conditions are extremely rare, making randomized controlled trials (RCTs) difficult. Others, however, are quite common, and rigorous scientific evaluation of immunoglobulin utility has been possible. Immunoglobulin holds great promise as a useful therapeutic agent in some of these diseases, whereas in others it is ineffectual and may actually increase risks to the patient. Thus, the evidence supporting the use of immunoglobulin in these conditions has been reviewed and categorized (Table II). Current recommendations for the appropriate use of immunoglobulin are outlined in this summary. There are relatively few studies looking at SCIG for indications other than PI; however, the SC route is emerging as an alternative for maintenance therapy in patients on IVIG for CIDP as well as other muscle and nerve disorders.[5-7]

This updated summary is current through June 2015 and does not reflect clinical research or reports that have become available since that time. Although prior reviews of evidence were considered to have arrived 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 *IGIV, IVIG, intravenous immunoglobulin, intravenous immune globulin, subcutaneous immunoglobulin,* and *subcutaneous immune globulin,* along with key words specific for each disease-related topic. The recommendations for appropriate use stated here were based on this literature review but will most certainly change over time as experience and understanding of these diseases increase.

PRIMARY IMMUNODEFICIENCY

Immunoglobulin replacement therapy via the IV or SC route is required in patients with certain PI diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infection (Table III).[8,9]

Replacement therapy for agammaglobulinemia and hypogammaglobulinemia in well-described immunodeficiencies such as X-linked agammaglobulinemia (XLA) or common variable immunodeficiency (CVID) is necessary and life-saving. Other more genetically complex PIs, however, may also involve defects in antibody function that contribute to an increased susceptibility to infections. Over 250 distinct PIs have been described to date, and with the advent of whole-exome sequencing, new PIs continue to be discovered at a rapid pace.[10] The effects of these newly described gene defects on the humoral immune system may not be fully understood or qualified with currently commercially available tests of antibody level and function. Therefore, the indications of immunoglobulin therapy in various clinical presentations of immunodeficiency are likely to broaden as the disorders are better understood, considering that a majority of PI diseases involve antibody deficiency. A recent publication reviewed the controversies surrounding immunoglobulin therapy, including the need for better laboratory assays of functional antibody responses and better clinical and microbiological evaluation and characterization of the recurrent infections seen in antibody-deficient patients.[11] Here, we provide a framework of 6 distinct phenotypes of PI disease for which immunoglobulin replacement is or may be indicated[12]: (1) agammaglobulinemia due to absence of B cells; (2) hypogammaglobulinemia with poor antibody function; (3) normal immunoglobulins with poor antibody function; (4) hypogammaglobulinemia with normal antibody function; (5) isolated IgG subclass deficiency with recurrent infections; and (6) recurrent infections due to a complex immune mechanism related to a genetically defined PI disease. These categories are briefly discussed subsequently (examples are not all-inclusive of the category described).

Agammaglobulinemia due to the absence of B cells

Agammaglobulinemia due to the absence of B cells is the clearest indication of immunoglobulin replacement. Evaluation of IVIG usage in patients lacking immunoglobulin has demonstrated a clear benefit in terms of reducing both acute

TABLE I. FDA-approved indications of IVIG

Disease state	No. of FDA-licensed products*	Indication†
PI disease, or primary humoral immunodeficiency	12	Indicated for the treatment of PI states, or for elevation of circulating antibody levels in PI, or for replacement therapy of PI states in which severe impairment of antibody forming capacity has been shown
Idiopathic thrombocytopenic purpura	5	Indicated when a rapid rise in platelet count is needed to prevent and/or control bleeding in idiopathic thrombocytopenic purpura, or to allow a patient with idiopathic thrombocytopenic purpura to undergo surgery
B-cell CLL	2	Indicated for the prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell CLL
CIDP	2	Indicated for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse
KD	2	Indicated for the prevention of coronary artery aneurisms associated with Kawasaki disease
MMN	1	Indicated as a maintenance therapy to improve muscle strength and disability in adult patients with MMN
Bone marrow transplantation	0	Indicated for bone marrow transplant patients ≥20 y of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic etiologies and acute GVHD in the first 100 d after transplantation
HIV infection	0	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

*Refer to Table XIII 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.

and chronic infections.[8,13,14] Retrospective analyses of data from agammaglobulinemic children have revealed that the number and severity of infectious complications are inversely correlated with the dose of IVIG administered.[14,15] In particular, when IgG trough levels were maintained above 800 mg/dL, serious bacterial illness and enteroviral meningoencephalitis were prevented.[14] A recent meta-analysis of data from studies in subjects with agammaglobulinemia described a decreased risk for pneumonia with increasing trough levels of up to 1000 mg/dL.[16] Although agammaglobulinemia is rare, it provides insight into the value of immunoglobulin replacement in preventing disease due to defective humoral immunity that can be extrapolated to other antibody-deficient states. In severe combined immunodeficiency (SCID), the T-cell defect is often accompanied by an absence of B cells or B-cell function. Therefore, immunoglobulin replacement is warranted at diagnosis because transplacental maternal IgG wanes over time. In the setting of SCID, immunoglobulin replacement is also necessary in the post-transplantation period, during gene therapy or enzyme replacement (for adenosine deaminase deficiency), until B-cell function is restored.[17,18] In some cases, B-cell function is never restored, and continual immunoglobulin replacement remains necessary.

Hypogammaglobulinemia with impaired specific antibody production

Deficient antibody production is characterized by decreased immunoglobulin concentrations and/or a significant inability to respond with IgG antibody on antigen challenge. In patients with recurrent bacterial infections, reduced levels of serum immunoglobulin, coupled with a lack of response to protein and/or polysaccharide vaccine challenge (ie, in patients who cannot make IgG antibody against diphtheria and tetanus toxoids and/or pneumococcal polysaccharide vaccine), are a clear indication of immunoglobulin replacement.

The prototype of this category is CVID, the most commonly diagnosed and heterogeneous antibody-deficiency disorder. An early study of IVIG in patients in this setting showed that IVIG was associated with a reduced prevalence of infection compared with the infection rate prior to IVIG treatment.[19] IVIG was also associated with lower infection rates compared with those with intramuscular immunoglobulin in patients in direct-comparison studies.[20,21] Because patients with CVID are at higher risk for chronic lung disease and pulmonary deterioration as a result of chronic or subclinical infection,[22,23] early recognition of the diagnosis and initiation of IVIG therapy are crucial.[23] Adequate replacement of IgG has been associated with a reduced frequency of sinopulmonary infections, including pneumonia, which can lead to chronic lung inflammation and bronchiectasis.[24] Several publications have suggested that immunoglobulin replacement can decrease acute and chronic lung infections and may prevent or slow the progression of their sequelae in antibody-deficiency disorders, including XLA, CVID, and hyper-IgM.[8,13,14,19-21,24-29] The findings from a recent prospective study in 90 patients with CVID[25] and in a smaller group of patients with XLA, followed for up to 22 years, support individualizing doses and trough levels to attain infection-free outcomes rather than using a standardized dose in all patients by disease.[30] Consensus among the Canadian expert panel of immunologists is to follow clinical outcomes to monitor the effectiveness of immunoglobulin, with an increase in the dose to improve clinical effectiveness and not merely to increase trough levels.[31] Several reports have suggested that monitoring trough levels is insufficient because individuals may need doses >0.4-0.6 g/kg/month to prevent breakthrough infections.[32] Although double-blind, placebo-controlled studies demonstrating a benefit of immunoglobulin replacement in CVID and other antibody deficiencies

TABLE II. Categorization of evidence and basis of recommendation

Number	Definition
Evidence category	
Ia	From meta-analysis of RCTs
Ib	From at least one RCT
IIa	From at least one controlled trial without randomization
IIb	From at least one other type of quasi-experimental study
III	From non-experimental 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
NR	Not rated
Ordinal category*	
Definitely beneficial	
Probably beneficial	
May provide benefit	
Unlikely to provide benefit	

*Consider evidence category and strength of recommendation in clinical decision making regarding benefit of treatment with IVIG or SCIG.

TABLE III. Uses of immunoglobulin 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
	Distinct genetically defined PIs with variable defects in antibody quality and quantity*	IV	D
Probably beneficial	CLL with reduced IgG and history of infections	Ib	A
	Prevention of bacterial infection in HIV-infected children	Ib	A
	Primary immune defects with normal IgG and impaired specific antibody production	III	C
May provide benefit	Prevention of neonatal sepsis	Ia	A
	THI of infancy	IIb-III	C
	Other immune mechanism driving recurrent infections that affect B-cell function	IV	D
	Selective antibody deficiency "memory phenotype"	IV	D
	Isolated IgG subclass deficiency (IgG_1, IgG_2, IgG_3) with recurrent infections	III	C
Unlikely to be beneficial	Isolated IgE deficiency	IV	D
	Isolated IgG_4 deficiency	IV	D
	Selective IgA deficiency	IV	D
	Isolated IgM deficiency	IV	D

*Hyper-IgE syndrome, dedicator of cytokinesis 8 (DOCK8), STAT-1, nuclear factor-κB essential modulator (NEMO) among others.

are not available, the historical evidence and existing studies are compelling enough to indicate this therapy in these patients.

A new diagnostic criterion of CVID was recently proposed. It emphasizes the importance of clinical symptoms as a sign of immune system impairment, and this criterion is required for diagnosis, along with the fulfillment of major criteria (<500 mg/dL IgG, age of >4 years, absence of a secondary cause) plus either additional laboratory evidence or the presence of specific histologic markers of disease.[33] The implications for clinical practice are that patients with hypogammaglobulinemia of unclear significance would be monitored closely over time and that immunoglobulin would be initiated only after the full criteria, including symptoms of immune system failure, were met. However, exceptions to this concept were also discussed and include: (1) that significant autoimmunity, hypogammaglobulinemia, and additional laboratory evidence supporting CVID or the presence of relatively specific histologic markers would be sufficient for diagnosis; and (2) asymptomatic patients with severe hypogammaglobulinemia whose risk for bacterial sepsis or severe viral infection is unknown. In the latter group, it is unknown whether a fatal infection may be the first presentation of disease; therefore, clinical judgement, counseling, and close follow-up are recommended as part of the decision to start immunoglobulin replacement.[33] In contrast, the International

Consensus Document on CVID,[34] published in 2016 by an international coalition among the American Academy of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; the World Allergy Organization; and the American College of Allergy, Asthma & Immunology defines a diagnosis of CVID using the following criteria: (1) a serum IgG below the local/regional clinical laboratory normal range (measured on 2 occasions at least 3 weeks apart unless IgG is very low or it is in a patient's best interest to start therapy right away); (2) low IgA or IgM; (3) impaired vaccine responses; and (4) other causes have been excluded.[34] These criteria do not require additional laboratory data, specific histologic markers of disease, or genetic testing (although genetic testing may be useful in some, more complicated, cases).[34] Additionally, according to International Consensus, the diagnosis can be made in the absence of recurrent infections if the other criteria are met. The term *unspecified IgG deficiency* or *unspecified hypogammaglobulinemia* instead of *CVID* is suggested for cases that do not meet all of the International Consensus CVID criteria on initial evaluation (due to low IgG and poor antibody responses but normal IgA and IgM, or low IgG and IgA but normal vaccine responses), and these patients should also be followed clinically.[34] Antibody class–switch immune function defects are a group of disorders characterized by hypogammaglobulinemia with severely impaired production of specific antibody. Antibody class–switch defects include an X-linked type (CD40L deficiency) and autosomal recessive types (activation-induced cytidine deaminase, uracil-DNA glycosylase, and CD40 deficiency). Children with class-switch defects due to these deficiencies, also known as *hyper-IgM syndromes,* have decreased levels of IgG and IgA, and elevated or normal levels of low-affinity IgM antibodies. Although B cells are present, there is an inability to class-switch or generate memory B cells. As a result, individuals with the autosomal recessive forms (activation-induced cytidine deaminase and uracil-DNA glycosylase) have recurrent infections similar to those in patients with agammaglobulinemia. The X-linked form (CD40L deficiency) and the autosomal recessive CD40 deficiency also result in a combined defect, predisposing to opportunistic infections as well. Regular replacement therapy with immunoglobulin is crucial in individuals with this disorder, whether the disorder is of the X-linked or autosomal recessive variety, as reported in the 2 largest-scale series of patients.[27,29] In patients treated with IVIG, meningitis did not develop, and the incidence of pneumonia was reduced from 7.6% to 1.4% per year.[27,29] Similar trends were found in other infectious diseases, including upper respiratory infections, bronchitis, skin and soft tissue infections, osteomyelitis, mastoiditis, and adenitis.[27]

Normal levels of immunoglobulins with impaired specific-antibody production (selective antibody deficiency)

Patients with normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens following vaccination, can present a diagnostic challenge. Immunoglobulin replacement therapy should be provided when there is well-documented severe polysaccharide nonresponsiveness and evidence of recurrent infections with a proven requirement for antibiotic therapy.[35] A protective concentration of polysaccharide antigens is considered to be 1.3 μg/mL and conversion of a concentration from nonprotective to protective. A normal antibody response to polysaccharide antigens is defined differently according to age: In children ages 2-5 years, >50% of concentrations tested were considered protective, with an increase of at least 2-fold observed, and in patients ages 6-65 years, >70% of concentrations tested were considered protective.[36] Four phenotypes of selective antibody deficiency were recently defined: memory, mild, moderate, and severe. Any of these phenotypes may warrant antibiotic prophylaxis, immunoglobulin replacement, or both, depending on the clinical situation.[36] Patients with the memory phenotype are characterized as able to mount adequate concentrations against polysaccharide antigen but in whom the response wanes within 6 months.[36] While antibiotic prophylaxis may represent a first-line intervention in these patients, the severity of infection and/or the efficacy of antibiotic prophylaxis should be the driving force behind any decision to provide immunoglobulin replacement therapy. Further evidence of infection, including abnormal findings on sinus and lung imaging, complete blood count, C-reactive protein, and erythrocyte sedimentation rate can additionally support the need for immunoglobulin supplementation in these patients. In this setting, immunoglobulin therapy is appropriate in, but not limited to, patients with difficult-to-manage recurrent otitis media at risk for permanent hearing loss, bronchiectasis, recurrent infections necessitating IV antibiotics, failed antibiotic prophylaxis, impaired quality of life due to recurrent infections despite antibiotic prophylaxis, or multiple antibiotic hypersensitivities that interfere with treatment.

When the severity of infections, frequency of infections, level of impairment, or inefficacy of antibiotic prophylaxis warrants the use of immunoglobulin in this form of antibody deficiency, patients and/or their caregivers should be informed that the treatment may be stopped after a period of time (preferably in the spring in temperate regions) and that the immune response will be reevaluated at least 3-5 months after the discontinuation of immunoglobulin.[37] While some patients, usually children, show improved responses to antigen challenge (typically with pneumococcal polysaccharide vaccine) after treatment with immunoglobulin for 6-24 months and improve clinically, others require restarting the immunoglobulin therapy because of a recurrence of infections.[38,39] One or two cessations of therapy are likely to identify whether a patient's defect in antibody specificity was transient. Repeated multiple cessations of therapy to affect this determination are not useful and can potentially harm the patient.

Hypogammaglobulinemia with normal-quality antibody response

IgG levels normalize with age in transient hypogammaglobulinemia (THI). Antibody function, however, is initially partially impaired but ultimately typically intact.[40] In select cases, treatment with replacement immunoglobulin may be considered temporarily for the same reasons as those in patients described in the preceding section. In a study from Italy of IVIG as first-line treatment of severely symptomatic THI, 13 children were treated with 400 mg/kg every 3 weeks for 2-3 months and followed up for 1-3 years. Although the study did not include a control group, the investigators reported a decreased frequency of overall infections (from 0.39 to 0.047 infection/month/child) during follow-up, and normal antibody response to vaccination

5 months after the end of infusions.[41] Another recent retrospective study of IVIG in THI showed a decrease from 91% to 21% in the percentage of children with THI having >6-fold the number of febrile infections in a year. The group that received IVIG had lower IgG levels and defective anti–*Haemophilus influenza* type B antibodies at entry; however, no difference was noted in time to resolution of THI between the groups. Only about 10% of cases with THI were treated with IVIG at this tertiary care center, and these were the more severe phenotypes.[42] Age-specific normal ranges of IgG vary, and 2.5% of healthy individuals have "lower-than-normal" IgG (below the lower limit of the 95% confidence interval for age), which may not be clinically significant, in the absence of recurrent infections. Isolated hypogammaglobulinemia (other than THI) can be a feature of many immune function defects, and must be differentiated from secondary causes resulting from an increased loss of IgG, such as chylothorax, lymphangiectasia, or protein-losing enteropathy. One of the most common secondary causes of hypogammaglobulinemia is medication, especially corticosteroids, some seizure medications, and certain biologics such as rituximab.[43]

A subset of patients also present with very low IgG and no history of infection. Severe hypogammaglobulinemia should be considered a risk for infection and should be managed accordingly. In general, an IgG level ≤150 mg/dL is widely accepted as severe hypogammaglobulinemia, for which additional testing apart from verification of the low level is not required prior to starting replacement therapy. Levels between 150 and 250 mg/dL are also considered severely low but warrant consideration of additional testing for specific antibody against vaccines to assess function, depending on the clinical history.[44]

Normal immunoglobulin levels and normal quality with deficient IgG subclass (IgG_1, $_2$, $_3$)

Few controlled studies have addressed immunoglobulin replacement in isolated subclass deficiency. Isolated subclass deficiency is characterized by the IUIS within the predominantly antibody-deficiency category and is often asymptomatic, but a minority of patients may have poor antibody responses to specific antigens and recurrent infections.[10] Prophylactic antibiotics and the treatment of other underlying conditions, such as allergies or asthma, that may contribute to recurrent sinopulmonary infections are the usual management. Immunoglobulin replacement for this use has been controversial. However, at least 3 recently published studies—an open-label study in 10 patients,[45] a retrospective study in 17 adult patients with subclass 3 deficiency,[46] and a retrospective study in 132 patients with subclass deficiency[47]—demonstrated decreased infections, a need for antibiotics, and improved quality of life. In the open-label study in 10 patients, quality of life, prevalence of infection, and the need for antibiotics were reportedly improved with 12-month treatment with IVIG compared with 3-month observation without IVIG.[45] Four of the 17 patients in the retrospective study in adult patients with subclass 3 deficiency were treated with prophylactic antibiotics, and 13 of 17 were treated with IVIG. Of the 13 patients, 2 did not respond, 6 had "dramatic" relief from recurrent infections, and 5 had "moderate" relief.[46] In the retrospective study in 132 patients, 92 had a ≥50% reduction in the rate of respiratory tract infections requiring antibiotics ($P < .001$), and the overall reduction rate in respiratory tract infections was 61% ($P < .001$).[47] In concert with earlier studies of immunoglobulin therapy[48] (which showed a decrease in sinusitis with IVIG treatment to 1.8 ± 1.3 per year vs 8.2 ± 3.7 per year with antibiotics, and a decrease in otitis media from 4.6 ± 3.7 to 0.3 ± 0.5 per year), immunoglobulin replacement should remain a therapeutic option in patients in whom other ameliorative interventions have failed.

Immunoglobulin replacement therapy is not indicated for selective IgA deficiency; however, poor specific IgG antibody production, with or without IgG_2 subclass deficiency, may coexist with selective IgA deficiency. Sometimes immunoglobulin therapy may be required. In this case, however, it would be prudent to view this phenotype as one of selective antibody deficiency (see preceding text) owing to the known substantive role of missing antibody quality. Thus, while they are coincident and potentially compounding, focus should not be taken off of the selective IgG antibody deficiency as being the most relevant and more substantive than IgG_2 or IgA deficiency. IV administration of immunoglobulin can pose a risk for anaphylaxis in IgA-deficient patients who have IgE anti-IgA antibodies,[49] or reactions due to complement activation if IgG anti-IgA antibodies are present.[50,51] The vast majority of patients who have low serum IgA, with or without IgG anti-IgA antibodies, however, receive IVIG without difficulty, regardless of the IgA content.[50] A retrospective and prospective observational study evaluated the possible association of IgG and/or IgE anti-IgA with adverse reactions in a subgroup of IgA-deficient patients receiving immunoglobulin replacement. That study was unable to conclude any increased risk for adverse reactions associated with IgA deficiency, and recommended larger-scale, prospective trials to address this issue.[52] The investigators suggested that in an individual patient, the presence of IgG anti-IgA might be a biomarker of increased risk for non–IgE-mediated anaphylactoid reactions to immunoglobulin infusion containing IgA, but more studies are needed to determine whether class- or subclass-specific IgG anti-IgA antibodies have any clinical relevance.[52,53] In summary, if there is a specific concern, IgA-depleted IVIG might be safely used,[50] or the SC route of administration may also be used in patients with concerns about reactions to the IgA in immunoglobulin products.[54,55]

Recurrent infections due to an unknown immune mechanism

The need for immunoglobulin therapy may arise as the only viable option for therapy in PIs in which the mechanism underlying the susceptibility to recurrent infection is not yet characterized, yet the patient presents with recurrent infections and an otherwise normal or near-normal immune function evaluation. Likewise, there are other IUIS-defined immunodeficiencies[10] associated with variable defects in humoral immunity in which immunoglobulin replacement may be necessary, as in patients with the hyper-IgE syndrome who usually have normal serum IgG, IgM, and IgA levels, but who may have defects in antibody responses. These defects include poor anamnestic antibody responses to booster immunization with ϕX174, diphtheria and tetanus toxoids, pneumococcal and *H influenzae* vaccines, as well as poor antibody and cell-mediated responses to neoantigens such as keyhole limpet hemocyanin.[56,57] Rabies vaccine, which is available in the United States, has been used for assessing antibody responses in immunodeficient patients on immunoglobulin

replacement.[36,58,59] However, it is not currently recommended as a routine test in patients with PIs receiving immunoglobulin replacement, and further study is needed for defining its utility in these patients.[36] The *Salmonella typhi* Vi vaccine also has future potential use as a diagnostic neoantigen in patients with PIs, but more studies are needed.[36] Although there is significant phenotypic variation in the severity of pulmonary infections that is not necessarily predicted by deficits in antigen-specific antibody responses, some patients with hyper-IgE syndrome and recurrent respiratory infections may benefit from immunoglobulin replacement therapy.[60,61]

Wiskott-Aldrich syndrome (WAS) is another immunodeficiency typically characterized by normal total IgG, but with impaired specific-antibody responses against both protein and polysaccharide antigens.[62,63] Half of centers caring for WAS patients treat all patients with immunoglobulin replacement,[64] which appears to be effective in reducing the prevalence of infection.[65] Although it would be reasonable to consider patients with WAS as having selective antibody deficiency, not all patients with WAS exhibit this phenotype, and owing to the diffuse immune effects in WAS, immunoglobulin therapy should always be a consideration in this disease.

About 12-15% of patients with ataxia telangiectasia (AT) require immunoglobulin replacement. The best-characterized immunologic abnormalities observed in AT are deficiencies in IgA and IgG_2, affecting between 50% and 80% of cases,[25,35,39,62,66-68] and low total IgG levels, yet laboratory findings of deficiency in the specific adaptive immune system may correlate poorly with a history of susceptibility to infections.[66,69,70] The same considerations as for WAS apply to AT as well as others of these types of combined immunodeficiencies, including, but not limited to, deficiencies in STAT-3, nuclear factor-κB essential modulator (NEMO), and STAT-1.

Summary: Immunoglobulin in primary immunodeficiencies

PI was the first FDA-approved indication of immunoglobulin therapy. Immunoglobulin therapy is a mandatory and life-saving treatment in patients with severe PIs that directly affect B-cell function and antibody production, but it is also increasingly recognized as important in other PIs in which antibody or B-cell dysfunction is implicated but may not be as apparent by conventional testing. As more immunodeficiencies are described and their molecular mechanisms elucidated, it will be important to develop more refined laboratory tests for a comprehensive assessment of B-cell function. Immunodeficiencies are relatively rare disorders for which immunoglobulin therapy is vital for minimizing potentially fatal infections and improving quality of life and overall clinical outcomes. Clinical trials of immunoglobulin replacement are not feasible in the more rare disorders; hence, only lower evidence-based recommendation scores are available for some. Nonetheless, in some cases, clinical decision making supported by basic science must guide determinations regarding the benefits and necessity of immunoglobulin replacement therapy in PI diseases.

SECONDARY IMMUNODEFICIENCY

IG therapy has also been used in a number of diseases that result in or potentially result in a secondary humoral immunodeficiency. This section discusses immunoglobulin use in CLL, multiple myeloma (MM), pediatric HIV infection, prematurity, geriatrics, genetic syndromes associated with immunodeficiency, and hypogammaglobulinemia following bone marrow transplantation and solid organ transplantation and in patients treated with B cell–depleting therapies.

Chronic lymphocytic leukemia

The administration of immunoglobulin should be restricted to a carefully selected subset of patients with CLL. Patients with CLL, hypogammaglobulinemia, and recurrent bacterial infections should be considered for immunoglobulin replacement. These recommendations are based on several observations. First, the most common complication and cause of death in individuals with CLL is infection, which occurs mainly in patients with advanced disease and/or hypogammaglobulinemia. Second, hypogammaglobulinemia is prevalent; in one study, at least 1 isotype (IgG, IgM, or IgA) was found to be abnormally low in 48 of 50 patients (96.0%).[71] Third, IVIG was proven effective in reducing the number and severity of bacterial infections in a multicenter, cooperative, double-blind, placebo-controlled study that compared 0.4 mg/kg IVIG every 3 weeks to placebo. Following the report of a clinical response to IVIG in a patient with CLL and gram-positive pneumococcal infections, a European cooperative group conducted a multicenter, double-blind clinical trial that randomly assigned 84 patients with CLL and who were considered to be at increased risk for bacterial infection to receive IVIG 0.4 mg/kg body weight or placebo every 3 weeks for 1 year.[72] The at-risk group consisted of patients with IgG ≤50% of the lower limit of normal or a history of 1 or more serious infections since the onset of disease. Compared to the placebo group, the treatment group experienced significantly fewer bacterial infections and a longer time from study entry to first serious infection. Patients who completed a full year of treatment were most likely to benefit (14 vs 36; $P = .001$). That study demonstrated that selected patients with CLL deemed to be at risk can be protected from bacterial infections with regular IVIG infusions.

Another study constructed a model comparing treatment with IVIG and placebo.[73] Baseline estimates of the efficacy of IVIG were derived from the published results of the randomized trial from Europe. The analysis revealed that quality-adjusted life expectancy was not improved and that the expense of the therapy was thought to outweigh its benefits.[73] Thus, IVIG may not be a cost-effective way to prevent infection in most patients with CLL.[74] A systematic review and meta-analysis of RCTs comparing IVIG prophylaxis versus control showed no survival benefit, but there was a significant decrease in the occurrence of documented and major infections.[75] Adverse events that typically do not require the discontinuation of IVIG were significantly more prevalent with IVIG. The investigators concluded that IVIG cannot be recommended routinely in patients with CLL and hypogammaglobulinemia with or without recurrent infections and should be considered on an individualized basis.[75]

In summary, given the positive evidence that immunoglobulin therapy appears to be effective in reducing the prevalence of serious bacterial infections in some hypogammaglobulinemic patients with CLL,[76] and the fact that it is FDA-approved for this indication, it is reasonable to offer certain patients immunoglobulin replacement therapy. Nonetheless, the evidence for efficacy

is derived from studies primarily performed prior to the implementation of newer disease-control strategies, and there is little direct evidence that indefinite treatment with immunoglobulin prolongs life.[77] The measurement of antibody production capacity using pre- and postimmunization concentrations is often useful in determining whether a patient needs immunoglobulin replacement therapy. Given the state of the evidence, the current review panel recommends that patients with CLL and recurrent serious bacterial infections who are hypogammaglobulinemic with subprotective antibody levels following immunization to diphtheria, tetanus, or pneumococcal infection should be considered eligible for immunoglobulin replacement therapy. Evidence-based recommendations and areas of further study regarding the use of prophylactic immunoglobulin replacement in antibody deficiency secondary to CLL were discussed in detail in a recent publication.[76]

Multiple myeloma

Infections are a major cause of morbidity and mortality in MM.[78,79] An early study clearly documented the increased infection risk in patients with MM throughout the stages of disease.[79] An early randomized, placebo-controlled trial showed that IVIG decreased the prevalence of infections in patients with MM during the plateau phase of disease. No episodes of sepsis or pneumonia occurred in the treated group versus 10 in the placebo group ($P = .002$), and of 57 serious infections, 38 occurred in 470 patient-months on placebo versus 19 in 449 patient-months on IVIG ($P = .019$).[80] A 2-year crossover study of IVIG in MM during late-phase disease also showed a statistically significant difference in the prevalence of infections, with 30 infections (9 life-threatening) occurring in 250 patient-months without IVIG versus 10 (0 life-threatening) occurring in 261 patient-months with IVIG ($P < .02$).[81] A later systematic review and meta-analysis of data from 9 RCTs evaluated outcome measures of all-cause mortality and severe infections in patients with CLL and MM who received prophylaxis with IVIG versus no IVIG (control). While no survival benefit was demonstrable, there was a significant decrease in the occurrence of major infections, with a relative risk of 0.45, and a significant decrease in documented clinical infections, leading the investigators to recommend the consideration of IVIG in MM on an individualized basis.[75] A later retrospective study in 47 patients receiving immunomodulatory agents and autologous stem cell transplantation for MM from 2006-2009 showed a significant decline in the rate of infections ($P < .01$) in patients treated with IVIG and concluded that IVIG is effective in preventing infections in these patients.[82] Profound disease- and treatment-related humoral immunosuppression (as measured by tetanus- and influenza-specific antibody concentrations over time) appears to last for up to 3-5 years after allogeneic stem cell transplantation, providing another clinical rationale for the consideration of IVIG in patients with MM.[83] On the other hand, 2 retrospective, nonrandomized reviews did not show benefit of IVIG in the peritransplantation period in MM (n = 266 autologous stem cell transplantation from 2000-2009; n = 166 autologous stem cell transplantation from 2008-2013).[84,85] Given the state of the evidence, the current review panel recommends that patients with MM and recurrent serious bacterial infections who have subprotective antibody levels following immunization against diphtheria, tetanus, or pneumococcal infection be considered eligible for immunoglobulin replacement therapy, as in CLL.

Pediatric HIV infection

In the era before highly active antiretroviral treatment (HAART), HIV-infected children with CD4 T cells >200/μL and symptomatic children (CD4 T cells <200/μL and a history of AIDS defining illness) were given replacement doses of immunoglobulin to prevent bacterial (especially pneumococcal) infections, but improvement was seen only in the group with CD4 T cell levels of >200/μL.[86] HIV disease can lead to impaired specific-antibody production, although rarely hypogammaglobulinemia (hypergammaglobulinemia is more frequent with symptomatic, untreated disease). Placebo-controlled trials have found that IVIG treatment (400 mg/kg every 28 days) reduces serious and minor bacterial infections with decreased acute-care hospitalizations in HIV-infected children.[87,88] In those studies, the benefit of IVIG was not seen in patients treated with trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* (formerly *carinii*) pneumonia prophylaxis. It is important to note that these studies occurred prior to the era of HAART for HIV. It has been demonstrated that children who have been clinically stable on HAART with improvement on immunoglobulin therapy may be safely removed from the IVIG once T cells have been reconstituted with HAART.[89] More recently, a retrospective study from a hospital in South Africa investigated the efficacy of utilizing IVIG as an adjunct therapy for severe infection in hospitalized HIV-infected children. There was no advantage to 1-3 doses of IVIG replacement demonstrated in that retrospective study.[90]

Prematurity

Preterm infants are deficient in IgG, and the utility of immunoglobulin as an adjunct for enhancing antibacterial defenses in premature newborn infants has been studied in various RCTs. Several studies have suggested that immunoglobulin therapy may diminish the prevalence of sepsis.[91] This finding may be most apparent in low-birth-weight neonates.[92] Despite encouraging trials, there are substantial contradictory data and insufficient overall evidence to support the routine administration of immunoglobulin in infants at risk for neonatal infection.[91,93] Most recently, a Cochrane review concluded that there is no justification for additional RCTs to further test the efficacy of IVIG in reducing nosocomial infections in preterm or low-birth-weight infants, because its use was not associated with reductions in clinically important outcomes, including mortality, even though administration resulted in a 3% reduction in sepsis and 4% reduction in 1 or more episodes of any serious infection.[94] Prophylactic use of IVIG has not been associated with any short-term serious adverse events. The decision to use prophylactic IVIG depends on the costs and the values assigned to the clinical outcomes.

Aging

The relationship between aging and the immune system has recently attracted the attention of many researchers. Immunosenescence in the innate and adaptive arms of immunity have been described in the elderly population. These complex processes, together with age-related dysregulation of the immune system,

may account for the increased frequency and severity of infections observed in this age group. While theoretically immunosenescence could lead to immunodeficiency, some would argue that immunosenescence does not equate to immune function deterioration but refers rather to a remodeling of the immune system, as many functions are well preserved in the elderly population.[95] Although more studies are needed, the process of aging may affect the ability of B cells to produce antibodies against novel antigens, and the composition of B-cell subsets.[96,97] Deficient antibody responses to pneumococcal or influenza vaccines have also been described.[98,99] Elderly patients with vitamin B_{12} deficiency have been reported to have poor responses to pneumococcal vaccine.[100] Secondary immunodeficiency (due to poor nutrition, for example) may also be encountered in the elderly population. Older age alone is not an indication of immunoglobulin replacement; however, recurrent, severe, or difficult-to-treat infections in the elderly population should prompt an immune function evaluation, and immunoglobulin replacement should be considered if there is evidence of low immunoglobulin levels and impaired antibody production. CVID can present at any age.[22] Elderly patients may also be at higher risk for adverse events with IVIG due to underlying comorbidities, including heart failure, renal dysfunction, hypertension, and vascular disease.[101]

Syndromic deficiencies with antibody defects

A syndromic immunodeficiency is an illness associated with a characteristic group of phenotypic or laboratory abnormalities that compose a recognizable syndrome.[102,103] Many are familiar with a defined inheritance pattern and genetic mutation(s). Several PIs, such as WAS and AT, fit into primary and syndromic immunodeficiency categories because characteristic organ dysfunction or dysmorphology unrelated to the immune system coexists with a consistent, well-defined PI. In other syndromic immunodeficiencies, the immunodeficiency may not be a major part of the illness and is usually not present in all patients.[102,103] The most recent update on the classification of PIs by the IUIS recognizes a new category of PI, called *combined immunodeficiencies with associated or syndromic features,* which contains >30 conditions associated with low or variable immunoglobulin production.[10] The immune function defects present in syndromic deficiencies may include B-cell, T-cell, phagocytic, complement, or innate defects or a combination thereof. Table IV[103,104] represents those illnesses characterized by an antibody defect, and, in some, the associated other immune function defects. The severity of the antibody defect is often unsuspected because many of these patients have so many other conditions, including respiratory airway abnormalities, that the immunodeficiency is overlooked. Furthermore, the most common problem encountered, a selective antibody deficiency, may go undiagnosed because immunoglobulin levels are normal. Additional details of each illness are found in the referenced articles. The immunologic defects in these well-defined syndromes have in many cases been elusive, but the presentation of the patients and their increased susceptibility to infection is clear. Thus patients with these conditions should be considered as candidates for immunoglobulin therapy based on their confirmed diagnosis and clinical presentation. Advances in the understanding of the immunology of these patients will likely shed light on the specific defective mechanisms that result in infectious susceptibility in some cases out of proportion to the standard humoral immune function assessments. In this light, assays of specific antibody avidity and actual function may prove useful.[36]

Hematopoietic cell transplantation

A few decades ago, IVIG was FDA-approved and used for the routine management of allogeneic transplant recipients to prevent infections and provide immunomodulation in GVHD. The NIH consensus on IVIG endorsed this practice at the time, based on data from a series promising studies.[105] However, the advent of better and less expensive infection-prophylaxis regimens, other effective strategies for prophylaxis against GVHD, and subsequent mixed results in larger-scale studies significantly changed this practice over time.[106-113] The current gold-standard treatment of acute GVHD with hematopoietic transplantation consists of corticosteroids and calcineurin inhibitors.[114]

In 2006, the AAAAI expert panel advised that IVIG may be beneficial for the prevention of infection and acute GVHD after bone marrow transplantation (might provide benefit, evidence category Ib), but that the data did not support a recommendation in IVIG in HLA–identical sibling bone marrow transplantations. The National Advisory Committee on Blood and Blood Products of Canada and Canadian Blood Services, in convening a panel of national experts to develop an evidence-based practice guideline on the use of IVIG for hematologic conditions, made a specific recommendation for the use of IVIG in "acquired hypogammaglobulinemia (secondary to malignancy)" while not recommending it in hematopoietic stem cell transplantation.[115] Another review, in the Cochrane Database, concluded that in patients undergoing bone marrow transplantation, routine prophylaxis with IVIG is not supported.[75] Currently, IVIG is not recommended for routine use in the immediate peritransplantation period for the prevention of infection or GVHD after marrow or peripheral blood allogeneic transplantation. Selected patients with chronic GVHD and recurrent serious bacterial infections with demonstrable defect in antibody production capacity could benefit from IVIG. Some patients with glucocorticosteroid-refractory cytopenias may be candidates for a limited course of IVIG.[116-118] IVIG should be considered as contraindicated in the immediate post-transplantation period in patients with a history of sinusoidal obstructive syndrome.[106] There are insufficient data to guide a recommendation of its application in cord blood stem cell transplantation in either children or adults.

Post-transplantation immunoglobulin for severe combined immunodeficiency and other primary immunodeficiencies

Recipients of hematopoietic stem cell transplants for SCID or other conditions, and who are functionally agammaglobulinemic due to poor B-cell engraftment, benefit from immunoglobulin replacement. IVIG should be administered in all infants with SCID before transplantation and in all infants after transplantation for as long as it takes for humoral immunologic reconstitution. Immunoglobulin therapy should be administered in patients with other PI diseases and nonmalignant conditions according to individual patient requirements in the peritransplantation period and for a time post-transplantation determined by experts in the

TABLE IV. Genetic syndromic immunodeficiencies with antibody defects

Syndromic immunodeficiencies with antibody deficiencies	Other immune defects observed	IUIS category*
Hematologic		
Sickle cell disease	T	NC
β-Thalassemia major	—	NC
Shwachman syndrome	Ph	5
WHIM syndrome	Ph	3, 6
Transcobalamin II deficiency	—	2
Folic acid malabsorption (transport defect)	T	NC
Growth		
Schimke immuno-osseous dysplasia	T	2
Roifman syndrome	—	NC
Roifman-Cotsa syndrome	T	NC
Growth hormone pathway defect	T, NK	4 (Stat 5b)
Kabuki syndrome	—	NC
CHARGE association	T	2
Rubinstein-Taybi syndrome	T	NC
Gastrointestinal		
Familial intestinal polyatresia	T	2
Trichohepatoenteric syndrome	—	NC
Dermatologic		
Omenn syndrome	T	1
Griscelli syndrome, type 2	T, NK, Ph	4
Hypohidrotic/anhidrotic ectodermal dysplasia with immunodeficiency	T	6
WHIM syndrome	T, Ph	3, 6
Incontinentia pigmenti	T, Ph	NC
OLEADAID syndrome	–	NC
Dyskeratosis congenita	T, Ph	2
Acrodermatitis enteropathica	T, Ph	NC
Netherton syndrome	T, Ph	2
Neurologic		
Myotonic dystrophy	–	NC
Høyeraal-Hreidarsson syndrome	T, Ph	2
Inborn errors of metabolism		
Congenital disorders of glycosylation, types Ia, Ig, Ik	Ph	NC
Branched chain amino acidemias	T, Ph	NC
Lysinuric protein intolerance	T, Ph, NK	NC
Chromosomal instability/DNA repair disorders		
Nijmegen breakage syndrome	T	2
Bloom syndrome	T, NK	2
ICF syndrome	T	2
Syndromes number/structure deficiencies		
Trisomy 21 (Down syndrome)	T, Ph, NK	NC
Deletion of short arm of chromosome 4 (4p16) (Wold Hirshhorn syndrome)	—	NC
Missing or abnormal X chromosome (Turner, XO, isoX, ringX)	T	NC
Deletion of chromosome 11q (Jacobsen syndrome)	T, NK	NC
Microdeletion 17p11.2, including *TNFRSF13B* (*TACI*) (Smith-Magenis syndrome)	—	NC

Data from Ming et al and Picard et al.[103,104]
CHARGE, Coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies; *ICF*, immunodeficiency, centromeric region instability, facial anomalies; *NK*, natural killer cell defects; *OL-EDA-ID*, osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia with immunodeficiency; *Ph*, phagocytic cell defects; *T*, T-cell defects; *WHIM*, warts, hypogammaglobulinemia, infections, and myelokathexis.
*IUIS categories: NC = not categorized; 1 = combined immunodeficiencies; 2 = combined immunodeficiencies with associated or syndromic features; 3 = predominantly antibody deficiencies; 4 = diseases of immune dysregulation; 5 = congenital defects of phagocyte number, function, or both; and 6 = defects in innate immunity.

field and consistent with institutional transplantation center guidelines.

Solid organ transplantation

The evolution of IVIG from its introduction as a source of passive immunity in immunodeficient patients to an agent with powerful immunomodulatory and antiinflammatory activity has been remarkable. This evolution has resulted in extensive applications in autoimmunity and systemic inflammatory conditions.[119] IVIG use in solid organ transplant recipients has seen significant growth in the past decade.[31,120-123] Here, we discuss the rationale for the application of IVIG in solid organ transplant recipients.

The highly sensitized patient. Sensitization to HLAs or ABO blood group antigens has historically been an impenetrable barrier to successful transplantation. Approximately 30% of the patients with end-stage renal disease awaiting kidney transplantation in the United States are considered sensitized due to exposure to blood or tissues from other humans (blood and platelet transfusions, pregnancies, and previous transplantations). Sensitized patients remain on dialysis and incur higher morbidity, mortality, and costs than do transplant recipients.[31,120-123]

Improving transplantation rates in highly sensitized patients with IVIG. Over the past decade, several transplantation centers in the United States and worldwide have adapted HLA- and ABO-desensitization protocols to improve transplantation rates in this immunologically disadvantaged group. This adaptation was based on work from the 1990s showing that high-dose IVIG could reduce anti-HLA antibody levels in sensitized patients and ultimately improve transplantation rates.[123] Current protocols include the use of low-dose IVIG with plasma exchange (PE), or high-dose IVIG with or without B-cell depletion using rituximab.[120] Despite this considerable experience, there is still no FDA-approved drug for use in desensitization, although IVIG has the most supporting clinical data.[31] Overall, the use of IVIG for desensitization has been well accepted, although recent, smaller-scale studies have questioned efficacy.[124,125] IVIG has also been used as a desensitization agent in patients awaiting heart and lung transplants. However, data to support its use are not as robust as in kidney transplant recipients.[120] One study recently reported on the use of high-dose IVIG and high-dose IVIG + rituximab in lung allograft recipients in whom donor-specific HLA antibodies (DSAs) developed post-transplantation[126]; these antibodies appear to be an important risk factor for bronchiolitis obliterans syndrome. Of 65 patients who became DSA positive, the subgroup in whom DSAs failed to clear had higher mortality and bronchiolitis obliterans syndrome scores at 3 years. Among those in whom DSAs cleared, the combination of IVIG + rituximab was more efficacious than was high-dose IVIG alone.

IVIG + rituximab for immunomodulation in sensitized patients. The use of IVIG + rituximab as a desensitization regimen has been extensively described.[127-129] The efficacy, clinical outcomes, and cost-effectiveness of this approach compared with maintaining patients on long-term dialysis were recently demonstrated.[129] Transplantation rates in highly sensitized patients treated with IVIG + rituximab exceeded those in patients desensitized with IVIG alone, and the use of rituximab appeared to have prevented B-cell memory responses and anti-HLA antibody rebound.[130] Another study recently showed that

the use of IVIG + rituximab + PE was more efficacious compared with IVIG alone in the prevention of long-term antibody-mediated injury to allografts.[131] Ongoing trials of IVIG + rituximab will help to definitively answer which approach is optimal.

IVIG in the treatment of antibody-mediated rejection. Although no controlled studies regarding the most appropriate treatments of antibody-mediated rejection are available, the benefits of high-dose IVIG and PE with low-dose IVIG have been well described.[132-134] In a recent report of a small-scale, retrospective analysis of high-dose IVIG versus PE followed by high-dose IVIG + rituximab for the treatment of antibody-mediated rejection, investigators found that the combined therapies were more efficacious compared with IVIG alone, with 36-month graft survival being 91.7% versus 50% with long-term suppression of DSA levels.[135] Findings from another retrospective experience were similar.[120] Thus, the current approach to the treatment of antibody-mediated rejection requires a combination of IVIG + rituximab ± PE.[120]

Secondary hypogammaglobulinemia in transplant recipients. The use of potent immunosuppressive agents in transplant recipients can result in secondary immunodeficiency with hypogammaglobulinemia.[120,136] It would appear this trend is increasing, especially in patients who receive both T cell– and B cell–depleting agents. Patients often present with recurrent or multiple infections similar to those seen in patients with PI. IVIG may also have utility in treating drug-resistant or severe CMV, parvovirus B19, and polyoma BK viral infections.[120,137] After transplantation, patients should be monitored for hypogammaglobulinemia. Monthly replacement with IVIG or SCIG products is recommended.

Complications of IVIG therapy in transplant recipients. Briefly, the complications associated with high-dose IVIG have been previously described.[120,123,138,139] Initial experience from a placebo-controlled trial showed that IVIG was well tolerated and not associated with increased adverse events or severe adverse events in highly sensitized patients awaiting transplantation. Lyophilized products that are hyperosmolar should not be given in patients after transplantation, as they are likely to cause osmotic nephropathy and renal failure. Newer, chromatographically derived IVIG products are iso-osmolar but may contain higher concentrations of anti–blood group antibodies (anti-A, anti-B).[138] These products appear to pose an increased risk for hemolysis following high-dose (2 g/kg) IVIG infusions while patients are on dialysis. Patients with blood type A, B, or AB should be monitored carefully for hemolysis after high-dose IVIG therapy.[138]

B cell–depleting therapies

In general, patients who have received strong immunosuppressive therapies aimed at T or B cells are potentially at risk for hypogammaglobulinemia. Recently, a series of articles reported hypogammaglobulinemia after rituximab and recommended baseline immune function testing in patients with autoimmune disease placed on rituximab.[43,140-144] Some patients who have been treated with rituximab show persistently low serum IgG levels and have recurrent infections; these patients would be expected to benefit from immunoglobulin replacement therapy.[43,140-144] Antibody deficiency with a CVID-like clinical and immunologic phenotype also arises commonly in patients with lymphoma receiving repeated or prolonged courses of B cell–depleting therapies. Secondary immunodeficiency following lymphoma treatment was discussed in a recent review from 1 center.[145] More studies are needed for better characterizing immunodeficiency in these patients, especially given that lymphoma is a known complication of CVID.

Summary: Immunoglobulin in secondary immunodeficiency disorders

This section has described a variety of clinical disorders that may cause or be associated with a secondary immunodeficiency of antibody function, warranting consideration of immunoglobulin replacement. Treatment should be considered in patients with CLL or MM, after lymphoma treatment with B cell–depleting therapies, and in patients who are hypogammaglobulinemic with recurrent bacterial infections and subprotective antibody levels after immunization against diphtheria, tetanus, or pneumococcal infection. Although pediatric HIV infection is an FDA-approved indication of immunoglobulin, studies supporting the use of immunoglobulin for this indication predated the routine use of HAART in HIV, which effectively reconstitutes T cells (and hence T-cell help for B cells),[89] such that immunoglobulin replacement is no longer used as much for this indication. More recently, a retrospective study from a hospital in South Africa investigated the efficacy of utilizing IVIG as an adjunct therapy for severe infection in hospitalized HIV-infected children.[90] In prematurity, consideration of the prophylactic use of IVIG depends on the costs and the values assigned to the clinical outcomes, as recent reviews have indicated no benefit of IVIG in reducing mortality. In the elderly population, the occurrence of recurrent, severe, or difficult-to-treat infections should prompt an immune function evaluation, and immunoglobulin replacement should be considered if impaired antibody function is found. Patients with certain genetic syndromes and a history of recurrent infections may have an associated antibody deficiency, and therefore should be evaluated and treated if indicated. In general, IVIG is not recommended for routine use in the immediate peri–bone marrow transplantation period for the prevention of infection or for GVHD after marrow or peripheral blood allogeneic transplantation. Selected patients with chronic GVHD and recurrent serious bacterial infections with a demonstrable defect in antibody production capacity could benefit from IVIG. Importantly, however, recipients of hematopoietic stem cell transplants for SCID or PIs who are functionally agammaglobulinemic due to poor B-cell engraftment should receive immunoglobulin replacement for life, or until adequate humoral immunologic reconstitution can be demonstrated. Immunoglobulin replacement should be administered in all infants with SCID before transplantation. Immunoglobulin therapy should be administered in patients with other PI diseases and nonmalignant conditions according to individual patient requirements in the peri-transplantation period and for a time post-transplantation determined by experts in the field and consistent with institutional transplant center guidelines. With regard to solid organ transplantation, IVIG has been used for decreasing panel reactive antibody before transplantation (particularly in renal transplant recipients), for the treatment of antibody-mediated rejection (using regimens including rituximab and PE), and for secondary

immunodeficiency induced by potent T cell– and B cell–depleting therapies presenting with hypogammaglobulinemia and recurrent infections similar to those in patients with PI. The continued development of newer biologic agents targeting the immune system, and their increased clinical use, will require further detailed study of secondary immunodeficiencies in patients treated with these agents. The use of IVIG replacement in secondary immunodeficiencies, including CLL and MM, and following lymphoma treatment has been recently reviewed.[145,146]

AUTOIMMUNE DISEASES

IVIG has been used, with varying efficacy, in a number of systemic autoimmune disorders, as outlined in Table V and reviewed subsequently. These disorders are categorized into hematologic autoimmune diseases, rheumatic diseases, and organ-specific autoimmune diseases. The treatment approach to autoimmune diseases in general has significantly changed with the advent of newer biologic agents and immunomodulating therapies, minimizing the role for high-dose IVIG except in select situations. Rheumatic diseases are relatively rare, so evidence from controlled trials of IVIG is lacking. A priority stratification of autoimmune indications of IVIG was published in a very recent review.[147] The highest priorities of IVIG were assigned to KD, CIDP, and Guillain-Barré syndrome (GBS), with second-level priority given to inflammatory myopathies, and low priority to SLE without immune cytopenias, systemic vasculitides, and systemic juvenile idiopathic arthritis (JIA), among others.[147] Some of these disorders are discussed in other sections of this article.

Hematologic autoimmune diseases

Immune thrombocytopenic purpura. Immune thrombocytopenic purpura (ITP) is a disorder that may affect patients of all ages. Pharmacologic treatment of all children with ITP may not be required because most children will spontaneously recover.[148-150] Treatment is usually provided to those children at greatest risk for bleeding complications and those with chronic refractory disease. Commonly used therapeutic modalities include systemic corticosteroids, anti-D, IVIG, plasmapheresis, rituximab, and combinations of these.[148,151] The effectiveness of IVIG in increasing platelet counts has been supported in numerous studies, resulting in an FDA-approved indication of its use.[152-155] Importantly, high-dose IVIG has been compared to systemic corticosteroids in randomized, multicenter trials, and was found to provide a clinically relevant advantage.[153,154] Thus, at present, IVIG remains an important and useful treatment modality for preventing or controlling bleeding in the more severe presentations of immune-mediated thrombocytopenia. Anti-Rh(D) products have also been used as first-line therapy in patients with primary ITP. However, this product should be avoided in patients with preexisting hemolysis and other risk factors because the administration of anti-Rh(D) has been rarely associated with severe intravascular hemolysis, disseminated intravascular coagulation, and acute renal failure.[156,157] Corticosteroids, IVIG, or anti-D immunoglobulin are considered first-line therapies for ITP, according to the International Consensus Report and the American Society of Hematology 2011 evidence-based guideline.[158-160]

Neonatal alloimmune thrombocytopenia. Neonates may have thrombocytopenia as a consequence of fetomaternal alloimmune immunization, and high-dose IVIG has been successfully used for treatment. Unfortunately, neonates at greater risk for intraventricular hemorrhage (those with more severe thrombocytopenia, especially in those born prematurely) may not receive the benefit due to the delay in effect from high-dose IVIG delivered over 2 days.[161] In those at risk, or with clinical evidence of fetal alloimmune thrombocytopenia, antenatal treatment with high-dose IVIG infused each week has become routine first-line therapy, despite the lack of randomized studies and somewhat different conclusions between studies from Europe and the United States.[162,163]

Post-transfusion purpura. Post-transfusion purpura is a rare and potentially fatal disorder characterized by severe thrombocytopenia that develops 7-10 days following transfusion of blood products that contain platelets, due to alloantibodies against human platelet antigen 1 or anti-HLA class I directed toward donor HLA.[164,165] Standard therapies have included systemic corticosteroids, IVIG, plasmapheresis, rituximab, and combinations of these therapies.[151] A few case reports have shown benefit from the use of combination therapy with a corticosteroid + IVIG, although no controlled studies have been conducted.[164,166-170] Despite the lack of rigorous studies, therapy with IVIG can be considered given the potential life-threatening nature of the disease.

Thrombotic thrombocytopenic purpura. Thrombotic thrombocytopenic purpura is a rare microangiopathic coagulopathy, frequently arising after an infection or other immune system insult, especially in patients with mutations in *ADAMTS13*. Therapeutic PE (or plasmapheresis), fresh frozen plasma, cryosupernatant, solvent/detergent-treated fresh frozen plasma, and combinations of these are useful for therapy. IVIG use has been controversial but may be of benefit in those with more refractory disease.[171]

Autoimmune neutropenia. Primary autoimmune neutropenia is caused by autoantibodies directed against neutrophils, and in general spontaneously resolves. Children with primary autoimmune neutropenia rarely have significant infections and can mount a neutrophil response to bacterial infections. Granulocyte colony-stimulating factor is first-line therapy for more serious infections. The occurrence of more serious infections should prompt further workup to identify an associated underlying cause.[172] Clinical response (increased neutrophil counts) have been described in several small series of patients with autoimmune neutropenia who were treated with IVIG.[173-176] Anecdotal reports also suggest utility for IVIG in post–bone marrow transplantation neutropenia, which may have an autoimmune basis.[117,177,178]

Other autoimmune cytopenias. Multiple anecdotal reports demonstrate benefit from the use of IVIG in autoimmune hemolytic anemia,[176,179,180] but the use of IVIG should be considered only when other therapeutic modalities have failed.[181] IVIG has been associated with a decreased need for exchange transfusions in neonates with isoimmune hemolytic anemia.[182-184] However, there were flaws in these studies, such that routine use in neonatal hemolytic anemia is not currently recommended.[185] IVIG may have some benefit, when combined with other therapies, in Evans syndrome (autoimmune destruction of at least 2 of the 3 hematopoietic lineages).[186] Other reports have suggested that high-dose IVIG is beneficial in cytopenias in malignancy[187,188] and SLE.[189,190]

TABLE V. Uses of immunoglobulin in autoimmune diseases

Benefit	Indication	Evidence category	Strength of recommendation
Definitely beneficial	Graves ophthalmopathy	Ib	A
	Immune thrombocytopenic purpura	Ia	A
Probably beneficial	Dermatomyositis	IIa	B
	Birdshot Retinochoroidopathy	IIa	B
	Henoch-Schönlein purpura	IIb	B
May provide benefit	Juvenile idiopathic arthritis	Ia	A
	Anti–phospholipid antibody syndrome in pregnancy	Ib	B
	Severe RA	IIb	B
	Still disease	IIb	B
	Felty syndrome	IIb	B
	Macrophage activation syndrome	IIb	B
	Polyarteritis nodosa	IIb	B
	Post-transfusion purpura	III	C
	Thrombotic thrombocytopenic purpura	III	C
	ANCA syndromes	III	D
	Autoimmune neutropenia	III	D
	Autoimmune hemolytic anemia/Evan syndrome	III	D
	Autoimmune hemophilia	III	D
	SLE	III	D
	Neonatal alloimmune thrombocytopenia	III	D
	Neonatal isoimmune hemolytic jaundice	III	D
Unlikely to be beneficial	Inclusion body myositis	Ib	B
	Autoimmune diabetes mellitus	III	C
	Inflammatory bowel disease	III	C

ANCA, Anti–neutrophil cytoplasmic autoantibody.

Acquired hemophilia. Acquired hemophilia is a coagulopathy caused by the development of autoantibodies directed against specific domains of the coagulation factor VIII molecule, resulting in a risk for systemic hemorrhage. Treatment modalities include corticosteroids, cyclophosphamide, cyclosporine, and more recently rituximab. Patients who do not respond to immunosuppressive regimens may benefit from high-dose IVIG.[191-195] However, international guidelines recommend initial treatment with a corticosteroid or a combination of a corticosteroid and cyclophosphamide and suggest second-line therapy with rituximab if first-line therapy fails or is contraindicated.[196] Furthermore, a study of data from the largest registry of patients with acquired hemophilia demonstrated that patients with acquired hemophilia A were more likely to achieve a stable remission after first-line therapy if treated with a combination of corticosteroids and cyclophosphamide.[197]

Rheumatic diseases

Autoimmune inflammatory myopathies. Dermatomyositis is an autoimmune inflammatory myopathy usually treated with systemic corticosteroids and additional immunosuppressive therapeutic agents, such as azathioprine or mycophenolate mofetil, as corticosteroid-sparing agents.[198] High-dose IVIG has been demonstrated to have efficacy in dermatomyositis in both controlled[198] and open-label[199] studies. In another report, IVIG was added to the therapeutic regimen of 9 children with refractory juvenile dermatomyositis. Clinical improvement was seen in all, and the maintenance dose of the corticosteroid could be reduced in 6.[200] In inclusion body myositis, however, a controlled trial failed to demonstrate objective improvement in those treated with IVIG.[201,202] Although IVIG may be useful in many inflammatory myopathies, generalized recommendations for use in all forms are not presently possible.[201-203]

Rheumatoid arthritis. Case reports, open-label trials, and controlled studies of high-dose IVIG have shown some benefit in patients with rheumatoid arthritis (RA).[204-209] In contrast, low-dose (5 mg/kg every 3 weeks) therapy in a randomized, double-blind, placebo-controlled trial in 20 patients with refractory RA demonstrated no benefit.[210]

Juvenile idiopathic arthritis. JIA is a group of arthritides arising in children <16 years of age. JIA is further classified as oligoarticular, polyarticular, or systemic onset. The majority of cases of JIA are not the adult form of RA developing in children (although there is a subset of children with early-onset adult RA).[211] NSAIDs and glucocorticoids are typically tried as first-line therapy for JIA, and then other agents, including other disease-modifying antirheumatic drugs, immunomodulators, and biologics, may be added to control inflammation. In systemic JIA, biologics such as IL-1 and IL-6 inhibitors are now used successfully,[212] leaving high-dose IVIG mainly as a corticosteroid-sparing option in more severe cases that have been unresponsive to the standard therapies.[213] Previously, high-dose IVIG had been reported in open-label and controlled trials in some 100 children with JIA.[213,214] Adverse events have been rare and relatively minor. Overall benefit has been reported, but well-controlled trials are lacking, and a follow-up study demonstrated that although the use of IVIG allowed for decreased corticosteroid doses and fever remission, the overall course of the disease was not affected.[213] In children with JIA not responding to other forms of therapy, high-dose IVIG may be a consideration.

Still disease, Felty syndrome, macrophage activation syndrome. Still disease appears to respond to high-dose IVIG, but in some cases, the remission may be transient.[215,216] Because nearly half of all cases will spontaneously improve, the benefit of IVIG can be difficult to measure. Due to the high rate of remission reported with high-dose IVIG though, benefit may

be achieved in more critically ill patients not adequately responding to other therapies. Felty syndrome is a variant of RA, with features of splenomegaly and neutropenia (may also exhibit lymphadenopathy and hepatomegaly) indicative of a systemic inflammatory process. Clinical disease symptoms are reported to improve with IVIG, but the neutropenia does not appear to improve.[217] Macrophage activation syndrome is a severe, life-threatening disease that may occur as a complicating feature of JIA (especially the systemic-onset subtype), SLE, following viral infections, with certain medications, or with toxin exposure. High-dose IVIG may be of benefit when used early in disease, especially when used in conjunction with other therapies, but well-controlled studies are needed to better direct its use.[218-221]

Disorders associated with vasculitis and vasculitides. Immunosuppressive agents and newer biologic therapies used more commonly in disorders associated with vasculitis and vasculitides are reviewed elsewhere.[147,222-226] IVIG is not considered first-line therapy for this group of disorders. Nonetheless, the literature supporting its use is reviewed subsequently.

SLE. In a retrospective study in patients with SLE, IVIG was associated with transient clinical improvement in 65% of the patients treated.[227] In case reports, high-dose IVIG was associated with disease resolution in patients with SLE affecting specific organs, including lupus nephritis,[228,229] lupus myocarditis,[230] polyradiculopathy,[231] lupus-induced bone marrow suppression,[189] and lupus-induced multiorgan disease.[232] Cautious use of high-dose IVIG is always advised in patients with SLE, as well as other disorders (especially neurologic disorders), due to potential prothromboembolic effects.[204] High-dose IVIG has been associated with worsened azotemia in patients with SLE.[233] In light of the fact that infusion of high-dose IVIG appears to be beneficial in patients with severe, life-threatening SLE and/or its complicating morbidities, cautious use with careful monitoring, and reducing the potentially adverse bolus effect by slowing the infusion rate or spreading the dose over several days may help to reduce the risks for some of these concerns.[226]

Other systemic small vessel vasculitides. Treatment options for the different organ system manifestations of systemic sclerosis/scleroderma include immunosuppressive drugs and novel biologics, and were recently reviewed.[234] Skin involvement is the most universal feature of this disease. One randomized, placebo-controlled trial of IVIG in the treatment of skin involvement in scleroderma reported no significant difference between the placebo and IVIG groups after a single course. However, improvements in the Rodnan skin score, a key outcome in clinical trials, was reported in patients who received additional doses.[234,235] The role of IVIG in systemic sclerosis/scleroderma, linear scleroderma, and morphea had been evaluated earlier in case reports and open-label trials[236-240] that suggested that IVIG could play a role in treatment. Only a few case reports were found to support any possible role of IVIG use in mixed connective tissue disease (n = 1 case) and Sjögren syndrome (n = 2 cases).[241,242]

Henoch-Schönlein purpura. Henoch-Schönlein purpura is a vasculitis occurring primarily in children, subsequent to a viral illness, that usually requires only symptomatic treatment.[224] The vasculitis primarily affects the gastrointestinal tract and kidneys, where massive hemorrhage of the former and impairment of the latter can be life-threatening. Corticosteroids may be used when symptoms are worsening, but there is debate over long-term benefit, and there can be worsening of gastrointestinal hemorrhage.[243] Others suggest that early institution of corticosteroids in a hospital setting may be beneficial.[244] Regardless, high-dose IVIG appears to be well tolerated and effective, without increasing the risk for gastrointestinal hemorrhage, while improving outcomes if gastrointestinal hemorrhage is present.[245] One recent case report suggested that IVIG might be a well-tolerated approach to treating the cerebral manifestations of Henoch-Schönlein purpura.[246] Given the relatively common nature of self-resolving Henoch-Schönlein purpura, however, patients in whom IVIG is to be utilized need to be carefully selected until further specific guidance is available.

Systemic vasculitides involving medium and large vessels. Polyarteritis nodosa (PAN) is a vasculitis affecting small to medium arterioles, before capillaries, in contrast with SLE, which primarily affects the capillaries and postcapillary venules. Treatment of PAN typically involves high-dose corticosteroids and cyclophosphamide, PE if needed, and newer biologics such as infliximab or rituximab.[224] In many respects, PAN and KD share similar features; therefore, it is of no surprise that numerous case reports indicate a beneficial role for high-dose IVIG in patients with PAN.[247] Takayasu arteritis is vasculitis of the larger arteries and is sometimes called "pulseless disease" due to the effects on the radial pulse, especially when the left aortic arch and branches are affected. Treatment primarily consists of corticosteroids and other immunosuppressives, and treatment with TNF-blocking agents has recently shown promise.[223] Few reports, and no studies, were found in the literature search for the use of high-dose IVIG in Takayasu arteritis. A case report indicated that Takayasu arteritis developed in a patient diagnosed with CVID while on IVIG, but that the features of Takayasu arteritis improved after an increase in the dose of IVIG.[248]

Anti-neutrophil cytoplasmic autoantibody disorders. The anti-neutrophil cytoplasmic autoantibody group of disorders includes granulomatosis with polyangiitis (formerly, Wegener granulomatosis), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly, Churg-Strauss syndrome), and renal-limited vasculitis.[224] Treatment typically involves corticosteroids, cyclophosphamide, PE if needed, and aspirin, with increasing use of newer agents, including mycophenolate mofetil for the induction of remission and rituximab in certain cases.[224] In past literature, IVIG used as an alternative therapeutic agent was found to be beneficial in individual cases[249] and in open-label studies[250,251] in patients with anti-neutrophil cytoplasmic autoantibody–positive vasculitis.

Organ-specific autoimmune disease

Autoimmune diabetes mellitus. No IVIG guidelines exist in diabetic patients, and IVIG use is not widely recommended because other therapies are more cost-effective. A case report[252] and other early studies[253] have identified subpopulations of patients who responded to IVIG therapy with a either a decrease in antibodies against islet cell antibodies or preserved C-peptide release, higher rate of remission, and longer duration of remission, respectively.[253] However, a single RCT evaluating the effects of IVIG administered every 2 months in children and adults with type 1 diabetes failed to demonstrate any benefit associated with IVIG therapy.[254] Of note, diabetes and the vascular disease that accompanies diabetes are risk

factors for adverse events when immunomodulatory doses of IVIG are given.

Autoimmune Graves ophthalmopathy. Graves ophthalmopathy is an autoimmune manifestation of hyperthyroidism that involves the orbital and periorbital tissues, secondarily resulting in proptosis and other ocular complications. Recently, an RCT comparing rituximab with methylprednisone demonstrated a greater clinical response with rituximab, supporting the findings from other preliminary studies of the use of rituximab in Graves ophthalmopathy.[255] A previous randomized study in patients with active Graves' ophthalmopathy compared systemic corticosteroids to 6 courses of IVIG at 1 g/kg for 2 consecutive days every 3 weeks. Both treatment modalities were equally successful, but the adverse events were more frequent and severe in the corticosteroid-treated group.[256] In a separate case report, IVIG was also noted as being more effective compared with systemic corticosteroids in controlling Graves ophthalmopathy.[257] In milder disease, treatment includes addressing the underlying hyperthyroidism, and symptomatic care. In more severe disease, corticosteroids have been the primary treatment; however IVIG has been associated with fewer adverse events and may be a better choice in some patients. Additionally, B-cell depletion with rituximab is emerging as an alternative, especially in severe disease, because it efficiently decreases autoantibodies. Multispecialty management, including endocrinology and ophthalmology, is advisable due to other treatment modalities available, depending on severity, including radiation and surgical decompression.[258]

Autoimmune uveitis. Autoimmune uveitis is a noninfectious inflammatory process of the vascular layer of the eye that without treatment can cause visual impairment and even blindness.[259] Current guidelines recommend a corticosteroid as the first-line treatment, with the addition of an immunosuppressive agent in corticosteroid-resistant cases or for corticosteroid-sparing effects. Newer biologics are also being considered, depending on the type of autoimmune uveitis.[259,260] IVIG has been used for the treatment of birdshot retinochoroidopathy, an autoimmune posterior uveitis that frequently requires immunosuppressive therapy. An open trial of IVIG treatment for 6 months (1.6 g/kg every 4 weeks with transition to every 6-8 weeks) has shown promise.[261] Visual acuity improved in 53.8% of patients' eyes during treatment, but decreased in 7.7%. When present, macular edema improved in half of the eyes during treatment. In another trial in therapy-resistant autoimmune uveitis, clinical benefit was seen in half of the patients treated with IVIG.[262] These data suggest that IVIG therapy may be an effective alternative in patients with this disease.

Autoimmune liver disease. Autoimmune hepatitis is typically treated with a corticosteroid and azathioprine or another immunosuppressive agent, such as rituximab, in refractory disease.[263] In an early case report, IVIG was successfully used for treating a patient with autoimmune chronic active hepatitis[264] who showed normalization of liver enzymes, undetectable circulating immune complexes, and improvement in periportal mononuclear cell infiltrates after treatment. Despite the overall lack of controlled studies, IVIG is considered as one of the treatment modalities in autoimmune hepatitis[265]; however, a variety of other available second-line immunosuppressive agents are often tried, and newer ones are in development.[263]

Inflammatory bowel diseases. Inflammatory bowel diseases are chronic inflammatory disorders involving the tissues of the gastrointestinal tract. Crohn disease may manifest from the oral cavity to the anus, whereas ulcerative colitis tends to be limited to the lower colon. IVIG therapy was investigated in an open-label, nonrandomized trial in patients with inflammatory bowel disease refractory to immunosuppressive therapies (3 with Crohn colitis; 9 with ulcerative colitis).[266] Therapy was well tolerated, with statistically significant reductions in disease activity, daily prednisone dose, and mucosal inflammation in 4 patients who underwent biopsy. However, disease relapse occurred in 3 patients after IVIG therapy was discontinued. Treatment with IVIG may be of benefit in subsets of patients with inflammatory bowel disease refractive to immunosuppressive therapy.

Summary: Immunoglobulin in hematologic autoimmune diseases, rheumatic diseases, and organ-specific autoimmune diseases

Of the hematologic autoimmune diseases, ITP remains the only FDA-approved indication of IVIG, with evidence recommendation Ia, and its use (along with other therapies) for this condition is endorsed by the International Consensus Report and the American Society of Hematology 2011 evidence-based guidelines.[158,159] The other disorders discussed are more rare, and are therefore without randomized studies. However, their life-threatening nature and potential benefit may justify the use of IVIG on a case-by-case basis. Of the rheumatic diseases discussed, dermatomyositis and severe cases of JIA with prolonged unresponsiveness to other therapies are supported by category IIa and Ia, respectively, as uses of IVIG. Although IVIG may provide variable clinical benefit in the other rheumatic diseases discussed, data are limited to open-label or retrospective studies and case reports. For the most part, the efficacy of immunoglobulin therapy in patients with organ-specific autoimmune disease or various forms of autoimmune vasculitides is limited, and immunoglobulin therapy may be beneficial in only a subset of patients. Importantly, new biologic therapies have emerged recently as better alternatives or even as primary therapies for many of these autoimmune diseases. See Table V for detailed, evidence-based recommendations.

USE OF IVIG IN ATOPIC DISEASES

Asthma

Asthma is a heterogeneous disorder characterized by chronic inflammation of the respiratory tract leading to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Atopy is the strongest identifiable predisposing factor for developing asthma. In susceptible individuals, chronic airway inflammation causes recurrent episodes of wheezing, chest tightness, coughing, and excessive mucus production. Patients with these symptoms are occasionally found to have antibody deficiency.[267-274] In some patients with immune abnormalities and infection-associated asthma, replacement doses of IVIG may eliminate the triggering infections and/or reduce the frequency and severity of pulmonary symptoms. This, in turn, may decrease the symptoms and morbidity of asthma.[274,275] This application, however, should be considered primarily as treatment of antibody deficiency and not of asthma, although the benefit of this comorbid diagnosis can be substantive.

The mainstay of treatment of severely affected asthmatic patients is high doses of inhalational and oral corticosteroids, and in those with identifiable perennial aeroallergen sensitivity, anti-IgE therapy has been used. Immunoglobulin has been utilized as a corticosteroid-sparing agent in severe asthma due to its potent anti-inflammatory properties, but the results from clinical trials have been conflicting, and no recent trials have emerged. Multiple open-label trials have examined the effects of high-dose IVIG on corticosteroid-dependent or severe asthma and demonstrated various positive outcomes, including reductions in corticosteroid dose and improvements in peak flows, symptom scores, and hospitalizations.[276-282] However, results from 3 double-blind, placebo-controlled studies of IVIG in asthma were not able to support the previous findings.[283-285] Despite data suggesting efficacy in uncontrolled studies, 2 of 3 RCTs showed no significant effect of immunoglobulin therapy in asthma,[283,284] while the third reported a significant corticosteroid-sparing effect in a subgroup that required relatively high daily doses of oral corticosteroids, but the difference between the IVIG and placebo groups was not significant.[285] This existing literature, therefore, does not support a recommendation for the routine use of IVIG in severe asthma. The efficacy in select groups, and the fact that adverse events were limiting in only 1 trial, suggest that additional studies of IVIG in carefully defined groups of asthmatic patients with persistent requirements for high doses of systemic corticosteroids may be of interest. It will be essential, however, that subsequent studies employ randomized and controlled study designs.

Urticaria

Chronic urticaria is a disorder that is often difficult to treat, although advances in the understanding of the underlying mechanisms have provided new insights and therapeutic rationale. An autoimmune process is implicated in about one third of patients with chronic urticaria.[286-288] Most case reports of successful treatment of chronic urticaria occur in those in whom an autoimmune mechanism is involved.[239,289,290] A single report of a patient with CVID and chronic urticaria documented amelioration of the urticaria in response to IVIG therapy.[291] However, in other case reports, patients did not respond or relapsed shortly after the completion of therapy.[292,293] A retrospective analysis of IVIG therapy in 6 patients with severe chronic urticaria who received 2 g/kg every 4-6 weeks demonstrated remission in 5 subjects and improvement in 1 subject after 1-11 treatments.[294] In one study,[295] 9 of 10 patients with chronic urticaria were reported to have benefited from IVIG therapy; in another,[292] no benefit was observed. Delayed-pressure urticaria is a variant of chronic urticaria that is also difficult to treat. The use of IVIG in patients with delayed-pressure urticaria was conducted as an open-label trial; one third of the enrolled patients experienced remission, another third experienced some benefit, and the rest did not respond.[296] Idiopathic solar urticaria is a rare, debilitating photodermatosis. In a retrospective review of data from 7 adult patients with chronic solar urticaria treated with 1.4-2.5 mg/kg for 1-3 courses, 5 had developed remission at 12-month follow-up.[297] Two patients with solar urticaria demonstrated resolution of symptoms after 3-6 courses of 0.4 mg/kg/day of IVIG.[298] In another report, a patient with solar urticaria had continued resolution following 3 courses of IVIG,[299] while another patient required concurrent phototherapy to achieve optimal benefit.[300] There is no clear evidence that the use of IVIG benefits patients with chronic urticaria, and additional placebo-controlled studies with long-term follow-up are needed. A recent review endorsed (based on level III, grade D evidence) a trial of IVIG in the treatment of refractory urticaria, when adverse events related to immunosuppressives, such as cyclosporine or corticosteroids, occur or when therapies including mycophenolate mofetil or omalizumab have failed.[301] Recently, omalizumab was approved by the FDA for the treatment of chronic idiopathic urticaria.[302]

Atopic dermatitis

The majority of patients with atopic dermatitis (AD) are satisfactorily managed using topical treatments. However, small numbers of patients have severe resistant disease despite receiving second-line therapies. In addition, these patients can develop unacceptable adverse events from therapy. Recent reports highlight some degree of success in the pediatric population affected by AD. A randomized, placebo-controlled study involving 40 children with moderate to severe AD receiving 2 g/kg IVIG monthly for 3 months showed significant improvement in severity scoring of AD (SCORAD) at the end of the series of infusions, but this improvement was not sustained.[303] A similar trend was seen in the allergic inflammatory parameters measured, including serum IgE. A retrospective case series in children with severe AD and a history of poor response to cyclosporin or azathioprine, and recurrent superinfections with *Staphylococcus aureus* or herpes simplex, reported responses ranging from good to complete remission. Dosing in each patient varied from 300 mg/kg to 2 g/kg, and duration ranged from 6 to 39 months. Time to response seen was 3-6 months. Significant decreases in serum IgE and eosinophils were seen at the 3-month time point, and the decrease in serum IgE persisted after discontinuation.[304] In a prospective cohort study in infants ages 7-12 months, infants who received 2 g/kg IVIG monthly for 3 months (n = 5) were compared to 7 infants who received no IVIG and 10 healthy infants. In the IVIG-treated group, SCORAD indices, serum ICAM-1, endothelial leukocyte adhesion molecule 1, and eosinophil cationic protein levels were improved significantly after 3 months, with sustained benefit at 6 months.[305] High-dose IVIG treatment has been suggested to be of benefit in an additional number of reports.[306-308]

The use of IVIG in adult patients with AD is less encouraging. An open-label study was conducted on the use of 2 g/kg of IVIG every 30 days for 7 infusions in 10 patients ages 7-69 years with severe AD (n = 9) and hyper-IgE syndrome (n = 1). The severity of eczema was determined by an ordinal scale skin score ranging from 0 to 5. Slight improvement in skin disease was observed in 6 patients; no improvement, in 2 patients; and worsening, in 1 patient. No concurrent decreases in IgE level were seen following therapy.[61] An open-label study in which 6 adult patients with severe AD received 2 g/kg every month for 6 months showed major improvement in modified Eczema Area and Severity Index scores in 4 patients.[307] In an evaluator-blinded trial, 10 adult patients with severe AD were randomized to immediate or delayed (by 30 days) treatment with 2 g/kg of IVIG. SCORAD at day 30 was not significantly different between the 2 groups. No significant changes in IgE levels were seen in the treatment cohort.[309]

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

Benefit	Indication	Evidence category	Strength of recommendation
Definitely beneficial	KD*	Ia	A
	Reduction of secondary infections in pediatric HIV infections*	Ib	A
	CMV pneumonitis in solid organ transplants	Ib	A
Probably beneficial	Neonatal sepsis	Ia	A
	Rotaviral enterocolitis	Ib	A
	Bacterial infections in lymphoproliferative diseases	Ib	B
	Toxic shock syndrome	III	C
	Enteroviral meningoencephalitis	III	C
May provide benefit	Cystic fibrosis with hypogammaglobulinemia	III	C
	Postoperative sepsis	III	C
	RSV lower respiratory tract infection (proven for palivizumab)	III	C
	Pseudomembranous colitis	III	C
	Campylobacter enteritis	III	C
	Chronic parvovirus B19	III	D
Unlikely to be beneficial	Chronic fatigue syndrome	Ib	A
	Cystic fibrosis without hypogammaglobulinemia	Ib	A
	Acute rheumatic fever	IIa	B
	Viral load in HIV infection	IIb	B

*FDA-approved indication.

Summary: Immunoglobulin in atopic disease

The use of IVIG in asthma lacks sufficient supporting evidence from RCTs. The few existing RCTs of IVIG in asthma have provided conflicting results, and the majority of successful reports were case series. Data to support the use of IVIG in chronic urticaria are lacking, and omalizumab, a newly developed and effective biologic therapy, is now FDA-approved for the treatment of chronic urticaria. IVIG has the potential to be effective therapy for AD in pediatric populations with severe disease. Long-term benefits following discontinuation of treatment are conflicting, and additional randomized, placebo-controlled studies with longer follow-up are needed. The use of IVIG in severe AD populations may be an alternative to other systemic therapies associated with more adverse events, particularly in the pediatric population with recurrent superinfection. The data from adult AD populations are less favorable, and reports of IVIG in the treatment of disease show little demonstrable benefit.

INFECTIOUS AND INFECTION-RELATED DISEASES

Despite improvements in antimicrobial therapies, there are a large number of pathogens that remain difficult to treat and others for which no specific chemotherapy exists. Thus, polyclonal immunoglobulin continues to be used for the treatment of a variety of infectious diseases and infection-related disorders (Table VI). Although there is significant anecdotal experience in a number of clinical settings, the cumulative evidence along with the cost-effectiveness and risks for complications must be taken into account when considering immunoglobulin for the treatment of infection. Of the conditions described in this section, only KD is an FDA-approved indication of IVIG. Several immunoglobulin products with high concentrations of specific antibodies to pathogens such as those causing tetanus, rabies, and diphtheria have been made available in the United States, and those currently approved by the FDA are listed in Table VII.

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 post-infectious origin.[310,311] IVIG, in conjunction with aspirin, is the standard of care in children during the first 10 days of the syndrome to prevent the development of coronary aneurysm.[312] Limited evidence suggests that treatment by day 5 of illness may be associated with even better outcomes,[313] but these data have been challenged.[314] All patients should be given a single dose of IVIG (2 g/kg) as soon as the diagnosis is established.[315] Reductions in fever, neutrophil counts, and acute-phase reactants typically occur within 24 hours following treatment. Although alternative IVIG regimens have been described, including 4 daily infusions (0.4 g/kg), they are less efficacious, as demonstrated in a prospective, multicenter trial.[315] The frequency of coronary artery abnormalities and duration of fever were significantly greater with the multidose regimen. A meta-analysis of data from RCTs of IVIG in KD also supported the use of a single 2-g/kg dose of IVIG and found that this regimen was associated with a significant decrease in new coronary artery abnormalities 30 days after diagnosis.[316] There were no distinctions among different IVIG products. Another meta-analysis of data from >3400 patients also demonstrated that a single, high dose of IVIG was more effective than were other IVIG regimens in preventing coronary aneurisms.[317] That analysis also found that low-dose (≤80 mg/kg) aspirin was comparable to high-dose (>80 mg/kg) aspirin in preventing coronary aneurysms when combined with high-dose IVIG.[317] Ten percent to 20% of patients with KD have persistent or recurrent fever after completing a regimen of IVIG and aspirin,[318] and the risk for coronary artery abnormalities is increased in nonresponders.[319-321] Age, duration of illness, neutrophil and platelet counts, elevated aspartate aminotransferase and C-reactive protein, and hyponatremia have been proposed to predict resistance to treatment.[322-325] Findings from recent clinical trials suggest that the addition of prednisolone (2 mg/kg) to a regimen of IVIG further reduced the occurrence

TABLE VII. Hyperimmune serum globulins approved by the FDA

Hyperimmune serum globulins	Manufacturer
Botulism antitoxin bivalent (equine)	Sanofi Pasteur
Botulism IGIV	California Department of Public Health
Cytomegalovirus immunoglobulin	CSL Behring
Hepatitis B immunoglobulin	Biotest Pharmaceutical Corporation, Cangene, Grifols
Rabies immunoglobulin	Grifols, Sanofi Pasteur
Tetanus immunoglobulin	Grifols
Vaccinia immunoglobulin	Cangene
Rho(D)	Cangene, CSL Behring, Grifols

of coronary artery abnormalities from 23% to 4%.[321] Early repeated treatment with IVIG may be considered in KD that is not responding to initial dosing within 48-72 hours (ie, when neutrophil counts, C-reactive protein, and N-terminal of the prohormone brain natriuretic peptide, which are independent parameters of retreatment, remain elevated).[326]

Reduction in viremia in HIV-infected individuals

Although IVIG is efficacious and FDA-approved for use in reducing the risk for secondary infection in HIV-infected children (discussed earlier),[86] its use in treating HIV infection *per se* has not been as widely evaluated. A single study examining the effect of a 2-g/kg IVIG dose on viral load found that p24 antigen levels and number of HIV RNA copies were significantly increased after treatment.[327] In one study, 6 chronically HIV-infected adults who were not receiving anti-HIV therapy were treated with 2 doses of IVIG at 400 mg/kg/dose with a 1-month interval, and demonstrated a transient, modest decrease in activated T cells, with an increase in total CD4 T-cell counts.[328] These changes were transient, and levels returned to baseline within 1 week of infusion. Thus, IVIG may be useful for preventing bacterial infections, but should not be considered an antiviral therapy in HIV-infected patients.[329] If B-cell function is not restored with immune reconstitution on HAART, there may be implications for the quality anti-polysaccharide antigen responses in particular. Since the advent of HAART, there have been no controlled studies examining the immunomodulatory effects of IVIG in HIV-infected patients taking HAART.[329]

Sepsis, septic shock, and toxic shock syndrome

Adjuvant treatment of bacterial sepsis or septic shock using polyclonal IVIG was reported to be associated with significantly reduced mortality, as demonstrated by a meta-analysis of data from 8 trials including 492 patients.[330] Likely beneficial mechanisms of IVIG include the improvement in serum bactericidal activity due to neutralization and opsonization of IgG and IgM antibodies, as well as stimulation of phagocytosis and neutralization of bacterial toxins.[175] IVIG may also suppress proinflammatory cytokine release from endotoxin or superantigen-activated blood cells.[331] Specific conditions in which IVIG preparations have been evaluated and may be useful include group B streptococcal disease in newborns,[332] streptococcal toxic shock/invasive streptococcal syndromes,[333-337] postoperative sepsis,[338] trauma-associated sepsis,[339] and neonatal sepsis.[340] Of these, neonatal sepsis has been most extensively evaluated, and a meta-analysis of trials found a 6-fold decrease in mortality when IVIG was added to conventional therapies.[340] This benefit was far greater than that derived from the prophylactic use of IVIG in preventing neonatal sepsis. Another meta-analysis report reviewed data from 10 randomized studies that assessed the use of IVIG in suspected fungal or bacterial infection in neonates <1 month of age,[341] and demonstrated a significant reduction in mortality (relative risk = 0.55; 95% CI, 0.38-0.89). The use of IVIG in treating streptococcal toxic shock has also been more rigorously evaluated and provided an odds ratio for survival of 8:1 in a case-controlled series.[335] Two, more recent multicenter studies, however, suggested that there were no differences in outcomes studied with use of IVIG. In a cohort of 192 children with streptococcal toxic shock syndrome, of whom 84 received IVIG, mortality, length of stay, and clinical variables studied were not different with regard to the use of IVIG.[342] A larger-scale study in 3493 infants receiving antibiotics for the treatment of sepsis did not show differences in mortality or major disability at 2 years between patients who received immunoglobulins and those who received placebo.[343] Therefore, polyclonal IVIG may represent a promising adjuvant in the treatment of neonatal sepsis, but indications of IVIG therapy in these settings require more precise definition.

Pneumonia and pneumonitis

The role of IVIG in the prevention of lung infection in patients with primary or acquired immunodeficiencies is well established (reviewed in the Primary Immunodeficiency section); in contrast, the use of IVIG for the treatment of pneumonia is not well established. The treatment of pneumonitis caused by CMV has been reported in several small series of immunodeficient patients using high-dose IVIG[344,345] or high-concentration anti-CMV polyclonal IVIG (CMV-IVIG).[346] High-dose IVIG combined with ganciclovir improved survival in patients, whereas either treatment alone did not. Similarly, the combination of CMV-IVIG with ganciclovir in the treatment of CMV pneumonitis was associated with better survival than would be expected from other treatment regimens.[346]

The treatment of respiratory syncytial viral (RSV) pneumonitis using IVIG[347,348] or high-concentration anti-RSV polyclonal IVIG (RSV-IVIG)[349] combined with ribavirin was reported in a small series of immunodeficient patients. Survival rates in these series compared with those expected based on historical cohorts were encouraging, and suggest that IVIG or RSV-IVIG may be of benefit as an adjunct therapy to ribavirin. RSV-IVIG has been extensively studied as a prophylactic agent in the prevention of acute RSV infection in populations considered to be at high risk for serious morbidity or mortality, including prematurity with or without bronchopulmonary dysplasia and congenital heart disease. A meta-analysis of data from these studies indicated effectiveness of RSV-IVIG in the prevention of hospital and intensive care unit admission, although there was a nonsignificant trend toward increased mortality in the treated infants.[350] The need for this hyperimmune IVIG preparation, however, has been reduced by the advent of palivizumab, a monoclonal antibody therapy specific for RSV. Immunoprophylaxis with 5 monthly doses of palivizumab is an effective intervention that has been reported to reduce hospitalization by 39-82% among high-risk infants.[351] RSV polyclonal IVIG is no longer available.

The role of the RSV-specific monoclonal antibody in the prevention of RSV is clear.

The anecdotal use of IVIG as adjunct therapy in varicella pneumonia[352] or adenoviral pneumonitis[353] has also been described. Although there are encouraging experimental data regarding the use of topically applied IVIG in the treatment of bacterial pneumonia,[354] there are no data from studies in humans that suggest that IVIG is of any benefit in the treatment of established bacterial pneumonia.

Infectious gastroenterocolitis and diarrhea

Orally administered IVIG was evaluated in a double-blind, placebo-controlled study in 98 children with acute rotaviral gastroenteritis. A single dose of 300 mg/kg was associated with significantly reduced duration of diarrhea, viral shedding, and hospitalization.[355] The benefit of orally administered IVIG in immunodeficient patients with rotavirus, or those with otherwise prolonged diarrhea, has been presented anecdotally but not rigorously evaluated.[356-359] The value of immunoglobulin therapy has also been described in *Campylobacter jejuni* infection (administered orally)[360] and in pseudomembranous colitis caused by *Clostridium difficile* (administered intravenously).[361,362] In a retrospective study, in 9 of 14 patients with refractory *C. difficile* diarrhea, symptoms were resolved within 10 days of IVIG administration, without recurrence.[363] In contrast, 2 other retrospective studies of severe *C difficile* colitis in patients who received IVIG were not able to demonstrate improved outcomes.[364,365] Those studies were of relatively small sample size and used different criteria for determining indication of IVIG. Those studies also differed in IVIG doses administered and suggested that the severity of systemic compromise may affect outcomes. IVIG (administered intravenously) is probably not an effective adjunct therapy in the treatment of gastrointestinal disease caused by CMV in immunosuppressed patients.[366] Orally or intravenously administered IVIG in chronic infectious diarrhea needs more study before a definitive recommendation can be made; however, some immunocompromised patients with recalcitrant diarrhea may have limited options for treatment, and IVIG or orally administered IVIG has been used with mixed results.

Enteroviral meningoencephalitis

Meningoencephalitis caused by enteroviral infection has been a complication of particular concern in patients with agammaglobulinemia and can occur despite IVIG therapy. Two methods of treating enteroviral meningoencephalitis using IVIG in small numbers of patients with agammaglobulinemia have been described: daily or frequent high-dose IV administration, and intrathecal administration.[367-374] Relapses after either treatment were common[369,370,373,374] and treatment failures did occur,[371] but the latter approach was associated with long-term eradication of *Enterovirus* spp. in several patients.[367,372] Although antienteroviral drugs are in development,[375,376] their anecdotal utility in this particular setting has been variable,[372,377] and IVIG remains a therapeutic option in this rare, but desperate, clinical scenario.

Parvovirus B19–associated syndromes

Several case reports have described the successful use of IVIG in the treatment of anemia caused by chronic parvovirus B19 infection.[378-380] IVIG therapy has been shown to clear viremia and improve symptoms and cytokine dysregulation in parvovirus B19–associated chronic fatigue.[381] This viral infection is prevalent in the general population, and IVIG contains a significant anti–parvovirus B19 concentration and was considered the only specific treatment of infection.

Carditis in rheumatic fever

A single, randomized trial did not demonstrate a benefit of IVIG in the prevention of cardiac sequelae of acute rheumatic fever.[382] A recent Cochrane database review called for new RCTs in patients with acute rheumatic fever to assess the effects of corticosteroids and other new anti-inflammatory agents.[383]

Summary: IVIG in infectious and infection-related diseases

This section includes 2 FDA-approved indications of immunoglobulin, KD (for the prevention of coronary artery aneurisms associated with KD) and pediatric HIV infection (for the reduction of secondary infections). While IVIG remains an important intervention in KD, its use in HIV has been minimized in the era of HAART. Category Ib evidence exists to support the use of IVIG as definitely beneficial in CMV pneumonitis in solid organ transplant recipients, and as probably beneficial in rotaviral enterocolitis and bacterial infections in lymphoproliferative diseases. Category Ia evidence supports the use of IVIG as probably beneficial in the treatment of neonatal sepsis (Ia), but not in prophylaxis of infection. However, other studies have indicated no improvement in mortality with IVIG. Therefore, indications of IVIG for the treatment of neonatal sepsis require more defined studies. Evidence-based recommendations in other conditions discussed are summarized in Table VI.

NEUROLOGIC DISORDERS

Despite the widespread use of IVIG in the treatment of a number of immune-mediated neurologic diseases, the consensus on its optimal use is insufficient. However, specialty-specific, evidence-based guidelines have recently been published.[203,384] IVIG has demonstrated some degree of effectiveness in a number of disorders of the peripheral and central nervous systems (Table VIII).

Demyelinating peripheral neuropathies

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 peripheral nervous system. Therefore, it is commonly treated with corticosteroids, PE, and IVIG. Data from the first large-scale, randomized, open-label, controlled trial of IVIG (0.4 g/kg/day for 5 days) versus PE suggested that the clinical outcomes were at least comparable.[385] A multicenter, randomized, blinded, controlled trial involving 383 patients from Europe, Australia, and North America revealed no significant differences in mean disability grade between patients treated with PE, IVIG, or PE followed by IVIG.[386] The addition of methylprednisolone (0.5 g/day for 5 days) after a course of IVIG did not show a significant benefit

TABLE VIII. Uses of immunoglobulin in neuroimmunologic disorders

Benefit	Disease	Evidence category	Strength of recommendation
Definitely beneficial	CIDP	Ia	A
	Multifocal motor neuropathy	Ib	A
	Guillain-Barré syndrome	Ib	B
Probably beneficial	IgM anti-myelin–associated glycoprotein paraprotein-associated peripheral neuropathy	Ib	B
	LEMS	Ib	B
	MG	Ib	B
	Stiff-person syndrome	Ib	B
May provide benefit	Relapsing-remitting multiple sclerosis	Ia	A
	Intractable childhood epilepsy	Ia	B
	Postpolio syndrome	Ib	B
	Rasmussen syndrome	IIb	C
	Acute disseminated encephalomyelitis	III	C
	Human T-lymphotropic virus 1–associated myelopathy	III	C
	Cerebral infarctions with anti-phospholipid antibodies	III	C
	Demyelinative brain stem encephalitis	III	C
	Lumbosacral or brachial plexitis	III	C
	Paraproteinemic neuropathy	III	C
	Autoimmune encephalitides	III	C
	Opsoclonus myoclonus syndrome	III	C
	Postinfectious cerebellar ataxia	III	D
	Acute idiopathic dysautonomia	III	D
	Autoimmune optic neuropathy	III	D
	Paraneoplastic cerebellar degeneration	III	D
	Brown-Vialetto-Van Laere syndrome	III	D
	Alzheimer disease	III	D
	Narcolepsy with cataplexy	III	D
	Limbic encephalitis	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
	Brachial plexopathy	III	C
	Autism	III	C

POEMS, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

in a multicenter, randomized, double-blind, placebo-controlled study in 233 patients.[387] Several other studies that have compared IVIG to supportive measures or PE in children[388] and adults[389,390] showed similar findings, but patients were not always randomized, and investigators were not blinded to the treatments.[391-395] A systematic review of data from randomized trials revealed no significant differences in any of the outcome measures between IVIG and PE. None of the treatments significantly reduced mortality.[396] Several Cochrane reviews have provided moderate-quality evidence that, in severe disease, IVIG started within 2 weeks from onset hastens recovery as much as does PE. Adverse events were not significantly more frequent with either treatment, but IVIG was significantly more likely to have been completed than was PE. Giving IVIG after PE did not confer significant extra benefit. IVIG may hasten recovery in children compared with supportive care alone. Evidence is insufficient to support or refute the use of IVIG in children with GBS.[203]

More research is needed in mild disease and in patients whose treatment is started >2 weeks after onset. Dose-ranging studies are also needed.[396] The risk for thromboembolic complications with IVIG is not negligible in patients with neuropathy,[397] especially with daily doses ≥35 g.[398] The age of patient, the presence of preceding diarrhea, and the severity of disability in the early course of disease were associated with poor response to IVIG in one study.[397] Under investigation are new treatment strategies with adapted IVIG dosages based on prognostic factors.[399] IVIG is thus considered similar to PE in the treatment of GBS, but is used more frequently because of difficult vascular access and tolerability issues with PE, particularly in children and in patients with autonomic instability.

Chronic inflammatory demyelinating polyneuropathy. CIDP 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 peripheral nerves.[400,401] It has been historically treated with corticosteroids, PE, or, in more resistant cases, cytotoxic immunosuppressive drugs. Earlier RCTs showed that IVIG improved disability within 2-6 weeks compared with placebo, and had efficacy similar to that of PE and prednisolone, although with an increased quality of life.[402-406] The standard dose is 0.4 g/kg/day for 5 days, but in relapsing patients this dose may need to be repeated every 2-8 weeks to maintain improvement.[407] A meta-analysis of data from 7 RCTs including 287 participants showed that IVIG improved

disability for at least 2-6 weeks compared with placebo. During this period, it had efficacy similar to that of PE and oral prednisolone. There were no statistically significant differences in the frequencies of adverse events between the 3 types of treatment.[408] A recent multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with CIDP reported that treatment of CIDP with IVIG for 6 months was less frequently discontinued because of a lack of efficacy, adverse events, or intolerance than was treatment with IV methylprednisolone.[409] One large-scale, randomized, double-blind, placebo-controlled, response-conditional crossover trial of IVIG-C (10% caprylate-chromatography purified) in the treatment of CIDP (the ICE study [IVIG (10% caprylate-chromatography purified) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy]) revealed that 54% of patients treated with IVIG-C and 21% of those who received placebo had an improvement in adjusted INCAT (inflammatory neuropathy cause and treatment) disability score that was maintained through week 24. Results were similar during the crossover period.[3] Data extracted from the ICE study revealed that treatment with 2 courses of IVIG-C administered 3 weeks apart may be required for initial improvement, and continued maintenance therapy may be necessary for achieving a maximal therapeutic response.[410] IVIG is considered the preferred treatment of CIDP 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.[401] It is currently FDA-approved for the treatment of CIDP.[411,412] However, based on common willingness-to-pay thresholds, IVIG was not perceived as a cost-effective treatment in a recent study from Canada of costs and QALYs over 5 years of CIDP treatment.[413] Another problem is that a third of patients do not respond to IVIG. The reasons for IVIG unresponsiveness remain unclear, although genetic factors may play a role.[414]

Multifocal motor neuropathy. Several randomized, double-blind, placebo-controlled, crossover clinical trials have shown IVIG to provide efficacy in treating MMN, a chronic inflammatory condition that selectively affects the motor nerves (especially the radial, ulnar, median, and common peroneal).[415] IVIG is now FDA-approved for use in treating MMN. Using a dose of 0.4-0.5 g/kg/day for 5 consecutive days, >80% of patients reported improvement as assessed by self-evaluation scores. IVIG had no consistent effect on IgM anti-ganglioside M1 antibody titers, nor was it invariably accompanied by improvement in motor conduction block or Medical Research Council scores.[416-418] A follow-up study in 11 MMN patients for 4-8 years demonstrated long-term beneficial effects of maintenance IVIG therapy on muscle strength and upper limb disability. IVIG influenced remyelination or reinnervation, but axon loss could not be prevented.[419] A retrospective study of response to IVIG in 40 patients with MMN confirmed a significantly high short-term response, but showed contrasted results on long-term follow-up. No predictive factors for response to IVIG were found.[417,420] Four RCTs with a total of 46 patients with MMN have demonstrated that IVIG is an effective treatment, leading to improved muscle strength in two thirds of patients.[417] IVIG is now the recommended therapy for this neurologic disease. There is no evidence to recommend other treatments,[3] taking into consideration that MMN is unresponsive to PE and might even be exacerbated by corticosteroid use.[401,415,416,418,421]

SCIG therapy was tried in 5 patients with MMN who received a dose equivalent to the IVIG maintenance dose. Four patients maintained muscle strength during the 6-month follow-up. Local adverse events were frequent but generally well tolerated.[422] Also, SCIG was as effective as IV infusion in a randomized, single-blind, crossover study in which 9 IVIG-responsive patients with MMN were allocated to receive either SCIG or IVIG for a period equivalent to 3 IVIG treatment intervals.[7] Another 2-year follow-up study provided class IV evidence of tolerability in a small-scale (n = 6) case series of patients with MMN preferring SCIG to IVIG.[423]

IgM anti-myelin–associated glycoprotein paraprotein–associated peripheral neuropathy. An analysis of data from 5 RCTs (79 participants) demonstrated some clinical short-term benefit of IVIG in the form of improvement in Modified Rankin Scale at 2 weeks and 10-m walk time at 4 weeks. None of the serious adverse events were encountered in these trials.[424-426]

Neuromuscular junction syndromes

IVIG therapy has been evaluated in myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS).

Myasthenia gravis. The benefit in MG of IVIG (0.4 g/kg/day for 3-5 days) was comparable to that of PE in 2 randomized, comparative studies, with a decrease acetylcholine receptor antibody concentration in one study[427] and the quantified MG clinical score in the other.[428] In the older study,[427] patient tolerance of IVIG was generally better than that of PE. However, Class I evidence that IVIG and PE have comparable efficacy and are similarly tolerated in adult patients with moderate to severe MG within 2 weeks of treatment was recently reported, and the only factor predicting response to treatment was baseline disease severity.[429,430] Nonetheless, a randomized, placebo-controlled study failed to demonstrate a significant effect after 6 weeks of IVIG therapy.[431] IVIG was considered of possible benefit in myasthenic crises[432] and juvenile myasthenia,[433] and in preparing myasthenic patients for surgery.[434,435]

In exacerbation of MG, 1 RCT of IVIG versus placebo showed some evidence of the efficacy of IVIG, and 2 did not show a significant difference between IVIG and PE.[436,437] Another showed no significant difference in efficacy between 1 and 2 g/kg of IVIG.[436,437] A further, but underpowered, trial showed no significant difference between IVIG and oral methylprednisolone.[436,437] A retrospective chart review of data from 53 patients with muscle-specific kinase antibody–positive MG at 9 university-based centers in the United States showed that the best clinical response was to corticosteroids and PE, and the poorest response was to IVIG.[438] In chronic MG, there is insufficient evidence from RCTs to determine whether IVIG is efficacious.[437]

Lambert-Eaton myasthenic syndrome. LEMS is a rare presynaptic autoimmune disorder of neuromuscular transmission that is characterized by proximal muscle weakness, depressed tendon reflexes, and autonomic dysfunction. It is identified by incremental responses on repetitive nerve stimulation and the presence of antibodies to the presynaptic calcium channels at the motor end plates.[439,440] Limited but moderate- to high-quality evidence from RCTs has shown that 3,4-diaminopyridine over 3-8 days or IVIG for up to 8 weeks was associated with improved muscle strength scores and compound muscle action potential amplitudes in participants with LEMS.[441] In 1 trial, 8 of 9 patients exhibited clinical improvement within 2-4 weeks of IVIG infusion (1 g/kg/day for 2 consecutive days), although it declined after

8 weeks, correlating with a rebound of serum calcium channel antibody concentrations.[442] A similar response and lack of serious adverse events have been reported in additional case reports and uncontrolled trials.[443-445] IVIG seems to have a positive short-term effect in LEMS (recommendation level based on good practice point).[446] It may thus be used as an alternative treatment in patients who fail to respond or do not tolerate other treatments of LEMS.

Multiple sclerosis

At least 3 randomized, double-blind, placebo-controlled studies[447-449] have demonstrated some benefit of IVIG treatment in reducing exacerbations of multiple sclerosis (MS). Combining the data from these studies showed that 34% of IVIG recipients had reduced exacerbations versus 15% of placebo recipients. The largest study (148 patients) revealed that IVIG (0.15-0.2 g/kg monthly for 2 years) was associated with reduced clinical disability.[448] When larger doses were tried (1 g/kg/d for 2 days at 4-week intervals), 65% (of 25 patients) had no exacerbations in 6 months versus 35% of the control group.[449] Nonetheless, its efficacy lags clearly behind that of β-interferon due to smaller study samples, partial deficits in study design, and unestablished optimal dosage. One RCT concluded that IVIG treatment in the first year from onset of the first neurologic event suggesting demyelinating disease significantly lowered the prevalence of a second attack and reduced disease activity.[450] So far, IVIG is the only therapy investigated for reducing postpartum relapses, whereas immunomodulatory drugs are contraindicated during pregnancy and breastfeeding.[451] A retrospective review of data from pregnant patients with relapsing-remitting MS concluded that IVIG could be considered as an option for reducing the prevalence of pregnancy- and postpartum-related relapses. However, further randomized, double-blind studies are needed to confirm these findings.[452] Although a reduction in the number and volume of gadolinium-enhanced MRI lesions was reported in one study,[453] this finding was nonsignificant in a 2-year follow-up study.[447] A meta-analysis of data from 265 patients revealed significant reductions in the disability score (Expanded Disability Status Scale), annual relapse rate, proportion of patients who deteriorated, and new MRI lesions.[454] IVIG therapy was found beneficial in 5 patients reported to have CIDP associated with definite relapsing MS.[455]

A multicenter, randomized, placebo-controlled trial concluded that monthly IVIG infusion could delay the progression of disease in patients with primary progressive MS.[456] However, IVIG 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.[457] A multicenter, randomized, double-blind, placebo-controlled trial that included 127 patients with relapsing-remitting MS did not substantiate a beneficial effect of IVIG at doses ranging from 0.2 to 0.4 g/kg.[458] More recently, IVIG at a dose of 0.4 g/kg/day for 5 days did not show inferiority compared with IV methylprednisolone in the treatment of an acute MS relapse using both clinical and MRI evaluation.[459]

Thus, IVIG should be considered a potentially effective second-line treatment in relapsing-remitting MS, but the optimal dosage still needs to be established.[457,460]

There also may be a potential role for IVIG in neuromyelitis optica, an idiopathic central nervous system inflammatory demyelinating disease (causing optic neuritis, transverse myelitis, and other central nervous system syndromes) that is associated with autoantibodies against the astrocyte water channel called aquaporin-4.[461] No RCTs of first-line therapies or IVIG in neuromyelitis optica are available. Relapse is usually prevented using azathioprine, mycophenolate mofetil, or rituximab, based on retrospective and prospective open-label studies only. Prevention of relapse was studied in a prospective, open-label, uncontrolled observational study evaluating the tolerability and clinical effects of IVIG in neuromyelitis optica spectrum disorders and demonstrated statistically significant decreases in relapse rate, from 1.8 in the previous year to 0.006 during follow-up, and in Expanded Disability Status Scale score, which fell from 3.3 to 2.6. In relapse treatment, this and other anecdotal reports suggest that IVIG could be considered in patients with severe relapses not responding to corticosteroids, who are not candidates for PE.[461,462]

Intractable childhood epilepsy

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 of IVIG treatment come mostly from uncontrolled, open-label series or case reports.[463-466] However, there are 2 randomized placebo-controlled trials that have been performed in Lennox-Gastaut syndrome. One was a small-scale (n = 10), single-blind, crossover study.[467] Two doses of IVIG at 400 mg/kg or placebo was given with an interval of 2 weeks. In 2 of the children, reductions in seizures of 42% and 100% were noted. The other 8 children showed no change over an observation period of 14 weeks. The other study was double-blind and found that IVIG therapy (0.1-0.4 g/kg/day for 4 days, then once each in weeks 2, 3, and 6, ± month 6) reduced clinical seizure frequency by half in 52% of the recipients (n = 40) compared with 28% of the placebo recipients (n = 18).[468] A prospective, open-label study that investigated the effect of IVIG on clinical electroencephalography, and serum/cerebrospinal fluid immunologic parameters in refractory, childhood-onset epilepsy revealed substantial reductions in seizure frequency that occurred in 7 of 13 patients, despite unchanged spike counts on electroencephalography, suggesting that it may hinder the progression of central epileptic activity into clinical seizures.[469]

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 IVIG has produced some encouraging results in childhood as well as adult-onset disease.[470,471] It led to reductions in seizure frequency in 8 of 9 recipients compared with 10 of 17 high-dose corticosteroid recipients in a retrospective case series.[472] The high-dose corticosteroid and IVIG therapies were associated with alleviated exacerbation of seizures in 27 patients with Rasmussen encephalitis, but they could not halt disease progression.[473]

Although the temporal relation between IVIG treatment and clinical improvement cannot be denied in individual children with Landau-Kleffner syndrome (another syndrome characterized by

continuous spikes and waves during sleep [CSWS), its real value remains to be determined.[474]

Due to the paucity of reliable studies that have demonstrated substantial efficacy of IVIG in these syndromes, its routine use cannot be recommended. A Canadian expert panel also did not recommend the use of IVIG in intractable childhood epilepsy.[475] However, the poor prognosis and quality of life of children who do not improve with antiepileptic drugs and corticosteroids might justify a trial of IVIG therapy, especially in patients who are otherwise not candidates for surgical resection. Although there is interesting theoretical potential for the treatment of refractory epilepsy in adults with IVIG, insufficient evidence exists to support its standard use. Further RCTs are needed.[476,477]

Other neurologic syndromes

Case reports and small-scale trials about successful IVIG treatment in other neuroimmunologic conditions exist, but its use remains investigational. Examples of positive reports include those describing IVIG treatment in patients with acute disseminated encephalomyelitis,[478,479] demyelinative brain stem encephalitis,[480] subacute rhombencephalitis optica,[481] and autoimmune encephalitis.[482] An analysis of data from 27 cases led to the conclusion that IVIG may be an option for the treatment of monophasic acute disseminated encephalomyelitis when first-line therapy with high-dose corticosteroids fails or when there are contraindications of steroid use.[475,483] It was also reported to improve acute disseminated encephalomyelitis following pertussis in an infant.[484] A recent semiprospective case series that included 6 patients with steroid-dependent recurring-relapsing autoimmune optic neuropathy from 4 medical centers concluded that IVIG can be considered an effective steroid-sparing agent in selected cases.[485] A beneficial effect of IVIG was reported in 2 patients with late onset of paraneoplastic cerebellar degeneration who showed a delayed response with significant neurologic improvement.[486] Case reports and small trials suggest some success with the use of IVIG with or without plasmapheresis and/or other immunosuppressive drugs in paraneoplastic and non–tumor-related central nervous system syndromes associated with the anti-glutamate receptor antibodies (anti–*N*-methyl-D-aspartate and anti–α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and anti–voltage-gated potassium channel antibodies, including limbic encephalitis and opsoclonus-myoclonus syndrome.[487] A systematic review of the use of IVIG in autoimmune encephalitis associated with antibodies to cell surface antigens (including *N*-methyl-D-aspartate receptor; leucine-rich, glioma-inactivated protein 1; contactin-associated protein 2; the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; γ-aminobutyric acid A receptor; γ-aminobutyric acid B receptor; glycine R; and other, rarer antigens) was recently published.[482] The studies highlighted in the review were mainly retrospective cohorts, and there were no RCTs. Clinicians treated these patients using corticosteroids, IVIG, or PE, and, if the condition was severe or refractory, other agents, such as rituximab and cyclophosphamide, as well as surgery to remove tumors when present.[482] The investigators cautioned that while some positive effects were reported, due to the retrospective, uncontrolled study design, the literature had inherent biases, including severity and reporting biases.[482]

Two case reports have suggested that IVIG temporarily stabilized the disease in the Brown–Vialetto–Van Laere syndrome, a rare neurologic disorder characterized by progressive pontobulbar palsy associated with sensorineural deafness.[488]

Emerging data suggest that IVIG may have a role in some neurodegenerative disorders associated with "neuroinflammation" mediated by proinflammatory cytokines, but this concept remains to be fully investigated.[489,490] In a double-blind, placebo-controlled trial in patients with stiff person syndrome and high anti–glutamate decarboxylase antibodies, IVIG was associated with improvement in stiffness and heightened sensitivity scores and increases in patients' ability to carry out daily activities. It also was associated with suppressed anti–glutamate decarboxylase antibody concentrations, probably via an anti-idiotypic effect.[491] IVIG had apparent effects on relevant quality-of-life variables and inflammatory cytokines for up to 1 year in patients with postpolio syndrome.[492] It was associated with increased SF-36 scores on physical activity concerning bodily pain, vitality, social function, role–emotional, as well as pain.[493] Moreover, evidence from RCTs has suggested that IVIG was effective in reducing pain in complex regional pain syndrome (low-dose IVIG) and postpolio syndrome (high-dose IVIG).[494] In a small number of patients with Alzheimer disease, IVIG was promising in reducing Alzheimer's Disease Assessment Scale–Cognition scores, suggesting a reversal of disease progression.[495] Another study reported increased plasma anti–β-amyloid antibody concentrations associated with decreased β-amyloid peptide levels in the cerebrospinal fluid following IVIG treatment. These changes at the molecular level were accompanied by improved cognitive function.[496-499] However, subsequent studies did not support the use of IVIG in Alzheimer disease.[500] An RCT in 2015 investigated the use of a short course of IVIG in the mild cognitive impairment stage of Alzheimer disease and showed a transient reduction in brain atrophy, prevention of cognitive decline, and delayed conversion to dementia, but these effects of IVIG waned by 2 years.[501]

In several case reports, IVIG was associated with a reduced number of cataplectic attacks in narcoleptic patients.[502-504] IVIG was reported to have partially neutralized the inhibitory effect of narcoleptic IgG on the colonic migrating motor complex.[505] This favorable effect was challenged by a report on 4 patients with narcolepsy and cataplexy who were treated with high-dose IVIG. Although some patients showed some transient positive effects in both objective symptoms (multiple sleep-latency test score and maintenance of wakefulness test scores) and subjective symptoms (Epworth Sleepiness Scale score and frequency of cataplexy), these effects lasted at the most for a few weeks and did not persist.[506]

Evidence supporting the use of IVIG in several neurologic disorders is clearly lacking or has showed negative effects. Polyneuropathy associated with IgM monoclonal gammopathy is an example of a disease in which IVIG was ineffective, or even had negative effects.[507] Additionally, there are no convincing data to substantiate the treatment of inclusion body myopathy, idiopathic neuropathies, brachial plexopathy, or diabetic amyotrophy with IVIG.[508] It is also not recommended for use in adrenoleukodystrophy, amyotrophic lateral sclerosis, critical illness polyneuropathy, or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes).[483]

TABLE IX. Miscellaneous uses of immunoglobulin therapy

Benefit	Indication	Evidence category	Strength of recommendation
Probably beneficial	Toxic epidermal necrolysis and Stevens-Johnson syndrome	IIa	B
May provide benefit	Prevention of infection and acute graft-versus-host disease post-bone marrow transplantation*	Ib	A
	Prevention of acute humoral rejection in renal transplantation	Ib	A
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection	IIb	B
	Delayed pressure urticaria	IIb	B
	Severe persistent high-dose steroid-dependent asthma	III	C
	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
	AD	Ib	B
	Prevention of unexplained spontaneous recurrent abortions	Ia	A
Unlikely to be beneficial	Non–steroid-dependent asthma	Ib	A
	Dilated cardiomyopathy	Ib	A
	Chronic fatigue syndrome	Ib	A
	Prevention of infection and acute graft-versus-host disease after bone marrow transplantation	Ib	A
	Cystic fibrosis without hypogammaglobulinemia	Ib	A
	Autistic disorders	III	C

*Current gold standard therapy for GVHD is corticosteroids and calcineurin inhibitors.

Summary: Immunoglobulin in neurologic conditions

Specialty-specific, evidence-based guidelines on the use of IVIG in neurologic conditions have recently been published.[203,384] IVIG has demonstrated some degree of effectiveness in a number of disorders of the peripheral and central nervous systems. Two recent neurologic indications have been FDA-approved, including CIDP (to improve neuromuscular disability and impairment, and for maintenance therapy to prevent relapse) and MMN (as maintenance therapy to improve muscle strength and disability in adult patients with MMN). The evidence categories and recommendation levels regarding these and other diseases are summarized in Table VIII.

MISCELLANEOUS USES

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

Nonatopic dermatologic disorders

Blistering skin diseases. The blistering skin diseases group of autoimmune disorders includes pemphigus vulgaris, bullous pemphigoid, and variants that can cause serious complications and even death. A single, randomized, placebo-controlled study in 61 subjects has been reported and demonstrated a benefit of IVIG in patients with poor response to corticosteroids.[509] A review of data from >200 additional patients contained in anecdotal reports and case series suggested a benefit of IVIG in 94% of treated patients.[510,511] Case reports and series extend to pregnant,[510] adolescent,[512] and infant[513] patients. IVIG has also been used in these disorders in combination with plasmapheresis[514] or immunosuppressive agents.[515] One reported patient was successfully treated with SCIG.[516] A consensus statement from the American Academy of Dermatology[517] on the use of IVIG in blistering skin diseases is conservative, given the general lack of high-quality studies (it antedates the single, randomized trial and the literature cited earlier). The consensus document offers a guideline on the indications of IVIG, including failure of conventional therapy with 1 mg/kg/day of prednisone for 6 weeks, failure of treatment with immunosuppressive agents, a history of adverse reaction to corticosteroids or immunosuppressive agents, progressive disease, and uncontrolled rapid progression of disease, and recommends a dose of 2 g/kg/cycle, given monthly, with a progressive increase in the intervals between the cycles after control has been achieved.[517] Another consensus document on this topic was published by dermatologists from Canada,[518] and the use of IVIG in blistering skin disorders was reviewed recently.[519] The most recent consensus document published by the European Dermatology Forum Guideline Subcommittee provides a guideline on the use of high-dose IVIG in dermatologic conditions, including blistering skin diseases, and encourages a standardized approach to these in order to facilitate larger-scale case series and to optimize the use of high-dose IVIG in dermatology.[520] According to a recent review,[521] IVIG effectively decreases the levels of pathogenic autoantibodies and is best used as adjuvant therapy in combination with an immunosuppressive agent. In patients refractory to IVIG and immunosuppressant, rituximab has been added, but its role in immunobullous disease requires further evaluation.[521]

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 have

shown that early administration of high-dose IVIG helped to halt the progression of disease and reduce fatality.[522] Most reported patients were treated with IVIG in conjunction with other drugs, such as corticosteroids. A more recent and relatively large-scale (65 patients), retrospective study of IVIG (in addition to corticosteroids) in these disorders also showed a trend toward earlier resolution and reduced mortality, although results were not statistically significant.[523] A recent systematic review and meta-analysis of 17 studies showed a nonsignificant trend toward reduced mortality with IVIG therapy for toxic epidermal necrolysis and concluded that the current evidence does not support a clinical benefit of IVIG and that randomized clinical trials are needed.[524]

Other skin diseases. Case reports suggesting improvement with IVIG exist in these additional disorders affecting the skin not covered elsewhere in this review: psoriasis, pyoderma gangrenosum, pretibial myxedema, and Mucha-Habermann disease.[522] More recent reports also include dystrophic calcinosis cutis[525] and scleromyxedema.[526]

Other organ-specific diseases

Cardiac disease. Case reports suggest that patients with acute myocarditis benefit from high-dose IVIG.[527,528] In addition, a series of 17 patients with high viral loads of parvovirus (erythrovirus) B19 and cardiomyopathy were treated with IVIG.[529] IVIG led to significantly decreased viral load and improved cardiac function. Placebo-controlled trials evaluating the benefit of IVIG use in recent-onset cardiomyopathy showed no benefit over placebo.[530]

Cystic fibrosis. RCTs comparing the benefit of IVIG with that of placebo showed no added benefit with the use of IVIG.[531] Patients with cystic fibrosis and normal immune systems did not benefit from the addition of IVIG to an existing regimen. Between 2% and 10% of patients with cystic fibrosis have hypogammaglobulinemia.[532] Some studies do not suggest any associated additional morbidity due to hypogammaglobulinemia,[532] while some anecdotal reports indicate a benefit of IVIG in cystic fibrosis with hypogammaglobulinemia.[533,534] This question has not been subjected to a randomized trial.

Renal disease. In an uncontrolled study in 6 male patients with IgA nephropathy, high-dose IVIG was associated with stabilization and delayed progression of loss of renal function.[535] A few reports in adults and children have suggested that IVIG may be beneficial in BK virus-associated nephropathy following kidney transplantation.[536] However, at least 1 report has described an increase in BK viral load immediately after IVIG therapy.[537]

Hematologic disorders

Acquired autoimmune coagulation factor inhibitors and acquired von Willebrand syndrome. A recent review considered the role of IVIG in treating acquired autoimmune coagulation factor inhibitors and acquired von Willebrand syndrome.[538] Those investigators concluded that IVIG alone was effective in 30% of cases, while IVIG plus immunosuppressive therapy (corticosteroids, chemotherapy) was effective in about 70%.

Anti–phospholipid antibody syndrome. There are numerous reports supporting a beneficial role of IVIG in anti–phospholipid antibody syndrome (APS).[539,540] Most reports have focused on the use of IVIG in the obstetric complications of APS (typically early fetal miscarriages after implantation into the uterine wall). Overall, studies have demonstrated successful pregnancy outcomes in patients with APS and a history of spontaneous abortion.[541-544] This finding is especially relevant in light of the teratogenic effects of the other forms of available therapies. IVIG also showed benefit in patients with APS undergoing in vitro fertilization.[540] However, a single meta-analysis of data from studies of several modes of therapy (heparin, aspirin, glucocorticosteroids, and IVIG) did not find improved outcomes with IVIG, but did suggest a possible association with increased pregnancy loss or prematurity.[539]

A meta-analysis of data from 6 randomized, placebo-controlled trials found that IVIG was not effective in the treatment of recurrent spontaneous abortion.[545] A few recent small-scale, uncontrolled studies have suggested a benefit of standard or high-dose IVIG. Some argue that when patients are selected for the occurrence of other autoimmune phenomena, the effectiveness of IVIG is demonstrated.[546,547] One study in 24 women with SLE and a history of recurrent abortion found high-dose IVIG to be more effective than corticosteroids and NSAIDs (12 patients each).[548] One recent study in 85 women with APS and recurrent abortion in found that low-dose aspirin and heparin were more effective compared with IVIG.[549] Another study compared anticoagulants alone to treatment with anticoagulants with the addition of IVIG, or the addition of IVIG and a TNF blocker.[550] Anticoagulants alone were found to be inferior to both of the other treatments.

Chronic fatigue syndrome. Chronic fatigue syndrome is a clinically defined disorder that has often been associated with mild immune dysfunction according to specific criteria.[551] There have been numerous anecdotal reports of IVIG use having subjective benefits; however, IVIG is not effective in the treatment of typical chronic fatigue syndrome, as demonstrated in a double-blind, placebo-controlled trial.[552] Chronic fatigue may be associated with specific viral infections, such as parvovirus (erythrovirus) B19. A few reports have suggested that IVIG may be of some benefit in these cases.[381,553]

Neurocognitive disorders

Autism. Autistic children reportedly may have mild abnormalities in their immune system, suggesting immunologic involvement in the pathophysiology of the disease. Elevated immunoglobulin levels[554] and autoimmune antibodies against neural antigens[555] may be found in subsets of these patients. No formal randomized studies have evaluated the use of IVIG in autism. Two reports of open-label trials including a total of 15 autistic children placed on IVIG for 6 months showed no benefit from the infusions.[556,557]

Available evidence does not support the use of IVIG in autism. Autism is now appreciated to have important underlying genetic factors, and great progress has been made in improving the lives of children diagnosed with autism through largely developmental interventions. Three case series revealed inconsistent results.[556-558] Although a few children appeared to improve dramatically after IVIG infusion, such improvement could be part of the natural history of autism or might reflect the effect of intensive psychological and developmental therapies.[475] Furthermore, some children with autism have a *bona fide* antibody deficiency.[559] Autistic children with humoral immune defects should be classified for the

TABLE X. Practical considerations in the use of immunoglobulin therapy

Benefit	Indication	Evidence category	Strength of recommendation
Definitely beneficial	SC therapy can reduce the occurrence of systemic adverse events in selected patients	IIa	B
	Expert monitoring to facilitate management of AEs	IV	D
	Maintenance of IgG trough levels >500 μg/mL in hypogammaglobulinemic patients to reduce infectious consequences.	IIb	B
Probably beneficial	Maintenance of IgG trough >800 μg/mL in hypogammaglobulinemic patients reduces infectious consequences	Ia	A
	Providing home-based IVIG 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 IVIG product for IgA-deficient patients having IgG–anti-IgA antibodies	IV	D
	Product changes may improve AE profiles	IV	D
	Premedication can improve mild AEs	IV	D
	Matching IVIG products to patients to reduce AEs	IV	D
	Stopping or slowing infusion rate to reduce AEs	IV	D
May provide benefit	SC therapy can improve quality of life for patients receiving IVIG intravenously	III	C
	Provision of area under the curve dosing to patients converting from IVIG to SCIG to prevent infection	IIa	B
	Single cessation of immunoglobulin therapy in patients with selective antibody deficiency to reevaluate IgG quantity/quality	III	D
	Use of SCIG in PI patients to prevent "wear off" effect	IV	D
Unlikely to be beneficial	Placement of indwelling catheters or ports for IVIG administration	IV	D
	Protocols for titration to minimally acceptable dose of IVIG or SCIG	IV	D
	Repeated cessations of immunoglobulin therapy in patients with antibody deficiency	IV	D

AE, Adverse event.

abnormality as per the Antibody Deficiency section, and treated in accordance with the recommendations offered in that section.

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection. Group A streptococcal infections lead to exacerbations of obsessive-compulsive and tic disorders in some children.[560] There may be cross-reaction between microbial and brain antigens, although this concept is not yet firmly established. The syndrome of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection is referred to as *PANDAS*. One case-control study showed benefit from plasmapheresis and IVIG therapy (1 dose only).[561] The study showed that IVIG was associated with significantly greater reductions in symptoms compared with those with placebo, and treatment gains were maintained long-term; however, additional studies are needed. At the National Institutes of Health, there is an ongoing trial of IVIG in PANDAS. The immune-based therapies should be used only in cases in which it is clear that the neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professionals.

Summary: Immunoglobulin in miscellaneous disorders

The use of IVIG may provide benefit in the variety of conditions discussed in this section. Importantly, conditions that are life-threatening and rare do not allow for RCTs. Nonetheless, clinical experience and other, less stringent studies lend support to the use of immunoglobulin in some of these conditions. Of mention, guidelines and consensus documents on the use of immunoglobulin, in conjunction with rituximab and other immunosuppressives, in blistering skin diseases have been published. Category IIa evidence supports the use of immunoglobulin in toxic epidermal necrolysis. In 2-10% of patients with cystic fibrosis, antibody deficiency may be a comorbidity; therefore, immune function evaluation may reveal a potential need for treatment. However, this concept has not been fully studied in RCTs. Likewise, immunoglobulin is unlikely to be beneficial in autism, except in the cases of comorbid *bona fide* antibody deficiency. Table IX summarizes the evidence-based recommendations from this section.

PRACTICAL CONSIDERATIONS FOR IMMUNOGLOBULIN REPLACEMENT THERAPY IN ANTIBODY-DEFICIENCY DISEASES

A number of practical considerations in the use of IVIG (Table X) remain central toward facilitating patient therapy and improving the life experience of patients receiving IVIG. The safe and effective use of immunoglobulin requires attention to numerous issues that relate to the both the product and the patient. The administration of immunoglobulin, and the diagnosis and management of adverse events, are complex and demand expert practice. It becomes crucial for the prescribing physician to carefully assess and monitor patients receiving immunoglobulin so that treatment can be optimized. The American Academy of Asthma, Allergy & Immunology, in conjunction with the Primary Immune Deficiency Subcommittee, has formulated 8 guiding principles on the safe, effective, and appropriate use of immunoglobulin therapy in patients with PIs. These guidelines are summarized in Tables XI and XII.[562]

Intravenous immunoglobulin therapy

Products. A number of products currently provide chemically unmodified liquid concentrates of polyclonal IgG (Table XIII).

TABLE XI. Eight guiding principles for effective use of immunoglobulin replacement therapy for patients with PI

Guiding principle issue	Guiding principle rationale
Indication of immunoglobulin therapy	IG is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production; PI is an FDA-approved indication of immunoglobulin, for which all currently available products are licensed.
Diagnoses	A large number of PI diagnoses exist for which IVIG is indicated and recommended; many diagnoses have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.
Frequency of immunoglobulin treatment	Treatment is indicated as ongoing replacement therapy for PI; treatment should not be interrupted once a definitive diagnosis has been established.
Dose	IVIG is indicated for patients with PI at a starting dose of 400-600 mg/kg every 3-4 wk; SCIG is generally used at a starting dose of 100-200 mg/kg/wk; SCIG dosing frequency is flexible (see text discussion); less frequent treatment, or use of lower doses, is not substantiated by clinical data.
IgG trough levels	IgG trough levels can be useful in some diagnoses to guide care but should NOT be a consideration in access to immunoglobulin therapy.
Site of care	The decision to infuse IVIG in a hospital, hospital outpatient, community office, or home based setting must be based on clinical characteristics of the patient.
Route	Route of immunoglobulin administration must be based on patient characteristics; throughout life, certain patients may be more appropriate for IV or SC therapy depending on many factors, and patients should have access to either route as needed.
Product	IVIG/SCIG are not a generic drugs and products are not interchangeable; a specific product needs to be matched to patient characteristics to ensure patient safety; a change of product should occur only with the active participation of the prescribing physician.

Modified from Primary Immunodeficiency Committee, American Academy of Allergy, Asthma & Immunology.[562]

TABLE XII. Guidelines for the site of care for administration of IVIG/SCIG therapy

The decision to infuse IVIG in a hospital inpatient, hospital outpatient, community office, or home-based setting must be based on clinical considerations. Failure to base this decision on patient experience and circumstance, and choose the appropriate site of care could place a patient at risk.
All initial infusions of IVIG should be provided under physician supervision in a facility equipped to handle the most severe of acute medical complications.
Changes of IVIG/SCIG product should be provided under physician supervision in a facility equipped to handle the most severe of acute medical complications.
Certain patients continue to require higher levels of monitoring and intervention during IVIG infusions.
Patients who have tolerated IVIG therapy without a history of adverse events may be considered for lower levels of supervision during infusions.
Given the options for providing IVIG therapy, specific patient experiences mandate or preclude specific sites of care.

Adapted from Primary Immunodeficiency Committee, American Academy of Allergy, Asthma & Immunology.[562]

These products are produced from plasma recovered from a large number of plasmapheresis donors. The number of donors contributing to a pool that will be processed to yield IVIG has been recommended by the FDA (Center for Biologics Evaluation and Research) and Plasma Protein Therapeutics Association: more than 15,000, but not to exceed 60,000, donors. Since 1994, due to the transmission of hepatitis C virus to recipients of IVIG, the FDA and manufacturers have improved steps for reducing pathogen contamination in pools of donor plasma, including donor screening, donor testing for viral pathogens, and pooled plasma testing by sensitive nucleotide testing. As with all blood products, tests are conducted for the presence of hepatitis B surface antigen, HIV-p24 antigen, and antibodies to syphilis, HIV-1, and HIV-2, and hepatitis C. PCR testing, especially for hepatitis B and C, has improved the detection of viral nucleotides in donor plasma to minimize the window period before donors produce specific antibodies. Cold ethanol fractionation, the first step in the process of all commercial immunoglobulin preparations, inactivates HIV. Other steps used for minimizing the transmission of viral pathogens include viral removal by depth filtration and nanofiltration and viral inactivation with low pH, caprylate, pasteurization, and solvent/detergent (see Table XIII for specific viral removal and inactivation steps used for a particular product). Usually, 5-7 steps are employed to reduce the risk for viral transmission to almost zero. The most recent addition of nanofiltration can remove both non–lipid-coated viruses and prions. The plasma is separated using alcohol-based fractionation procedures to precipitate the immunoglobulin-containing fraction and then treated with solvent, detergent, caprylate, acid, or pepsin to inactivate any residual pathogens. Excipients, such as sugars (eg, maltose or D-sorbitol) or amino acids, (eg, glycine and L-proline) are added to prevent aggregation of purified IgG, which can cause adverse reactions. The newer formulations of IVIG and SCIG are iso-osmolar, low-sodium, and low-IgA ready-made aqueous solutions. When giving maltose-containing products to patients who use glucose meters, particular care must be exercised to adjust doses of insulin or other hypoglycemic agents because some meters may falsely report high blood glucose readings due to interference by the maltose. Isohemagglutinins present in IVIG may theoretically contribute to IVIG-associated hemolysis. An additional isoagglutinin-specific immunoaffinity chromatography step was shown to reduce isohemagglutinins by 88-90% in one IVIG preparation, which might help to reduce this risk.[563]

Consideration of dosage. Recommendations on dosages of IVIG in patients with PI have evolved over the past 30 years. The original studies of IVIG compared the intramuscular route with the IV route, leading to package insert recommendations of 200 mg/kg. One study in patients with PIs initially reported improved lung function and decreased infections with IVIG doses that maintained a trough level of >500 mg/dL.[564] In 1999, a retrospective study in patients with XLA showed that trough levels of 500 mg/dL were effective in preventing serious bacterial infection but did not prevent pulmonary disease or enteroviral meningoencephalitis.[14] The investigators suggested more intensive therapy to maintain higher serum IgG trough levels, >700 mg/dL. Other studies have echoed these findings.[565] More recently, a study with 22 years of follow-up in >90 patients with CVID investigated the dose of IVIG needed to keep patients free of infection; the findings demonstrated that trough IgG levels of approximately 750-850 mg/dL improved infection outcomes.[30] In a meta-analysis of data form reported clinical trials of IVIG therapy in patients with PI, a strong correlation was identified between increasing trough IgG serum levels and decreasing pneumonia.[566] Importantly, it has been proposed that the "biological trough level"[567] should be the serum IgG trough level that best improves a patient's clinical course and infection rate. Thus, because the dose of IVIG needed to keep patients free from infection varies between patients, the goal of replacement therapy should be to improve clinical outcomes and not to achieve a specific trough level.

An acceptable starting point for maintenance dosing is 400-600 mg/kg every 3-4 weeks and is consistent with majority practice by focused immunologists in the United States and Europe.[568,569] Trough IgG levels do not need to be measured frequently; annually is often satisfactory. However, physicians should be aware of weight changes in growing children and adjust doses accordingly. They should be obtained whenever a significant infection occurs or when the clinical response to treatment does not meet expectations. After the fifth infusion, a steady state will have been achieved, and the dose or dosing interval should be adjusted to achieve the optimal clinical result. Periodic measurement of trough IgG levels may detect noncompliance by patients who are receiving infusions with home care (or self-administering SCIG at home). The IgG trough increase over baseline IgG level has been shown to significantly correlate with pneumonia susceptibility, with increases of <430 mg/dL being inferior.[570] Because significant variability exists in the pharmacokinetics of IgG between patients, a given IVIG dose has the potential to result in different trough levels in different patients having similar body mass.[571] Treating physicians must be mindful of patients' changing body mass (particularly in children) and/or the possibility of protein-losing conditions, and dose adjustments should be made accordingly. When initiating therapy, patients with extremely low IgG levels at presentation may 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 in agammaglobulinemic patients. However, caution is advised because many patients, especially those with newly diagnosed CVID, have ongoing infection and/or inflammation, resulting in a higher occurrence of adverse reactions when initializing IVIG therapy.[572] Other centers have given half-doses every 2 weeks prior to a full dose to minimize adverse events.

IVIG dosing in patients with normal IgG levels but impaired specific-antibody production remains more challenging, as IgG trough levels are not particularly useful. Several studies comparing different maintenance doses have yielded conflicting results.[573] Most studies, however, have demonstrated that doses ≥400 mg/kg have improved efficacy in reducing the prevalence of infections compared with lower doses.[15,68,565,573-575]

Despite the number of studies comparing different IVIG doses in PI, none have directly compared different dosing intervals. Without additional data, dosing intervals should be selected according to the ability of a given regimen to maintain an acceptable clinical effect, such as keeping the patient infection-free and improving the quality of life. If a patient who is receiving IVIG every 28 days experiences malaise or upper respiratory symptoms during the week prior to the next infusion (ie, "wear-off" effects), the practitioner should consider a more frequent dosing schedule or a switch to the SC route. In this regard, a wide array of dosing regimens are currently employed by focused immunologists in the United States and Europe,[569,576] and dosing decisions should be left to the discretion of the treating physician in order to adequately address each patient's needs.

Adverse reactions. IVIG is a complex therapy and can lead to adverse events.[577] The prevalence of adverse reactions is surprisingly high, as documented in licensing studies described in the information for prescribers that accompanies the products. Similarly, a survey of >1000 patients with PIs conducted by the Immune Deficiency Foundation found that 44% report experiencing adverse reactions, and that this rate was unrelated to rate of infusion.[578] The rates of reactions in clinical practice are higher than observed in clinical studies and highlight the complexity of routine IVIG treatment. Fortunately, most IVIG reactions are rate-related, are mild, and occur in only 5-15% of infusions. They are typically characterized by back or abdominal pain, nausea, breathing difficulties, chills, flushing, rash, anxiety, low-grade fever, arthralgia, myalgias, and/or headache.[572,579] Slowing or stopping the infusion for 15-30 minutes will reverse many reactions. Pretreatment with NSAIDs, acetaminophen (15 mg/kg/dose), diphenhydramine (1 mg/kg/dose), or alternatively a nonsedating antihistamine and/or hydrocortisone (6 mg/kg/dose; maximum, 100 mg) 1 hour before the infusion may prevent adverse reactions. Oral hydration prior to the infusion is often helpful.

Adverse reactions are more likely to occur in patients who have not previously received IVIG and who either have or have recently had a bacterial infection or underlying chronic inflammation. The reactions may be due to complement activity caused by immune complexes that form between infused antibodies and antigens of infectious agents in the patient. Another possible mechanism includes the formation of oligomeric or polymeric IgG complexes that interact with Fc receptors and trigger the release of inflammatory mediators. These rate-related reactions occur less frequently with the newer IVIG products that are liquid formulated and iso-osmolar. The Immune Deficiency Foundation survey found that 34% of reactions occurred during the first infusion of an IVIG product.[578] After 2 or 3 treatments with the same product, however, additional infusion reactions become less likely. Other factors that contribute to adverse reactions include higher concentrations, lyophilized products, and rapid infusion rates. Particular caution is advised when switching IVIG products because significant adverse reactions occur during the process in approximately 15-18% of patients.[580] Reactions to

TABLE XIII. Currently available immunoglobulin products and their properties

Route/product	Dosage formulation	Diluent	Refrigeration required?	Filtration required?	Osmolality (mOsm/L)	Sodium	pH	IgA (μg/mL)	Stabilizer or regulator	Pathogen inactivation/removal*
IV										
Bivigam	10% Liquid	NA	Yes	No	Not Available	0.100-0.140 mol/L	4.0-4.6	≤200	Glycine	FP, S/D, NF
Carimune NF	Lyophilized	0.9% sodium chloride, sterile water, 5% dextrose	No	No	498 (3%), 690 (6%), 882 (9%), 1074 (12%)	0.01 mEq/mL (3%), 0.02 (6%), 0.03 (9%), 0.041 (12%)	6.6	720	Sucrose	DF, pH 4, pH 4/pepsin, NF
					192 (3%), 384 (6%), 576 (9%), 768 (12%)	None				
					444 (3%), 636 (6%), 828 (9%), 1020 (12%)	None				
Flebogamma DIF 5%	5% Liquid	NA	No†	Optional	240-370	Trace	5-6	<50	D-sorbitol	Past, S/D, NF, FP, PEG, pH 4
Flebogamma DIF 10%	10% Liquid	NA	No†	—	240-370	Trace	—	<100	D-sorbitol	—
Gammagard 5% S/D	Lyophilized	Sterile water	No	Yes	636	8.5 mg/mL NaCl	6.8	<1	2% Glucose and glycine	CEF, pH 4.2, DF, CAP, CHROM
Gammaplex	5% Liquid	NA	No	15-20 micron filter preferred	420-500	30-50 mmol/L	4.8-5	<10	Sorbitol and glycine and polysorbate 80	S/D, VF, low pH
Octagam 5%	5% Liquid	NA	No†	No	310-380	0.03 mEq/ml	5.1-6.0	<100	Maltose	CEF, S/D, pH 4, UF, CHROM
Octagam 10%	10% Liquid	NA	No†	No	310-380	<30mmol/L	4.5-5.0	106 μg/mL	Maltose	CEF, S/D, pH 4, UF, CHROM
Privigen	10% Liquid	NA	No	No	240-440	Trace	4.6-5	<25	L-proline	pH4, NF, DF
IV or SC										
Gammagard liquid	10% Liquid	NA	No	No	240-300	None added	4.6-5.1	37	Glycine	S/D, low pH, NF
Gammaked	10% Liquid	NA, incompatible with saline	No‡	No	258	None added	4-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM
Gamunex-C	10% Liquid	NA, incompatible with saline	No‡	No	258	None added	4-4.5	46	Glycine	CEF, pH 4.2, DF, CAP, CHROM
SC										
Cuvitru	20% Solution	NA	No§	No	208-290	None	4.6-5.1	80	Glycine	CEF, CHROM, NF, SD
Hizentra	20% Liquid	NA	No	No	380	Trace, <10 mmol/L	4.6-5.2	≤50	Proline	pH 4, DF, VF, OAF
Hyqvia	10% Liquid + hyaluronidase	NA	No	No	240-300	None added	4.6-5.1	37	Glycine	S/D, low pH, NF

(Continued)

TABLE XIII. *(Continued)*

Route/product	Dosage formulation	Diluent	Refrigeration required?	Filtration required?	Osmolality (mOsm/L)	Sodium	pH	IgA (μg/mL)	Stabilizer or regulator	Pathogen inactivation/removal*
Intramuscular										
Gammastan	15-18% Liquid	NA	2-8°C	No	Not available	0.4-0.5%	6.4-7.2	Not measured	Glycine	CEF, S/D, UF

For the specifics of each indication, the please see the text and the manufacturer's product information.
CAP, Caprylate; *CEF*, cold ethanol fractionation; *CHROM*, chromatography; *DIF*, dual inactivation and filtration; *DF*, depth filtration; *FP*, fraction precipitation; *HIV*, pediatric HIV infection; *NA*, not applicable; *Nano, NF*, nanofiltration; *OAF*, octanoic acid fractionation; *Past*, Pasteurization; *PEG*, PEG precipitation; *S/D*, solvent detergent; *UF*, ultrafiltration; *VF*, virus filtration.
*Pathogen inactivation/removal using CEF, DF, UF, CAP, CHROM, Nano, double sequential nanofiltration, VF, S/D, Past, PEG, FP, or OAF.
†Not required (+2-25°C).
‡Storage is 2-8°C for 36 m or 25° for 6 m.
§Storage is 2-8°C × 36 m or room temp 25° × 12 m.

TABLE XIV. Adverse events with IVIG administration

Frequency	Adverse event
Common‡	Headache; myalgia, back pain, arthralgia; chills; malaise, fatigue, anxiety; fever; rash, flushing; nausea, vomiting; tingling, infusion site pain/swelling, erythema; hypo- or hypertension, tachycardia; fluid overload
Uncommon (multiple reports)	Chest pain or tightness; dyspnea; severe headaches; aseptic meningitis; pruritis. urticaria; thromboembolic*; (cerebral ischemia, strokes; myocardial infarction; deep vein thrombosis; pulmonary emboli; renal toxicity†); hemolytic reactions due to isoagglutinins to Rh or other blood groups; anaphylactic/anaphylactoid reactions
Rare (isolated reports)	Anaphylaxis due to IgE or IgG antibodies to IgA in the immunoglobulin product; progressive neurodegeneration; arthritis; cardiac rhythm abnormalities; transfusion-related acute lung injury (granulocyte antibody mediated); neutropenia; pseudohyponatremia; uveitis; noninfectious hepatitis; hypothermia; lymphocytic pleural effusion; skin (leukocytoclastic vasculitis of the skin, erythema multiforme, urticaria, dyshidrotic eczema, maculopapular or eczematoid rashes, alopecia)

*Related to the procoagulant activity in the IVIG, eg, Factor XIa as well as hyperosmolality.
†Majority due to sucrose containing IVIG products, osmotic nephrosis with injury to proximal renal tubules.
‡Infusion rate related and/or higher doses, eg, 2 g/kg.

IVIG remain unpredictable: The Immune Deficiency Foundation survey identified 23% of patients who experienced a reaction to products that they had previously received without issue.[578] Thus, vigilance needs to be maintained for detecting and managing reactions irrespective of an individual patient's personal experience with IVIG.

IVIG can be administered in IgA-deficient patients. An important study reported true anaphylaxis in patients with selective IgA deficiency and CVID who developed IgE antibodies to IgA after treatment with immunoglobulin.[49] However, this adverse event appears to occur much less frequently than originally believed. Patients with CVID can develop IgG antibodies (10-22% in various studies) to IgA, but no correlation has been found between the presence of these antibodies and adverse reactions.[581] Patients with anti-IGA antibodies who have had reactions to IVIG have tolerated SCIG.[54,55]

Unfortunately, a number of IVIG reactions have been reported that include more serious adverse events and that have occurred during or soon after infusion. They have been reviewed elsewhere[577,582-586] and are shown in Table XIV. Expert monitoring of patients receiving an IVIG infusion is therefore necessary. Prompt diagnosis and treatment of these events are required to ensure patient safety. Some of the more serious adverse events associated with the administration of IVIG include acute renal failure, neurodegeneration, and thromboembolic events. Acute renal failure is more commonly observed in patients receiving IVIG products that contain sucrose as a stabilizing agent. Many of the newer products have eliminated sugars as stabilizing agents and have substituted amino acids to eliminate this potential risk for renal compromise. An association with neurodegeneration has been reported; however, a mechanism is currently unknown. Some of the most significant adverse complications of IVIG administration are thromboembolic events, such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism. These adverse events are quite rare, but are more likely to occur in patients with autoimmune disease receiving larger doses of IVIG, but have been reported in patients with PIs.[587] Risk factors for these reactions include preexisting cardiovascular disease, diabetes mellitus, dehydration, age >65 years, sepsis, paraproteinemia, increased blood viscosity, hypercholesterolemia, and hypertension. A recent FDA meeting implicated the presence of procoagulant factors (eg, Factor XIa in some IVIG products) that may have been involved in the thromboembolic events.[588] By agreement between the FDA and manufacturers, steps to correct this issue were incorporated into the manufacturing process to eliminate these procoagulant factors.

The placement and use of indwelling venous catheters for IVIG administration should be carefully weighed against the thrombotic and infectious risks inherent in these devices that may be further amplified in immunodeficient or autoimmune patients or by administration of IVIG itself. As these devices have the potential to cause additional adverse events, their use for the sole purpose of providing IVIG is discouraged.[35]

Subcutaneous immunoglobulin therapy

Products. The SC route of immunoglobulin administration has been explored since as early as the 1940s.[589] In fact, the first immunoglobulin infusions used for the treatment of a PI disease were given subcutaneously by Bruton[590] in a patient with XLA.

Intramuscular application of immunoglobulin replaced SCIG in popularity, which was in turn replaced by IVIG. However, in the 1980s, SCIG began to be reconsidered as an alternative approach to intramuscular immunoglobulin and IVIG.[591-594] The use of SCIG was initially more widely adopted in Europe[595]; FDA-licensing studies were eventually performed, and several SCIG products (Table XIII) have recently been FDA-approved for use in the United States. These products include a 16% preparation,[596] a 20% formulation,[597,598] and two 10% products that had previously been approved only for IV use.[599,600] The 16% preparation was discontinued by the manufacturer in 2011. Recently, a new formulation for the administration of SCIG was approved by the FDA, using recombinant human hyaluronidase to facilitate the SC administration of large volumes of immunoglobulin on a monthly basis. Although designed for giving the total monthly dose of immunoglobulin at one SC site, this facilitated SCIG approach allows for flexible SCIG dosing by varying the number of sites and the period between infusions.[601]

Adverse reactions. The safety profile of SCIG has been extensively reviewed. SCIG is well tolerated when used in both children and adults, including pregnant women and the elderly population.[592,595,596,602-616] While FDA-approved labeling information carries specific warnings, published clinical evidence demonstrates that SCIG is also well tolerated in patients who have IGA deficiency.[53,55,603,617] Providers should be aware that systemic adverse reactions have been reported in patients receiving SCIG therapy: While most reactions have been mild,[55,595,598,603,618] severe reactions rarely occur. Patients who have had severe systemic adverse reactions to IVIG may have particularly greater risk for severe reactions to SCIG, although severe reactions to SCIG in these patients also generally tend to be milder.[55]

The most common adverse reaction to SCIG is a localized infusion site reaction (ISR).[55,595,596,619] ISRs affect the majority of patients receiving SCIG and range from mild to severe. Severe ISRs, however, rarely occur. Interestingly, the prevalence and severity of ISRs decrease with repeated infusions.[595,603,619,620] These reactions may be further minimized by carefully cleaning the skin prior to each infusion and ensuring that the length of the infusion needle or catheter is appropriate for reaching the SC compartment.[595,621] Accidental IV administration of the 10% products is not likely to cause acute harm, as these preparations either have been approved for IV use or are similar in composition to an existing IV product. The 20% SC formulation is not intended for IV use.[564,622-624] Unlike IVIG, premedication for SCIG is generally not required,[595,621] although in children local anesthetic creams can be considered.[613,625] In general, SCIG self-administered at home is well tolerated after a patient demonstrates adequate comfort and competence with the delivery techniques.[593,609,614,626-628] For at-home administration, patients should have access to containers for biological waste and sharp-object disposal.[627] Provision of an epinephrine autoinjector may be left to the provider's preference or discretion but should be considered in patients who have had prior anaphylaxis or allergic reactions to IVIG.[55,598,613]

Dosing subcutaneous immunoglobulin. As in IVIG therapy, SCIG administration should be individualized for each patient. SCIG is usually given at a starting dose of 100-200 mg/kg of body weight each week.[12] In patients already receiving IVIG, the total monthly dose of IVIG is multiplied by a conversion factor (1.37 for the 16% preparations; 1.53 for the 20% formulation) before dividing by the number of SCIG infusions to be given each month.[600] This conversion factor is meant to supply the patient with the same tissue levels of IgG from SCIG as would have been received from IVIG over the course of an IgG half-life. In clinical trials in the United States, as mandated by the FDA, pharmacokinetic parameters using the area under the serum concentration–time curve were used for determining the bioavailability of the immunoglobulin administered subcutaneously compared to intravenously.[600] This dose adjustment has not been standard in Europe or in other reported experiences with SCIG.[595,603,607,618,620] In fact, a general lack of correlation between dosing regimens and pharmacokinetic parameters has been noted, in part due to wide individual variations in pharmacokinetics.[622] The subtleties comparing the use and nonuse of the conversion factor are beginning to be specifically evaluated.[629] Infection-related and other patient-oriented outcomes may be improved when using the higher area under the curve–based dosing,[622,630] although direct comparisons between adjusted and unadjusted SCIG doses still require testing in randomized clinical trials.[622] A statistical analysis of all reported trials to date, however, was able to correlate IgG level with the prevalence of infection.[566] Doses may need to be further adjusted in patients with a very low or very high body mass index (BMI; >30 kg/m^2).[622] Studies of 16% and 20% SCIG formulations have suggested that subjects with a high BMI might require higher dose adjustments when switching from IVIG to SCIG. While a combined analysis of the data revealed a significant correlation between BMI and the required dose adjustment, when the highest BMI and the lowest BMI were excluded, the relationship between dose adjustment and BMI was no longer significant. The investigators ultimately recommended dosage based on measured serum IgG levels and the clinical response instead of mean pharmacokinetic parameters.[622] In a retrospective analysis of data from patients from a center where the immunoglobulin dose was capped at 80 g/month, an almost identical relationship was found between SCIG dose and serum IgG level between patients with high and low BMI when transitioned 1:1 from IVIG to SCIG.[631] A consistent bioavailability among high- and low-BMI categories was supported by similar dose–immunoglobulin response curves in obese and nonobese patients using SCIG.[631] Other publications support the use of ideal body weight in calculating SCIG dose in obese patients.[632,633]

Protocols for implementing SCIG therapy will vary according to patients' needs. Greater flexibility now exists in the frequency of SCIG dosing, with products available that are FDA approved for daily to weekly,[622] biweekly,[634,635] or monthly[636,637] dosing. Monthly SCIG dosing is achieved with the addition of hyaluronidase, a spreading factor that allows for higher volumes to be administered and absorbed subcutaneously.[637] Additionally, some patients may benefit from receiving smaller doses several times a week due to personal preference or improved tolerance.[607,621,634,635,638] Infusion rates generally range from 10 to 35 mL/h/site by pump, with volumes of 15-40 mL/site.[603,639] Lower volumes and rates may be used with the 20% SCIG formulation, and it is generally recommended to follow the manufacturer's guideline on each product before adjusting as tolerated. Typical sites of infusion include the abdomen, outer thigh, upper arm, and buttock. The number of sites will depend on the number needed to provide the total volume for the calculated target dose. Rapid-push protocols (that are manual and do not require infusion pumps) have been used with reported success but require further

testing in larger-scale clinical trials.[614,638] Steady-state serum IgG levels should be monitored periodically after approximately 3 months, as the half-life of SCIG can vary significantly (ranging from 18 to 46 days).[614,635,640] Absorption can be particularly erratic in the first 24 hours.[640] The serum IgG levels can be used for monitoring patient adherence.[627] Total serum IgG levels alone, however, may not serve as the most appropriate parameter for determining optimal SCIG dosing in all patients, as the half-life of specific antibodies in SCIG that may be required for a given patient can be significantly less than the half-life of the total IgG as a whole.[599,618,635]

Treatment considerations for route of administration. In terms of efficacy, a large number of studies support equivalence between SCIG and IVIG therapy for managing PI diseases, and noninferiority has been a standard prerequisite of FDA approval.[12,595,599,603,605,607,619,641,642] Patients who maintain low trough levels of serum IgG levels while receiving IVIG infusions may especially benefit from conversion to SCIG therapy through the ability to achieve higher mean serum IgG levels with lower immunoglobulin doses.[643] It should be noted, however, that outcome measures in patients receiving reduced doses of SCIG compared with IVIG are not available, with the exception of hospitalization, which was 30% higher in those receiving the reduced dose. Thus, dosage reductions in general should be approached with great caution, and there is no prescribed or proven protocol for a step-down approach to find the minimal dose of immunoglobulin replacement therapy required for keeping a patient infection-free.

Although most studies of SCIG have employed a design in which subjects were given IVIG therapy before being switched to SCIG, SCIG therapy is expected to be equally effective without the prior administration of IVIG.[614,621] Nonetheless, specialized regimens targeted toward more rapidly increasing serum IgG levels may be appropriate. It is important to note that SCIG studies have not been powered to demonstrate differences in infection rates[639] between SCIG and IVIG therapy and that long-term data comparing SCIG to IVIG, especially in the prevention of sinopulmonary infections, are lacking.[603] Three crossover studies have been reported using a 1.00 conversion factor from IV to SC therapy; none included subject numbers substantive enough to enable a formal analysis.[605,618,629] Patients who are switched from IVIG to SCIG may thus continue to develop infections of the sinopulmonary tract and may require treatment with an antibiotic.[595,619] It also remains possible that susceptibility to these infections may improve if higher serum IgG levels are achieved, particularly utilizing the correction factor for bioequivalence with area under the curve–based dosing for SC administration.[630,644] For example, in a recent analysis that reviewed data from 7 studies of 4 different SCIG preparations,[644] steady-state serum IgG levels correlated inversely with the annualized rate of nonserious bacterial infections. A more extensive study comparing data from 10 SCIG prospective clinical trials reported that serum IgG levels (not necessarily SCIG dosages) correlated inversely with the annualized infection rate.[566] These reports argue that recommendations and practices of some managed care organizations and third-party payers that define "adequate" treatment using only minimal or suboptimal IgG levels can potentially harm patients. Instead, treatment regimens should be individualized for each patient.[567,645] As mentioned earlier, none of these studies have documented procedures of reducing dosages, and this is a practice on which there is no currently available guidance and that can potentially put patients at risk for harm.

Several other factors should be considered when deciding whether to place a patient on SCIG versus IVIG therapy. First, numerous studies have demonstrated an enhanced quality of life in patients receiving SCIG compared with IVIG therapy as an advantage of the SC route of administration.[603,607,612,614,620,627,628,639,642,646-649] These studies have shown that increased quality of life comes mostly from a patient's freedom to administer SCIG at home and at their convenience. This benefit results in greater patient satisfaction and fewer missed days of work or school for infusion-clinic appointments.[620] In addition, because patients have steady-state serum IgG levels with SCIG, they experience minimal withdrawal effects, such as malaise or symptoms of infection, in the week prior to the next IVIG infusion.[603,612] Second, the benefit of SCIG over IVIG in cost-savings is emerging. Several analyses from Europe and Canada have suggested that SCIG therapy results in significant reductions in health care resource utilization and expenditures compared with IVIG.[603,614,620,621,650] Further studies are needed to determine whether these models apply (especially issues of dose equivalence) to clinical practice in the United States. Any economic benefits of SCIG are known to differ by country.[639,647,651] Third, other potential advantages of SCIG therapy over IVIG include the lack of known reports of renal impairment with SCIG use, and the eliminated need for an indwelling venous catheter, especially in patients with poor IV access, such as infants or elderly patients.[12,621,625] Finally, SCIG therapy may not be optimal in all patients. Providers must be able to offer adequate education, training, and support for patients.[613,627,639] Patients, especially children, may object to the multiple and more frequent needlesticks with SCIG therapy compared with the single monthly needle stick required for IVIG, and some may need to be switched back to IVIG from SCIG if repeated technical difficulties or challenges are encountered.[12,625,646] Some patients clearly prefer IVIG to SCIG administration,[603] and adolescents in particular are more likely than are other age groups to revert to IVIG therapy to decrease the infusion frequency.[627] In addition, SCIG therapy may not be optimal in patients who require frequent provider encounters or who have poor adherence to treatment.[12]

SCIG summary. At the time of the preparation of this article, SCIG therapy was FDA-approved for use in the treatment of PI diseases only. With the overall success of SCIG therapy, additional formulations, indications, and improvements may be expected over time. For example, recent FDA approval of a 10% formulation of SCIG with the addition of a human recombinant hyaluronidase step allows for the infusion of monthly volumes of SCIG.[603,614,636] The administration of hyaluronidase with SCIG was shown to improve the bioavailability of SCIG, resulting in decreased infusion times and frequencies. This process results in pharmacodynamics more similar to those observed after standard IVIG infusions than seen following the administration of current SCIG preparations.[637,652] Dosing options have also been broadened for the 20% SCIG formulation such that appropriately titrated doses can be well tolerated and effectively delivered daily to weekly to every 2 weeks.[622,634,635,653,654] In addition, SCIG has been used in a limited number of other autoimmune, inflammatory, and neuromuscular conditions.[5-7,422,423,516,603,614,655-658] In the absence of data from large-scale clinical trials, more widespread use of SCIG in these

nonlicensed conditions cannot be recommended at this time. It should be noted that while anecdotal reports of the utility of SCIG as off-label immediate therapy in certain autoimmune conditions have been encouraging, the long-term effects of SCIG therapy on modulating the frequency and severity of autoimmune comorbidities in patients with PI diseases remain unknown compared with the outcomes of standard IVIG therapy, and thus warrant further evaluation. Nonetheless, SCIG remains a valuable alternative to IVIG in the treatment of antibody deficiency in the context of PIs.

CONCLUSION

Immunoglobulin therapy is essential for a broad array of diagnoses and can be clinically useful in many others. As immunoglobulin has diverse therapeutic mechanisms of action, the list of indications in which it is useful is likely to grow. Given the limited nature of this therapeutic agent, careful consideration of particular clinical indications is of the essence. Our recommendations do not relate to the severity of these particular diseases or to the potential for alternative therapies to be effective. Immunoglobulin therapy should be applied where it is most supported by evidence and where it will provide the greatest clinical benefit. The evidence considered in this document, as well as the recommendations based therein, should be viewed as currently relevant but likely to change given ongoing research and cumulative experience.

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