

# Adverse Effects of IgG Therapy

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**IgG is widely used for patients with immune deficiencies and in a broad range of autoimmune and inflammatory disorders. Up to 40% of intravenous infusions of IgG may be associated with adverse effects (AEs), which are mostly uncomfortable or unpleasant but often are not serious. The most common infusion-related AE is headache. More serious reactions, including true anaphylaxis and anaphylactoid reactions, occur less frequently. Most reactions are related to the rate of infusion and can be prevented or treated just by slowing the infusion rate. Medications such as nonsteroidal anti-inflammatory drugs, antihistamines, or corticosteroids also may be helpful in preventing or treating these common AEs. IgA deficiency with the potential of IgG or IgE antibodies against IgA increases the risk of some AEs but should not be viewed as a contraindication if IgG therapy is needed. Potentially serious AEs include renal dysfunction and/or failure, thromboembolic events, and acute hemolysis. These events usually are multifactorial, related to combinations of constituents in the IgG product as well as risk factors for the recipient. Awareness of these factors should allow minimization of the risks and consequences of these AEs. Subcutaneous IgG is absorbed more slowly into the circulation and has a lower incidence of AEs, but awareness and diligence are necessary whenever IgG is administered. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2013;1:558-66)**

IgG has come into wide use, not only for replacement therapy in patients with immune deficiency but also for a broad range of patients with autoimmune and inflammatory diseases.<sup>1</sup> The allergist-immunologist is frequently called upon not only to manage primary immune deficiency diseases (PID) but also as a consultant for other specialists who may be unfamiliar with IgG and when there are adverse reactions to IgG therapy. IgG is purified from large pools of normal plasma and is treated to remove and inactivate possible bloodborne pathogens. All currently marketed products are believed to be safe.<sup>2</sup> However, because IgG preparations contain antibodies against a number of common pathogens and immunizing agents, it should be

remembered that patients who receive IgG therapy may test positive for antibodies against infectious agents to which they have not actually been exposed. Patients should be informed that IgG is a blood product and should give signed consent before receiving IgG. The consent form used in the practitioner's institution or local hospital for other blood products is usually satisfactory for IgG products as well. Careful screening and routine follow-up of patients before beginning and while receiving IgG therapy, including the use of nucleic acid amplification tests or PCR when necessary, should clarify whether chronic infections may be present. IgG infusions may be associated with a wide variety of possible adverse events (AE). Nevertheless, recognition of risk factors, appropriate selection and adjustment of IgG treatment regimens, and the use of adjunctive therapies should allow safe use of IgG in virtually any situation.

## ACUTE SYSTEMIC AEs COMMONLY ACCOMPANYING OR IMMEDIATELY AFTER IgG INFUSIONS

Up to 40% of intravenous Ig (IVIG) infusions may be accompanied or followed within 72 hours by AEs.<sup>3-6</sup> These are mostly uncomfortable or unpleasant, but they are not often serious. Symptoms may include headache, nausea, musculoskeletal pain, flushing, and tachycardia. In most cases, these can be easily managed by slowing or temporarily stopping the infusion until the symptoms subside. These symptoms can often be relieved by acetaminophen, nonsteroidal anti-inflammatory drugs (NSAID), and/or antihistamines. Some patients may require corticosteroids; and many patients are given NSAIDs or corticosteroids prophylactically. Most of these kinds of AEs are related to the rate of infusion and can be avoided by beginning the infusion slowly (0.01 mL/kg/min of 10% IgG solution [1 mg/kg/min IgG]) and gradually increasing the rate stepwise, as tolerated. In general, infusion rates should not exceed 0.08 mL/kg/min of 10% IgG solution (8 mg/kg/min IgG). Patients who are naive to IgG replacement, have had interruptions in their therapy, or who are actively or chronically infected have an increased risk of infusion-related AEs. This may be related, in part, to formation of antigen-antibody complexes as the IgG is being given or to the rapid release of lipopolysaccharide or other components of pathogens already present in the recipient. The risk of these reactions may be reduced by making certain that patients are afebrile and that active infections are being treated with antibiotics before beginning IVIG therapy or giving any scheduled infusion. Fractionating the total IgG dose into aliquots given over several days may also be useful in decreasing AEs in this situation. The incidence of reactions often increases when patients already on therapy are given a different brand of IVIG.<sup>4,7</sup> For example, in one licensing study of a new IVIG product in patients with PID who had been on stable treatment with other products

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#### Abbreviations used

AE- Adverse event  
FDA- US Food and Drug Administration  
IV- Intravenous  
IVIG- Intravenous immunoglobulin (human)  
NSAID- Nonsteroidal anti-inflammatory drug  
PIDD- Primary immune deficiency disease  
SC- Subcutaneous  
SCIG- Subcutaneous IgG  
TEE- Thromboembolic event

before being switched, 20% of subjects had AEs during or within 72 hours of their first infusion of the test product, 16% after the second, 6% after the third, and only 2% after the fourth infusion.<sup>7</sup> IVIG products are not the same, and brands should not be substituted for each other without informing the physician, so that slow rates of administration and premedication (if necessary) may be used.<sup>8</sup> A similarly high rate of AEs, which then decreases with continued therapy, is often noted when naive patients receive IVIG for the first time. Some studies of subcutaneous IgG (SCIG) therapy have also reported a high incidence of local reactions initially, which then decreased with continued therapy.<sup>9</sup> The reasons for initially high rates of reactivity and the decrease with subsequent doses of the same product are not known. Complement activation due to dimers and larger aggregates in the IgG solutions was believed to account for problematic reactions in early attempts at IV administration of IgG.<sup>10</sup> To reduce dimer formation and preserve the native conformation of IgG in concentrated solutions, all currently marketed IVIG products contain stabilizers, such as glycine, proline, or sugars (Table 1). These rarely cause problems, but maltose may cause false readings with certain glucose meters, sucrose may contribute to renal toxicity, and proline should be avoided in the extremely rare patients with hyperprolinemia.<sup>11,12</sup>

When severe, infusion reactions may resemble anaphylaxis but usually do not involve IgE and, therefore, have been termed “anaphylactoid.”<sup>3-6</sup> A key difference between these anaphylactoid reactions that accompany IVIG infusions and true IgE-mediated anaphylaxis is that the former are usually associated with hypertension, whereas hypotension is uncommon. Furthermore, with repeated administration of the same IVIG preparation, these reactions often decrease in severity, rather than increasing as would be expected with reexposure to an antigen that induced IgE. It is not clear whether these “anaphylactoid” reactions involve mast cell activation. They may primarily involve activation of the kallikrein-kinin system by active enzymes in IgG preparations, activation of complement, induction of cytokines, or production of lipid mediators. As expected, because reactions in different patients and with different products are heterogeneous, skin testing has not been found helpful in predicting reactivity.

A study of small cohorts of patients with common variable immune deficiency suggested that the presence of a novel splice variant of the type IIa Fc $\gamma$  receptor, which increases its proinflammatory signaling, is associated with an increased risk of recurrent anaphylactoid reactions to IVIG in patients with common variable immune deficiency and with IgG antibodies against IgA.<sup>13</sup> The roles of this receptor variant and the IgG anti-IgA antibodies remain to be clarified, and additional studies in larger cohorts of patients are necessary to determine the importance of this mutation.

## Headache, migraine, and aseptic meningitis

Headache is a common AE of IVIG in both adults and children, and is the most commonly reported AE in most licensing studies of new IVIG products.<sup>3-6</sup> In a prospective study of 58 children (median age, 4 years) that evaluated AEs after 345 IVIG infusions, headache was the most common AE, which accounted for 8 of 10 school days missed after infusions.<sup>14</sup> Symptoms began during administration (5% of patients) or just after completion of the infusion (24%) but were sometimes delayed by 24 to 48 hours. Most headaches resolved within 24 hours, but severe headaches that lasted as long as 72 hours have been reported. A small number of patients, particularly those with a history of migraine, may develop more serious headaches, which may be accompanied by photophobia, nausea and vomiting, or other symptoms of migraine.<sup>14-18</sup> These headaches typically begin after the infusion is complete and may be delayed in onset by 24 to 48 hours. Signs of meningismus, including nuchal rigidity, may also be present, which suggests that there is a continuum of symptoms, which extend to include aseptic meningitis with pleocytosis. In rare cases, these headaches may be accompanied by high fevers.

Severe, prolonged headaches are more frequent in patients who receive high doses of IVIG (eg, 1-2 g/kg) for autoimmune diseases.<sup>15-18</sup> In 1 study of patients who received 2 g/kg of IVIG for neuromuscular diseases, 11% developed severe headache accompanied by other signs that suggested aseptic meningitis, an unusually high rate compared with studies in patients with PIDD.<sup>16</sup> Five of these patients had lumbar punctures within 48 hours. Cerebrospinal fluid IgG was elevated in all affected patients, and 4 had pleocytosis with a predominance of neutrophils.<sup>16</sup> This report suggests that some of the severe headaches may be due to meningeal irritation, inflammation caused by the IgG itself, or, more likely, by immune complexes formed between therapeutic and endogenous IgG in the cerebrospinal fluid. The duration of these headaches and delays in onset may be due to the time necessary for IgG to cross the blood-brain barrier. In many patients, headaches diminish after the first few infusions, although some develop a recurrent pattern of symptoms that occur at seemingly reproducible intervals after each infusion.

## Prevention and treatment of infusion-related headaches

Mild headaches during IVIG infusions can be prevented or relieved by treatment with aspirin, acetaminophen (preferred in children), or other NSAIDs. The use of slow infusion rates may also help prevent recurrent headaches. Post-IVIG migraine-like headaches have been successfully treated with 5-hydroxytryptamine receptor antagonists.<sup>17</sup> Patients may also be premedicated with cyproheptadine (an antihistamine and serotonin receptor antagonist) (2-4 mg for children or 4-12 mg for adults) or another type of antimigraine preparation, which can then be repeated at the first sign of symptoms. Severe postinfusion headaches may be prevented or ameliorated by treatment with prophylactic glucocorticoids (0.5-1 mg/kg prednisone or equivalent in children or 30-60 mg prednisone or methyl prednisolone in adults), alone or in combination with an NSAID or other antimigraine preparation. In some cases, one or more of these medications may be required for as long as 72 hours after the infusion is completed. However, glucocorticoids do not appear to be useful in treating aseptic meningitis induced by IVIG.<sup>18</sup>

**TABLE I.** IgG content, IgA content, and stabilizers in IgG products

| Product                 | IgG concentration (%) | Route of administration | Stabilizer           | IgA content (μg/mL) |
|-------------------------|-----------------------|-------------------------|----------------------|---------------------|
| Bivigam                 | 10                    | IV                      | Glycine 0.25 mol/L   | ≤200                |
| Carimune NF             | 3, 6 or 12*           | IV                      | Sucrose 1.67 g/g IgG | 1000-2000           |
| Flebogamma DIF          | 5                     | IV                      | Sorbitol 50 mg/mL    | <6                  |
| Gammagard liquid        | 10%                   | IV, SC                  | Glycine 0.25 mol/L   | 37                  |
| Gammagard S/D           | 5 or 10†              | IV                      | Glucose 20 mg/mL‡    | ≤2.2                |
| Gammagard S/D (low IgA) | 5 or 10†              | IV                      | Glucose 20 mg/mL‡    | ≤1                  |
| Gammaked                | 10                    | IV, SC                  | Glycine 0.2 mol/L    | 46                  |
| Gammaplex               | 5                     | IV                      | Sorbitol 50 mg/mL    | <10                 |
| Gamunex-C               | 10                    | IV, SC                  | Glycine 0.2 mol/L    | 46                  |
| Hizentra                | 20                    | SC                      | Proline 250 mmol/L   | <50                 |
| Octagam                 | 5                     | IV                      | Maltose 100 mg/mL    | ≤200                |
| Privigen                | 10                    | IV                      | Proline 250 mmol/L   | ≤25                 |

SC, Subcutaneous.

Note. Company information: Bivigam, Biotest Pharmaceuticals, Boca Raton, Fla; Gammaked, Kedrion Biopharma, Fort Lee, NJ; Hizentra, CSL Behring, King of Prussia, Pa.

\*Supplied as lyophilized powder; can be reconstituted to 3%, 6%, or 12 % IgG.

†Supplied as lyophilized powder; can be reconstituted to 5% or 10% IgG.

‡When prepared as a 5% IgG solution, would contain 20 mg/mL glucose, 22.5 mg/mL glycine, 2 mg/mL polyethylene glycol, and 3 mg/mL albumin.

### Decreased rate of systemic AEs after SCIG

One approach to the problem of headaches associated with IVIG infusions is to fractionate the usual monthly dose into smaller doses given weekly or even more frequently, which can be facilitated by administering SCIG. Systemic AEs due to SCIG are infrequent. In a 2004 review that summarized data from several studies that together included more than 40,000 SCIG infusions in 232 patients with PIDD, the overall incidence of systemic AEs was only 0.43%.<sup>19</sup> None of the recent licensing studies of SCIG products currently marketed in the United States reported an incidence of infusion-related systemic AEs higher than 5%.<sup>20-22</sup> This may be due to use of frequent (ie, weekly) small doses of IgG with SCIG, which minimizes the large shifts in the serum IgG levels seen after versus before IVIG boluses, and to the relatively slow systemic absorption of IgG from the subcutaneous infusion sites.

### SERIOUS INFUSION-RELATED AEs, “BLACK BOX” WARNINGS, AND PRECAUTIONS

In contrast to the typical infusion-related reactions, more serious types of AEs have led to the requirements (in the United States) that the labels of all IVIG products contain a “Black Box” warning about acute renal dysfunction and/or failure and thromboembolic events (TEE).<sup>23,24</sup> The US Food and Drug Administration (FDA) also requires prescribing information for all IgG products to include “Warnings and Precautions”<sup>25</sup> about the risks of aseptic meningitis syndrome, acute hemolysis and hemolytic anemia, and transfusion-associated acute lung injury. In addition, IgA deficiency is considered a risk factor for severe hypersensitivity and true anaphylactic reactions.

### Thromboembolic events

Determining the true rates of IgG-related TEEs and definitively establishing causality is difficult. Arterial as well as venous events have been reported, including acute coronary syndrome, myocardial infarctions, transient cerebral ischemia attacks, and stroke as well as deep vein thrombosis and pulmonary emboli.<sup>26-38</sup> Local thrombosis can occur at the site of an IVIG infusion and can extend from the extremity to larger veins.<sup>27</sup>

The FDA relies on spontaneous reports through its Adverse Event Reporting System (AERS)/Medwatch, and manufacturers’ pharmacovigilance efforts rely on voluntary efforts of patients and providers.<sup>31-33</sup> In addition, the FDA has reviewed large health-claims-related (payor) databases for claims that suggest thrombotic or embolic events that occurred within 24 hours after IgG infusions.<sup>31,32</sup> The epidemiologic challenges are illustrated by reviewing the rates of TEEs associated with one particular IVIG product. Before 2008, there were approximately 0.6 reports of TEE for every 1 million grams of the product sold, this rose to 1.92 cases per million grams in 2008-2009, and 5.5 cases per million grams in 2010, when the product was withdrawn from the market to be reformulated.<sup>34,35</sup> If one assumes 50 g as a median adult dose, then this would represent roughly 1 case in 36,500 doses. In actual fact, the withdrawal from the market occurred after reports of 9 cases of TEE associated with 7 different lots of that product. In contrast, a different brand of IVIG had a constant rate of approximately 0.16 cases per million grams from 1993 to 2010.<sup>34</sup> An SCIG preparation made by another manufacturer also was found to have an increased number of thromboembolic AEs during the FDA review of the insurance data.<sup>31</sup> That product also was withdrawn from the US market, but this observation serves as an important reminder that TEEs can follow administration of IgG by any route: intramuscular, subcutaneous, or IV.<sup>24</sup>

A “root cause” analysis of the withdrawn IVIG product by using newly developed high-sensitivity thrombin-generation assays suggested that subtle changes in the production procedures, including the use of resins to isolate certain clotting proteins, apparently resulted in increased contact activation of factor XI to XIa.<sup>35</sup> Because the total factor XI plus XIa was still within limits of acceptability by the older assays, the product passed all criteria for safety in effect at the time. Factors XI, XIa, and kallikrein coprecipitate with IgG and are difficult to separate because their isoelectric points are similar to most IgGs. Problems with contamination by factors XI, XIa, prekallikrein activator (factor XIIa), and kallikrein have been recognized since the earliest attempts to make safe IVIG products.<sup>36</sup> On one hand, the results suggest that contamination of individual “rogue” lots or random breakdowns in quality control were not responsible

for the increase in factor XIa because many lots were affected. On the other hand, even with the affected products, the proportion of patients who experienced TEEs was extremely low. Thus, multiple risk factors in the individually affected patients also likely contributed. Risk factors identified by epidemiologic studies include advanced age, prolonged immobilization, hypercoagulable states, history of venous or arterial thrombosis, use of estrogens, in-dwelling central venous catheters, and cardiovascular disease.<sup>24</sup> With high-dose IVIG, increases in blood viscosity can occur. Although most patients tolerate temporarily increased viscosity, others may be more susceptible to complications from decreased flow through sensitive vascular beds. In addition to increased viscosity caused by the IgG itself,<sup>37</sup> hypertonic conditions created by the large amounts of sugars or other osmotically active stabilizers in some IVIG formulations may have effects on erythrocytes and platelets, which contribute to inducing thromboembolic complications.<sup>37,38</sup> Endothelial cell and/or platelet activation, as in systemic inflammatory states, may also contribute. However, it is important to recognize that TEEs can occur in the absence of known risk factors.

### Mitigation of the risk of TEEs

Improvements by the manufacturers in chromatographic purification procedures when applicable, and the use of specific immunoadsorbents to remove FXI/FXIa from products that are made by multiple precipitations should decrease the risk of factor XIa-related AEs.<sup>35</sup> Furthermore, the use of the new thrombin-generation assays should provide reassurance about the absence of procoagulant activity in current and future IgG products.<sup>33,35</sup> It is incumbent on prescribers to take thorough histories, seek information about previous TEEs and identify risk factors that should be carefully considered in developing the patient's IgG treatment regimen. Patients should be checked closely for risk factors before starting infusions and should be monitored closely during and after infusions. In addition, patients should be educated and should be encouraged to report any signs or symptoms suggestive of a TEE. Patients should be well hydrated before IgG is administered, and rates of IV infusions should be as slow as practical if any risk factors have been identified. The use of 5% or even 3% IV solutions, and fractionating doses into multiple aliquots to be given on different days may be helpful. In high-risk cases, in addition to the above measures, prophylaxis with low-dose aspirin, antiplatelet drugs, or low-molecular-weight heparins may be warranted.

### ACUTE RENAL DYSFUNCTION AND/OR FAILURE

Acute kidney injury is a rare complication of IVIG infusions.<sup>39</sup> Clinical manifestations can vary from asymptomatic elevation in serum urea nitrogen and creatinine to anuric renal failure. Although spontaneous resolution typically occurs within 4 to 10 days after IVIG has been discontinued, permanent renal failure is possible. Acute kidney injury after IVIG has predominantly been associated with products that contain sucrose, although other stabilizers have also been implicated.<sup>40</sup> The pathogenesis of most cases is believed to involve osmotic damage to tubular cells, which take up sucrose, then water, and which results in swelling that can obstruct the tubules.<sup>40,41</sup> Sucrose-containing products should be avoided for patients with pre-existing renal disease or who are at risk, and all patients should be well hydrated before an IVIG infusion is started. Acute

severe hemolysis, a separate complication (see Hemolysis and hemolytic anemia) can also lead to hemoglobinuria and renal failure.<sup>42</sup>

### Risk factors and mitigation

Risk factors for renal complications of IgG therapy include pre-existing renal insufficiency, diabetes mellitus, dehydration, age older than 65 years, sepsis, and concomitant use of nephrotoxic agents. Increased blood viscosity and deposition of immune complexes may also contribute to the risk of kidney damage. For all patients, particularly those with one or more risk factors, careful monitoring, assuring adequate hydration, and administering IV fluids may be useful in preventing renal complications. If questionable, blood viscosity can be checked before beginning the IVIG infusion. IVIG solutions more concentrated than 5% should be avoided in patients with decreased renal function, and fractionating large doses into smaller doses given on different days should also be considered. Sucrose-containing products should be avoided in patients with any compromise or risk for compromise in renal function. The only preparation presently available in the United States that contains sucrose is Carimune NF (CSL Behring, King of Prussia, Pa) (Table I). When a sucrose-containing product must be used, adequate hydration should be assured before administration, and the infusion rate should not exceed 3 mg sucrose per kg per minute. If renal function deteriorates during the course of IgG replacement therapy, then the use of sucrose-containing products should be discontinued.

### OTHER POTENTIALLY SERIOUS AEs

#### Anaphylaxis and other reactions due to IgA

Anaphylaxis can occur in patients who have preformed IgE or IgG antibodies against IgA because most IgG preparations contain at least trace amounts of IgA (Table I).<sup>43,44</sup> The presence of preformed IgE against IgA is extremely rare, but true anaphylaxis may be life threatening. The potential for anaphylaxis should be considered in patients with partial B cell immunodeficiencies who are capable of some antibody production but who have undetectable levels of serum IgA (<5 or <7 mg/dL in different laboratories). In contrast, this is not usually a concern in patients with X-linked (Bruton) agammaglobulinemia because those patients cannot make IgG or IgE anti-IgA antibodies. However, IgG-mediated reactions to IgA-containing products have been reported in patients without detectable IgA or IgM. Patients with low, but detectable, circulating endogenous IgA are presumably not at risk for anaphylaxis from this cause, although such patients may still have serious transfusion reactions if whole blood, fresh frozen plasma, or unwashed packed cells are given, because these blood products contain much more IgA than IVIG products. True anaphylaxis due to IgE anti-IgA antibodies has been reported in very few cases.<sup>43-45</sup> However, it is possible for serious reactions to occur in patients who produce other classes of antibodies against IgA. Up to a third of patients with IgA deficiency have been reported as having IgG against IgA by some investigators, but the percentage of patients with IgA deficiency who experience anaphylactic reactions to IVIG is much lower.<sup>45,46</sup> A recent literature search for reports of reactions mediated by anti-IgA identified 27 patients with IgG anti-IgA antibodies, some with extremely high titers.<sup>45</sup> All had serum IgA of <10 mg/dL. Twenty-four of these patients carried the diagnosis of common variable immune deficiency, and 23 had

experienced anaphylactic reactions, mostly to IVIG products that contained  $\geq 50$   $\mu\text{g/mL}$  IgA, whereas 4 had only moderate reactions.<sup>45</sup> Ten of these patients tolerated other IVIG preparations with lower IgA contents, and 8 tolerated SCIG therapy. Indeed, several investigators reported the development of clinical tolerance, with the apparent disappearance of anti-IgA, in association with the use of SCIG in patients with PIDD who were previously persistently positive for anti-IgA antibodies while on IVIG.<sup>44-48</sup> Cautiously continuing IVIG has also been reported to result in neutralization of circulating anti-IgA and apparent clinical tolerance in selected patients.<sup>48,49</sup>

IgA deficiency should not be regarded as a contraindication to treatment with immunoglobulin replacement in patients with IgG deficiency. Rather, a product with low IgA content should be selected, and caution should be used in its administration. Currently available IVIG products vary widely in IgA content, which range from  $\leq 2$  to  $\geq 700$   $\mu\text{g/mL}$  (Table I). Flebogamma (Grifols, Clayton, NC), Gammagard-SD (Baxter, Westlake Village, Calif), Gammaplex (Bio Products Laboratory, Elstree, Hertfordshire, UK), and Privigen (CSL Behring) contain  $\leq 25$   $\mu\text{g/mL}$  and are well tolerated by most patients with IgA deficiency. In any at-risk patients with IgA deficiency, administration of IVIG should be started slowly, (eg, 0.001 mL/kg/min) and epinephrine, other medications, and equipment necessary to treat anaphylaxis must be available. If a patient with an IgA deficiency tolerates an initial infusion of IVIG, then the rate of administration can be increased, and premedications can be reduced gradually with subsequent infusions. If true anaphylaxis occurs, then switch to the lowest IgA content product available. Another safe option would be to change to subcutaneous immunoglobulin therapy, which has a very low rate of systemic reactions and is generally well tolerated even by patients who have reacted to IgA-containing IV infusions.<sup>6,17,44-48</sup> There have not been sufficient studies of the reproducibility and utility of skin testing to recommend its use in managing patients with IgA deficiency who also require IgG replacement.

### Hemolysis and hemolytic anemia

A problem somewhat analogous to that of TEEs is the potential sensitization of recipient red blood cells due to isoagglutinins in IgG preparations, which may result in asymptomatic Coombs test positivity, occasional cases of clinically significant hemolytic anemia, and extremely rare episodes of acute severe intravascular hemolysis.<sup>42,50-54</sup> Although data are somewhat inconsistent because different assays have been used at different times by different manufacturers and regulatory agencies, it seems likely that increased amounts of antibodies to blood group substances A and B in many of the IVIG products introduced in the past several years are the major contributors to the increased incidence of erythrocyte sensitization and clinically significant hemolysis. In the original Cohn-Oncley fractionation scheme, isoagglutinins, which have higher isoelectric points than other IgGs, were greatly reduced by removing fraction III and proceeding to purify the IgG from fraction II alone.<sup>55</sup> Several more recent production schemes use the combined fraction II and III precipitates as the starting material for IgG purification, and some manufacturers have substituted precipitation with caprylic acid (also known as caprylate or octanoic acid) for the ethanol steps that removed more of the isoagglutinins. As with TEEs, true rates of Coombs positivity, hemolytic anemia, and acute severe hemolysis in relation to IVIG therapy are difficult to estimate. However, risk factors that have been identified

include blood groups other than O, underlying systemic inflammatory state, and high doses of IVIG.<sup>53,54</sup> Recent US and Canadian reports of case series of clinically significant hemolysis after IVIG include a combined total of 37 patients. Of these 37 patients, 23 were blood type A, 9 were type B, 4 were AB, and only 1 was type O.<sup>51-53</sup> In a licensing study of 2 g/kg IVIG for immune thrombocytopenic purpura, 12 patients of 56 (21.4%) who were Coombs negative at baseline converted to positive after the IVIG. There was an overall median decrease in hemoglobin of 1.2 g/dL by day 8, followed by a return to near baseline by day 29.<sup>56</sup> Estimated rates of clinically significant hemolysis after high-dose IVIG for immune thrombocytopenic purpura or neurologic diseases range from 1.6% to 6.7%.<sup>54</sup> In contrast, clinically significant hemolytic anemia or acute hemolysis is extremely unusual in licensing studies of IVIG for PIDD, which generally use doses  $\leq 800$  mg/kg. Some manufacturers are instituting steps such as the use of specific immunoabsorbents to lower the titers of anti-A and anti-B without sacrificing the yield or purity of the IgG.<sup>57</sup>

Acute hemolysis after high-dose IVIG is more likely with patients with one or more pre-existing risk factors. In such patients, the total IVIG dose should be fractionated into 4 to 5 aliquots, which may be given on consecutive days. Careful monitoring and review of the patient's history before and after each aliquot, looking for signs and symptoms of hemolysis or decreased oxygen delivery (ie, dark urine, tachycardia, shortness of breath, dizziness) before starting any IVIG infusion should be routine, although this may not prevent the complication in all cases.<sup>53,54</sup> Similarly, switching brands of IVIG does not guarantee that hemolytic reactions will not recur with subsequent infusions.

Acute hemolytic reactions are most likely to occur in patients with active inflammatory disorders (suggested by elevated erythrocyte sedimentation rate or C-reactive protein level). Patients who receive high-dose IVIG should have Coombs tests before repeated infusions and should be monitored for signs of hemolysis or anemia. In 1 study of 16 cases of acute hemolytic reactions associated with IVIG, the mean decrease in hemoglobin was 3.2 g/dL (range, 0.8-5.2 g/dL), and 3 of the 16 patients required red blood cell transfusions.<sup>51</sup> Risk factors included high cumulative dose of IVIG ( $>100$  g per course), A or B blood group, and positive serum markers of systemic inflammatory response, each present in 94% of the patients. Direct Coombs tests were positive in 88%, spherocytes were present on peripheral blood smears in 75%, and 63% were women.<sup>53</sup>

If acute hemolysis is suspected, a complete blood cell count, Coombs test, and urinalysis should be obtained. Serum haptoglobin and urinary hemoglobin may help to differentiate intravascular hemolysis from increased reticuloendothelial sequestration. In addition, the patient's red blood cells should be sent to a blood bank for elution and identification of the responsible antibodies. Treatment should include IV fluids to prevent renal damage, oxygen if needed, and corticosteroids in most cases. Transfusion of type O red blood cells should be considered in severe cases.

### Neutropenia

Transient neutropenia can occur after IVIG infusions,<sup>58,59</sup> which may be due to immune complex or complement-mediated neutrophil activation and upregulation of adhesion molecules, and which results in intravascular neutrophil aggregation and increased margination. Alternatively, neutropenia may be due to the presence of antineutrophil antibodies in the IgG product.<sup>60,61</sup> Because neutropenia is most often transient and

**TABLE II.** Considerations in the choice of the SC vs IV routes for IgG replacement therapy in primary immunodeficiency diseases

| Parameter                   | SC                                                                                                                           | IV                                                                                          |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Infusion site               | SC sites are easily identified and initiated                                                                                 | IV access usually requires trained personnel, may be difficult                              |
| Location                    | Usually given at home                                                                                                        | Usually given in the office, hospital, or infusion center                                   |
| Personnel                   | Self, partner, or parent                                                                                                     | Usually requires a nurse or physician                                                       |
| Characteristics of patients | Reliable, seeks independence                                                                                                 | Dependent, wants to be cared for                                                            |
| Costs                       | Product and infusion supplies, pump                                                                                          | Product, IV supplies, facility fee, nursing charges                                         |
| AEs                         | Local site reactions are common but not usually clinically significant; systemic AEs are rare; premedications are not needed | Some patients have systemic AEs may limit rate, may require pre- or postinfusion medication |
| Dose per treatment          | Limited by volume tolerated per site and number of sites                                                                     | Large dose may be given through a single IV                                                 |
| Infusion frequency          | Usually weekly or more often                                                                                                 | Once every 3-4 wk                                                                           |
| Pharmacokinetics            | Steady state achieved by weekly therapy                                                                                      | Peak may be $\geq 3$ times "trough"                                                         |
| "Wear-off effects"          | Usually eliminated by steady-state IgG level                                                                                 | Many patients "feel IVIG effects wearing off before next dose is due"                       |

SC, Subcutaneous.



**FIGURE 1.** **A**, "Moderate" local reaction at various times during and after infusion of 20 mL of 20% SCIG in a patient with common variable immune deficiency. Note erythema and swelling before the end of the infusion. By 8 hours, only slight, diffuse erythema is evident. **B**, "Mild" local reaction during and after infusion of 20 mL of 20% SCIG into a different patient. By 8 hours after infusion, the site is barely detectable. Data on file, CSL Behring LLC.

does not usually involve impaired production, an increased risk of infection is not likely. However, activation and aggregation of neutrophils by antileukocyte antibodies in the IVIG or by rapid complement activation can induce transient dyspnea similar to that seen with reactions to hemodialysis membranes. This mechanism is probably responsible for reports of "transfusion-related acute lung injury" in recipients of

IVIG.<sup>3,5,60,61</sup> Premedication with oral glucocorticoids may help to prevent this complication in patients who have experienced it previously.

#### Pseudohyponatremia

Decreased serum sodium levels may be observed during or after IVIG infusions but most likely this is actually

pseudohyponatremia, as demonstrated by decreased calculated serum osmolality or an elevated osmolar gap,<sup>62</sup> which, in turn, is most likely due to hyperproteinemia or high concentrations of sugars. It is critical to distinguish this from true hyponatremia because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion and further increases in serum viscosity, which could increase the risk of TEEs.

### Skin reactions

Although many patients experience flushing or urticaria with IVIG infusions, rashes that persist after the infusion is completed are unusual. A literature review identified 64 cases of eczematous dermatitis associated with IVIG therapy, mostly in patients who receive high doses for neurologic diseases.<sup>63</sup> This most commonly appears as a vesicular eruption of the palms and/or soles (dyshidrotic eczema) beginning within 8 days after IVIG administration. Most patients responded well to topical corticosteroids, with resolution within 3 weeks. This reaction tended to recur with subsequent IVIG treatments. Alopecia has been reported in patients with PIDD who received IgG replacement, but it seems more likely that this is an autoimmune phenomenon related to the underlying immune deficiency rather than an AE of the IgG therapy.

### REACTIONS AFTER SCIG

Systemic AEs due to SCIG are unusual.<sup>9,20-22</sup> Gardulf et al<sup>64</sup> reported only 30 systemic reactions in 25 patients with immunodeficiency who were given 3232 infusions (0.93%).<sup>64</sup> A subsequent review of multiple studies reported only one with a rate of systemic AEs >1%.<sup>65</sup> In a 2004 review that summarized data on more than 40,000 SCIG infusions in 232 patients with PIDD, the overall incidence of systemic AEs was 0.43%.<sup>19</sup> Although nearly 75% of patients at some point may have some local discomfort associated with swelling and redness at the site of the infusions,<sup>20-22,64-67</sup> the swelling and local symptoms usually subside within 24 to 48 hours and do not usually deter patients from continuing with their SCIG regimen. Because of the rarity of systemic AEs with SCIG, premedication is rarely necessary nor is close monitoring required during the infusion. SCIG has thus emerged as an ideal route for home use in many patients.<sup>64-67</sup> Some considerations in the choice of SCIG versus IVIG are presented in Table II and in other literature.<sup>68,69</sup> As noted above, SCIG may offer a better tolerated alternative to IVIG in patients with previous problems associated with fluid overload, post-infusion headaches, hemolytic reactions, and reactions presumed due to anti-IgA.

The infusion of 20-30 mL of IgG solution into a single subcutaneous site in ≤2 hours causes some swelling, as expected, due to the infused volume itself. Additional fluid may be drawn into the site osmotically and by locally released mediators, which increase vascular permeability. Locally produced mediators also may cause erythema, warmth, and an itching or burning sensation.<sup>66,67</sup> These "reactions" generally resolve over 12 to 24 hours (Figure 1), usually do not require any treatment, and are subjectively graded by most patients as "mild" or "moderate." Probably because the reactions resolve quickly and are not very troublesome, results of biopsies and detailed histopathologic or immunopathologic studies of SCIG infusion sites are not available in the literature. Several studies in patients with PIDD have

reported initially high rates of local reactions, which decreased over time (reviewed by Wasserman<sup>66</sup>).<sup>9</sup>

The large differences in the reported frequency of infusion site reactions in different studies of the same product and with different products, are likely due to assessments at different times after the infusions, different observers (ie, the patient versus the physician), and different grading systems. Decreases in the reported incidence of reactions to the same product over time may be due to the eventual recognition by the patients that some swelling and redness is routine, and should have been expected, rather than to actual physiologic changes in the subcutaneous tissues or in IgG metabolism.<sup>66,67</sup> However, phenomena analogous to those responsible for the transiently increased frequency of systemic reactions when IVIG products are switched cannot be ruled out. Long-term changes at injection sites such as lipodystrophy, fibrosis, atrophy, or long-lasting subcutaneous nodules have not been reported. Nevertheless, rotating the sites used for consecutive infusions seems prudent but is not absolutely necessary. Patients who are instructed to recognize and expect these injection site "reactions," particularly those who were shown photographs or who had talked with patients already on SCIG rarely complain or discontinue the SCIG because of local AEs.<sup>66</sup> More severe local reactions and infected sites are extremely rare and may be due to poor technique and/or contamination of the infused drug. Most patients who have been on SCIG in trials prefer to remain on SCIG. However, this likely includes selection bias because patients who might have pre-existing reasons for preferring SCIG may self-select by volunteering for trials.

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