

## Intravenous immune globulins: an update for clinicians

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**I**ntravenous immune globulin (IVIG)\* is currently the most widely used plasma component in the world.<sup>1</sup> Immunoglobulins provide the body with an important defense mechanism against infectious agents for the patient with hypogammaglobulinemia. Less well understood is the ability of infused immune globulins to modulate immune-mediated diseases. Many excellent reviews have been written about the scientific and technical aspects of IVIGs. This review uses a different slant, with emphasis on the role of IVIGs in clinical practice and particular attention to the many research and clinical studies published in the past 5 years pertaining to currently available products, indications for use, and reactions, and other complications.

### USE OF IVIG: HYPOGAMMAGLOBULINEMIA

The earliest use of human immunoglobulin, nearly 80 years ago, was to ameliorate measles; in this setting, the antibodies were obtained from human placenta.<sup>2</sup> A plasma derivative followed, and this material was used,

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**ABBREVIATION:** CNS = central nervous system; FTA-ABS = fluorescent treponemal antibody absorption test; HBIG = hepatitis B immune globulin; ITP = immune thrombocytopenic purpura; RES = reticuloendothelial system; RGD = arginine-lysine-aspartic acid; TSE = transmissible spongiform encephalopathy.

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\*In this review, the vernacular abbreviation IVIG is used. However, it should be noted that in the United States the proper name for this product is Immune Globulin Intravenous (Human), and the relevant abbreviation used by the FDA is IGIV.

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additionally, for prophylaxis against HAV.<sup>3-5</sup> The value of intramuscularly injected immune globulin in preventing bacterial infections became clear after the description of the congenital agammaglobulinemias by Bruton in 1952.<sup>6</sup> However, IM administration was painful; in addition, the immunoglobulins were absorbed slowly from the injection site. Initial attempts to inject the same preparations of immune globulins intravenously resulted in serious side-effects, including chills, fever, and shock.<sup>7</sup> The discovery of high-molecular-weight aggregates as instrumental to anaphylactic and other reactions was an important milestone. Changes to Cohn's original plasma fractionation method<sup>8</sup> reduced the incidence of these complications and accelerated the use of these new preparations.<sup>9</sup> The first licensed IVIG for sale in the US (Cutter, now Bayer) appeared in 1981.

### USE OF IVIG: IMMUNOMODULATION

Unexpected increases in platelet counts after administration of either FFP or IM immune globulin to patients with immune thrombocytopenic purpura (ITP) had been reported beginning in the 1960s. Both the volume required (for plasma) and the IM route of administration (for immune globulin and especially in the case of a recipient with severe thrombocytopenia) limited the applicability of these observations.<sup>10</sup> However, in 1981, Imbach et al.<sup>11</sup> made a fortuitous observation in two children with congenital agammaglobulinemia and concomitant thrombocytopenia: after the administration of IVIG to treat the hypogammaglobulinemia, the platelet counts rose. His research group subsequently tested the role of IVIG at what has become a standard dosage regimen (400 mg/kg/day × 5 days) to 13 children without agammaglobulinemia but with acute or chronic ITP; in all 13 children, the platelet count increased within 10 days of administration. Although the mechanism was not understood, the potential for its use in other immune-mediated disorders inspired numerous opportunities for investigation and application. IVIG is now widely employed as a primary or adjuvant therapy, or as an alternative to plasmapheresis, in an array of diseases either caused by, or attributed to, autoantibodies or immune complexes or possibly linked to an immune etiology.

Just as IVIG contains an array of alloantibodies directed against infectious agents, this pooled material also has a broad spectrum of allo- and autoantibodies, and other substances, that may be key to immune function and regulation. However, IVIG's immunomodulatory actions are not well understood. A range of mechanisms have been postulated.

### Inhibition of pathologic autoantibodies

Human sera contain natural autoantibodies, among them anti-idiotypic autoantibodies that have a humoral regulatory function in damping down the effects of other autoreactive antibodies. Antibodies with anti-idiotypic specificity in IVIG have been shown to neutralize the effects of a variety of human autoantibodies.<sup>12-14</sup> The anti-idiotypic activity of plasma pools is more potent than that of individual donors, presumably because of a broadening of the antibody repertoire.<sup>13</sup> Anti-idiotypic antibodies may also suppress antibody synthesis by binding to surface immunoglobulins on auto-reactive B cells and down-regulating their maturation, or by a direct or complement-mediated cytopathic effect on B cells and plasma cells secreting specific autoantibodies recognized by the anti-idiotypic.<sup>15</sup> Alternatively, B cell anergy or even apoptosis can be induced by the binding of IVIG to Fc( $\gamma$ )RIIB (low-affinity receptor for IgG) on B cells, or to both this receptor and the B-cell receptor simultaneously.<sup>16,17</sup>

### Enhanced clearance of IgG

IgG is endocytosed by reticuloendothelial cells, but some endocytosed IgG is bound to the protective receptor FcRn (Fc receptor of the neonate), preventing its catabolism. So protected, the immunoglobulin can be released back into the circulation. IVIG may increase the destruction of pathogenic autoantibodies by competing for binding to this salvage receptor.<sup>18,19</sup> Recent pharmacokinetic studies have concluded that this mechanism can explain the gradual decrease in autoantibody levels but not the more rapid effects of IVIG observed in some clinical studies.<sup>20</sup>

### Complement modulation

When administered to patients with spontaneous abortions and congestive heart failure, modest peripheral blood complement activation by IVIG has been demonstrated both *in vivo*<sup>21</sup> and *in vitro*.<sup>22,23</sup> The increased blood concentration of activated complement components (such as C1q, C3, and C4) after IVIG infusion may be due to a diversion of complement away from target tissues, thus possibly reducing tissue damage.<sup>22,24,25</sup> Several mechanisms have been proposed for this action of IVIG, including interference with deposition on target cells or

saturation of receptors on activated macrophages.<sup>26</sup> However, a clear correlation between complement activation and the therapeutic effects of IVIG remains to be established.

### Inhibition of macrocyte-mediated phagocytosis

Fc $\gamma$  receptors are involved in the destruction of antibody-coated platelets. IVIG may up-regulate a receptor that inhibits clearance of opsonized platelets<sup>27</sup> or bind to and interfere with receptors that facilitate clearance.<sup>28</sup> Curiously, although IVIG is effective in blocking autoantibodies to platelet glycoproteins, it has almost no effect on alloantibodies.<sup>29</sup>

### Suppression of pathogenic cytokines

Abnormal cytokine production may be responsible for some forms of autoimmune disease, such as inflammatory myopathies. The infusion of IVIG results in rapid changes in concentrations of both pro- and anti-inflammatory cytokines, as well as soluble cytokine receptors and receptor antagonists, above and beyond that expected from direct infusion. These changes may be responsible for the rapid improvement in symptoms in some treated patients.<sup>30</sup>

### Neutralization of superantigens

Bacterial superantigens have been implicated in a number of disorders that respond to IVIG, such as Kawasaki's disease and toxic-shock syndrome.<sup>31</sup> Although the pathophysiology that links superantigens to disease is unclear, IVIG appears to interfere with superantigen activation of cytotoxic T cells.<sup>32</sup>

### Modulation of B- and T-cell function

IVIG contains antibodies to cell surface molecules important to immune recognition, including CD4, CD5, and T-cell receptor determinants. These antibodies may be important in modulating autoimmune responses, for example, by inhibiting cytotoxic T cells or autoantibody-producing B cells.<sup>33-35</sup> This mechanism may be key in T-cell-mediated neuromuscular diseases such as dermatomyositis,<sup>36</sup> as well as in multiple sclerosis.<sup>37,38</sup> In addition to a direct effect on T cells, some of these antibodies can bind to dendritic cells and inhibit their ability to stimulate allo- and autoreactive T cells. In an *in-vitro* system, IVIG inhibited differentiation and maturation of dendritic cells and modulated cytokine secretion by mature DC.<sup>39</sup> IVIG also contains soluble CD4, CD8, and HLA class I and II antigens;<sup>40,41</sup> these may interfere with antigen recognition by T cells and may contribute to general immunosuppression.

**Miscellaneous effects**

In multiple sclerosis, IVIG may mediate repair of toxin- or viral-mediated demyelination, by stimulating enhanced phagocytosis of central nervous system (CNS) myelin debris, and spontaneous remyelination.<sup>42</sup> However, a separate study demonstrated the ability of IVIG to enhance Fc-receptor-mediated phagocytosis of peripheral nervous system myelin only.<sup>43</sup> IVIG contains autoantibodies to arginine-lysine-aspartic acid (RGD)-containing integrin ligands, and interference with a variety of cell-cell and cell-matrix interactions, including WBC and platelet adhesion, may be part of IVIG's immunomodulatory effect.<sup>44</sup> IVIG also contains both agonistic and blocking antibodies directed at Fas (CD95). In this regard, IVIG has been shown to enhance B- and T-cell apoptosis in vitro.<sup>45</sup> On the other hand, a mechanism involving inhibition of Fas-mediated death of keratinocytes has been implicated in what may be a beneficial effect of IVIG in toxic epidermal necrolysis (Lyell syndrome).<sup>46</sup> The inhibitory effect of high-dose IVIG on tumor metastases might be partly explained by the down regulation of matrix metalloproteinase 9 in macrophages at both mRNA and protein levels.<sup>47</sup> Other postulated effects in relation to specific diseases are described in Table 1.

**APPROVED INDICATIONS FOR IVIG**

In the US, the FDA has regulatory control over IVIG as a drug and has approved its use for six conditions in which efficacy has been proven in well-controlled clinical trials (Table 1).<sup>7,48,49</sup> However, more than half of the

40,000 kg of IVIG produced annually is used off label.<sup>49,50</sup> Manufacturers are only allowed to list indications that have been demonstrated in clinical trials using their own preparations (Table 1). Prompting this conservative approach to labeled indications are differences in the manufacturing and physico-chemical characteristics of individual manufacturers' IVIG preparations (see below), as well as in the plasma donor populations from which the IVIG is prepared. However, it remains to be proven whether these are of sufficient magnitude to affect therapeutic efficacy. In clinical practice, brands of IVIG are often used interchangeably for the same therapeutic objectives.

After infusion, approximately 55 percent of the immunoglobulins are distributed extravascularly. The half life of infused immunoglobulin varies among patients and is similar to that of the native immunoglobulins, averaging 21 to 25 days. Faster clearance of immunoglobulins from the circulation is observed in conditions that enhance metabolism such as fever, infection, hyperthyroidism, or burns. Furthermore, because the degradation of immunoglobulins depends on reticuloendothelial Fc availability and the amount of immunoglobulin, IVIG is thought to be removed faster in the presence of polyclonal or monoclonal hypergammaglobulinemia or if high concentrations of IVIG are given to the patient.<sup>18,51</sup> Given this variable half life of infused IVIG, some authors have suggested that serum IgG levels be monitored during treatment for dose adjustment,<sup>7</sup> although this information should be weighed in light of the patient's clinical response (incidence of infections) as well.

**TABLE 1. FDA-approved uses for IVIG**

Disorder	Examples of IVIG dosage schedule	Approved IVIG sources*					
		Carimune† and Panglobulin	Polygam S/D and Gammagard S/D	Iveegam EN	Gamimune N	Gammar-PIV	Venoglobulin-S
ITP	400 mg/kg/day times 5 days or 1 g/kg/day	X	X		X		X
Primary immunodeficiency	300-400 mg/kg, monthly; adjust for trough IgG of 400-500 mg/dL, and correlate with patient response	X	X	X	X	X	X
Secondary immunodeficiency due to CLL	Monthly, 400 mg/kg		X				
Pediatric HIV infection	200-400 mg/kg, every 2-4 weeks				X		
Prevention of GVHD and infection in adult BMT	Weekly 500-1000 mg/kg				X		
Kawasaki syndrome	Single dose of 2 g/kg, plus aspirin 80-100 mg/kg/day		X	X			X

\* For manufacturing information, see Table 3.  
 † Previously known as Sandoglobulin.

## ITP

Responses to IVIG infusions are more common in patients with acute ITP than chronic forms.<sup>11,52</sup> Some patients appear to be cured or stabilized as a result of the infusion;<sup>53</sup> this is especially true in children, where the vast majority (>90%) respond to a single course of IVIG; the infusion may tide patients through the typically acute illness and thus forestall splenectomy.<sup>10</sup> Over 80 percent of adults also respond with a peak platelet count higher than 50,000 per mm<sup>3</sup>, and nearly 65 percent exceed 100,000 per mm<sup>3</sup>.<sup>54</sup> Some of these responses are long term.<sup>55</sup> More commonly, after an infusion cycle, the platelet count is sustained for only 2 to 3 weeks before retreatment is necessary. Therefore, IVIG is often reserved for use during serious bleeding episodes or to raise the platelet count before splenectomy.<sup>56</sup> The optimal dosage schedule of IVIG remains in question. Many clinicians continue to use an early popularized schedule of 2 g per kg, divided into five daily doses of 400 mg per kg, but alterations involving higher doses over shorter time intervals (e.g., 1 g/kg/day for 2 days) are also now advocated.<sup>57</sup>

## Primary immunodeficiencies

IVIG has replaced IM immune globulin in these patients because of ease of use and equivalence of effect. Congenital syndromes with hypogammaglobulinemia that can be treated with IVIG include X-linked agammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, and X-linked immunodeficiency with hyperimmunoglobulinemia M. IVIG is also useful for patients with Wiskott-Aldrich syndrome and ataxia telangiectasia; in both syndromes, children have difficulty with primary and anamnestic antibody responses.<sup>7</sup> IVIG preparations are assumed to be equivalent in their ability to prevent infections despite variations in product manufacturing.<sup>48</sup>

## Secondary immunodeficiencies due to chronic lymphocytic leukemia

The value of immunoglobulin replacement therapy in acquired hypogammaglobulinemia has been demonstrated in clinical trials in patients with chronic lymphocytic leukemia. Dosages as low as 250 mg per kg every 4 weeks have been shown to be protective against bacterial infections.<sup>58</sup> However the cost effectiveness of this approach remains controversial.<sup>59</sup> IVIG is generally reserved for patients who have had one or more bacterial infections; here, a regular schedule of prophylactic infusions reduces infection rate.<sup>60</sup>

## Pediatric HIV infection

Most children with AIDS acquire the infection perinatally and develop deficits in both cell-mediated and humoral

immunity. Their clinical course resembles primary immunodeficiency, with deficient antibody synthesis; recurrent bacterial infections are a common cause of mortality. Several studies have shown that monthly administration of IVIG (400-800 mg/kg) markedly reduces infectious episodes and improves overall clinical conditions in these patients.<sup>60-64</sup>

## Adult BMT: prevention of infection and GVHD

IVIG therapy has a role in fighting septicemia, interstitial pneumonia, and cytomegalovirus disease. Moreover, it ameliorates the intensity of acute GVHD and reduces transplant-related mortality in adult recipients of related BMT.<sup>65</sup> Dosage schedules and administration schedules are still under investigation for some of these indications. For hypogammaglobulinemic allogeneic recipients, higher and more frequent doses of IVIG are recommended than are standard for other (nontransplant) indications because the IVIG half life among transplant recipients is short (1-10 days, as compared to 21-25 days in healthy adults). Additionally, infections can accelerate IgG catabolism; therefore, the IVIG dose for a hypogammaglobulinemic recipient should be individualized to maintain trough serum IgG concentrations higher than 400 to 500 mg per dL.<sup>66</sup>

## Kawasaki syndrome

In this childhood vasculitis, a single dose of IVIG concomitant with daily aspirin is successful in eliminating fever in over 85 percent of patients within 48 hours; in nearly all cases, this prevents coronary aneurysm formation.<sup>67</sup> Patients who are not better within 6 days are probably nonresponsive to IVIG and may benefit from the use of steroids.<sup>68</sup> The pathogenesis of coronary artery aneurysms is thought to involve nitric oxide production and the expression of inducible nitric oxide synthase in blood MNCs; IVIG treatment significantly decreases both.<sup>69</sup>

## OFF-LABEL USES FOR IVIG

The majority of IVIG use is in the immunomodulatory setting, and except for the treatment of ITP and Kawasaki syndrome, such indications are considered off label. Off-label uses have emerged through case reports, clinical trials, and reviews from national expert panels and other organizations, including an NIH consensus conference<sup>70</sup> and the University Hospital Consortium's Expert Panel for Off-Label Use of Polyvalent Intravenously Administered Immunoglobulin Preparations.<sup>71</sup> Systematic meta-analyses of IVIG for some uses have been performed by the Cochrane Collaboration (<http://www.update-software.com>). Table 2 is an alphabetical synopsis of the most frequently reported additional conditions for which

**TABLE 2. Off-label uses for IVIG (in alphabetical order)**

Disorder	Mechanism of action and other comments
Abortions, recurrent spontaneous	Although a Cochrane meta-analysis has found no benefit to IVIG use, <sup>185</sup> small studies continue to be published suggesting the efficacy of IVIG in specific settings, including, for example, a two-arm study (IVIG vs. no treatment) of 47 women with immunologic disorders such as anti-phospholipid syndrome. <sup>186</sup> In another randomized controlled pilot study of 16 patients with this syndrome, a trend toward a reduced risk of fetal growth retardation was observed. <sup>187</sup>
Asthma	Debate rages over a role for IVIG, which in some double-blinded, placebo-controlled studies, <sup>188</sup> but not others, <sup>189</sup> reduced dependence on steroids. IVIG has also reduced the severity of upper respiratory tract infections in a controlled, blinded study of 31 asthmatic children. <sup>190</sup>
Autism	Although immune system abnormalities have been associated with autism, responses to IVIG are uncommon. <sup>191</sup>
Chronic inflammatory demyelinating polyneuropathy (CIDP)	In a double-blind, placebo-controlled trial involving 30 patients with this diagnosis, two-thirds responded to a 5-day course (0.4 g/kg/day) and maintained long-term improvement with periodic single-day infusions of up to 1 g/kg. <sup>192</sup> Two other similarly sized recent randomized controlled trials supported the use of IVIG as the initial treatment for CIDP. <sup>193,194</sup> Beneficial effects, albeit small, were observed in an uncontrolled study of nine patients with concomitant distal symmetric axonal polyneuropathy and CIDP. <sup>195</sup>
Dermatomyositis, polymyositis	Responses are reported in individual case reports; controlled clinical trials show marginal if any effect in comparison to placebos. <sup>36</sup>
Diabetes mellitus	Although immune destruction of pancreatic islet cells occurs in diabetes mellitus, a controlled trial of IVIG involving 52 patients was not effective in changing insulin dosage or diabetic control. <sup>196</sup> On the other hand, diabetics have an increased incidence of chronic inflammatory demyelinating polyneuropathy, and a pilot open-label study of IVIG in 26 patients led to improved neurologic function in 80%. <sup>197</sup>
Guillain-Barré syndrome	IVIG appears to be equivalent to plasmapheresis in curtailing period of hospitalization and disability, <sup>198,199</sup> and may be preferable to the latter, in the subgroup of patients with IgG anti-GM1, as suggested by a small, nonrandomized study of such patients. <sup>200</sup>
Hematologic coagulation disorders: acquired FVIII inhibitors; acquired vWD	IVIG (alone or with steroids) can effect a rapid response in titer in patients with acquired FVIII inhibitors; <sup>201,202</sup> however, other authors believe that immunosuppression with steroids and cyclophosphamide is more reliable. <sup>202</sup> A response to IVIG in acquired vWD occurred in only 1 of 3 patients in one study. <sup>203</sup> In another, involving 10 patients with vWD inhibitors, IVIG curtailed bleeding and increased factor levels in the setting of IgG (but not IgM) monoclonal gammopathy. <sup>204</sup>
Hematologic immune-mediated cellular disorders: autoimmune hemolytic anemia, autoimmune neutropenia, fetal-neonatal alloimmune thrombocytopenia; HLA-alloimmune thrombocytopenia	Isolated case reports continue to appear attesting to a possible role for IVIG in refractory autoimmune hemolytic anemia, however, it is difficult to sort out effects of other simultaneously administered medications and procedures. <sup>205,206</sup> In a test of IVIG in autoimmune neutropenia in infancy, 10 of 20 treated patients responded transiently. <sup>207</sup> Maternally administered IVIG (1 g/kg/week) appears to prevent intracranial hemorrhage and raises platelet counts in the majority of fetuses with alloimmune thrombocytopenia. <sup>187,208,209</sup> In a retrospective review of 74 women enrolled in three multicenter studies, response rates were lower in fetuses with severe thrombocytopenia (<20,000/mm <sup>3</sup> ). <sup>210</sup> Although IVIG has not been effective in treating thrombocytopenia due to HLA-alloimmunization, new research suggests IVIG prepared from multiparous women has higher levels of anti-HLA-specific anti-idiotypic antibodies; in SCID mice producing human anti-HLA, this preparation resulted in a significant reduction in anti-HLA titers. <sup>211</sup>
Infection prophylaxis in high-risk neonates	A large randomized controlled trial of IVIG versus placebo in neonates found no effect of exogenously administered IVIG on the risk of neonatal sepsis. A recent Cochrane review of 19 randomized, controlled studies has also concluded that there is insufficient evidence to support the efficacy of this use. <sup>212,213</sup>
Inflammatory bowel disease (Crohn's disease; ulcerative colitis)	In an isolated case report of Crohn's disease, IVIG appeared to suppress recruitment of immunocompetent cells into colonic mucosa. <sup>214</sup> A rat model mimicking ulcerative colitis substantiates this effect. <sup>215</sup>
Myasthenia gravis	A number of trials, including some which were randomized and placebo-controlled, point to IVIG being as effective as plasmapheresis, with a lower complication rate, although a longer time to response. <sup>217-220</sup>
Multiple sclerosis	Two recent reviews analyzing a set of randomized, placebo-controlled trials confirm that only modest effects on disease have been reported, with no clear superiority to other modalities. <sup>221,222</sup>
Multifocal motor neuropathy	Compared to placebo, IVIG improved conduction block and produced subjective and objective functional improvement in 16 patients in a randomized, controlled study. <sup>223</sup>
Parvovirus-B19-associated anemia	In a set of case reports of patients with impaired humoral immunity, such as common variable immunodeficiency, and parvovirus-associated pure RBC aplasia, daily IVIG restored the reticulocyte count in 1 week due to the presence of viral-neutralizing antibodies. <sup>145</sup>
Posttransfusion purpura	Although study populations are small, due to the rarity of the diagnosis, IVIG has emerged as the treatment of choice for PTP, replacing therapeutic plasma exchange. <sup>224,225</sup>
Rheumatoid diseases	IVIG is ineffective in adult rheumatoid arthritis; despite reports of beneficial effects in a placebo-controlled trial of 32 patients with systemic-onset disease and 20 others with polyarticular juvenile chronic arthritis, it is still considered experimental therapy. <sup>216</sup>
Sepsis; toxic-shock syndrome	IVIG reduced sepsis-related mortality in some studies; <sup>226,227</sup> however, in another, a randomized, controlled, double-blinded study of 39 patients, the incidence of infections dropped, but not mortality rate. <sup>228</sup> One mechanism of action may be antibodies in the IVIG against pyrogenic toxin superantigens. <sup>31</sup> In neonatal sepsis, IVIG has a small but measurable effect as an adjunct to antibiotic treatment. Its role as a prophylactic treatment in newborns to prevent infection is possibly too small to warrant routine use, according to a recent meta-analysis. <sup>229</sup>

TABLE 2. *Continued*

Disorder	Mechanism of action and other comments
Stiff-person syndrome	In one study of 16 patients randomized to receive either IVIG or a placebo, the use of 2 g IVIG/kg monthly led to objective improvement and increased ability of patients to perform the activities of daily living, with concomitant declines in anti-GAD65 titers. <sup>230</sup>
Systemic lupus erythematosus, systemic vasculitis	Small studies continue to appear sporadically, concerning the efficacy of IVIG in the vasculitis setting, including to treat exacerbations of SLE (13 patients, uncontrolled), <sup>231</sup> and as an alternative to cyclophosphamide (14 patients, randomized to one or the other). <sup>232</sup>
Toxic epidermal necrolysis (Lyell syndrome)	IVIG blocks Fas-mediated keratinocyte apoptosis and was effective in two case reports <sup>233,234</sup> and a small uncontrolled series of ten patients. <sup>46</sup> IVIG may also have been effective in a severe cutaneous reaction to the antiepileptic drug phenytoin. <sup>235</sup>
Transplantation: CMV-negative recipients of CMV-positive organs	It remains unclear whether IVIG (either broad spectrum or CMV specific) plus gancyclovir prophylaxis is better than gancyclovir alone for prophylaxis in BMT recipients. However, IVIG has other benefits and is likely to continue to be used. <sup>236</sup> In a retrospective study of 23 patients in a high-risk transplant setting (CMV-negative recipient CMV-positive donor) IVIG reduced the incidence and severity of CMV infection, <sup>237</sup> although with more potent immunosuppressive regimens, the effect of IVIG appeared muted. <sup>238</sup>
Transplantation: renal graft rejection	Results of two small (7 patients in one, 17 in the other) uncontrolled studies suggest that IVIG may be able to reverse steroid and ATG-resistant rejection. <sup>239,240</sup>
Transplantation, solid organ: alloimmunization and hypogammaglobulinemia	Administration of IVIG has led to reduction in HLA-antibody titers and reversal of antibody-mediated allograft rejection in a number of small studies (41 patients, in the largest cohort). <sup>241-246</sup> Mechanisms may include anti-idiotypic antibodies in the IVIG, complement scavenging, down regulation of B lymphocyte activity, or accelerated catabolism of native IgG. Posttransplant hypogammaglobulinemia occurs in up to one-third of patients; IVIG appeared to reduce the incidence of infections related to this. <sup>247</sup>

IVIG has been used. Many remain controversial and in need of large, controlled trials.

### IVIG MANUFACTURE AND PHYSICOCHEMICAL PROPERTIES

Plasma for use in the production of IVIG comes from two avenues: approximately 20 percent is from blood donors (usually recovered plasma from donated whole blood), and the other 80 percent is from plasma donors, usually through plasmapheresis (generating the licensed biologic product known as Source Plasma). Individual plasmas are pooled; the pool size is a minimum of 1000 donors, but may be up to 60,000 donors. The maximum number of donors in pools is treated as proprietary information by each manufacturer. The many thousands of donors who contribute to a typical pool of plasma used for isolation of immunoglobulins represent a wide range of antibody specificities against infectious agents. These preparations contain IgG subclasses in an array typically similar to that found in normal humans. However, manufacturing variations can exist, especially for IgG4, which is often reduced in amount.<sup>72,73</sup> Because some congenital hypogammaglobulinemias involve IgG subclass deficiencies (e.g., deficiencies of IgA or IgE in association with reduced IgG2 or IgG4), some authors have raised concerns about whether more attention should be paid to subclass distribution in choice of a product for a specific patient;<sup>74</sup> at this time, however, no clinical evidence exists that this is an important issue.

In the US, most manufacturers of IVIG use Cohn-Oncley ethanol fractionation (fraction II) as an initial step in the preparation of immunoglobulin.<sup>8,75</sup> In this process, pooled plasma is mixed with cold liquid ethanol and frac-

tions are separated by varying ionic strength, pH, temperature, ethanol concentration, and the concentration of protein itself. Modifications to this process have been employed to increase immunoglobulin yield.<sup>76,77</sup> However, other manufacturing steps are then added by individual manufacturers to complete production, including removal of IgG aggregates and other contaminants, and inactivation of viruses. Any of a variety of stabilizing agents are also employed, including human albumin, glycine, PEG, and sugars such as sucrose, glucose, or maltose. Some manufacturers employ DEAE Sephadex chromatography to remove IgA from their product. Some of these modifications affect the product, although the biologic relevance remains to be established. For example, enzyme-treated IVIG may have a shorter circulatory half life and abnormal IgG subclass proportions; chemically treated IVIG may lack IgG3, and some alteration in Fc function has been noted; and products purified with an anion-exchanger (such as DEAE Sephadex) have reduced IgG4 levels.<sup>78</sup> All told, the numerous steps in the process contribute to a yield of only about 30 percent; in a pool with an average initial plasma IgG of 12 g per L, the end yield is typically only 3.5 g per L.

Current US-licensed versions of IVIG contain IgM in trace levels only. However, a role for IgM antibodies may exist, not only because of its antibacterial activity but also for its potent complement binding activity, far in excess of that of IgG. In particular, manufacturers of Pentaglobin (Biotest Pharma GmbH; available for clinical use in Europe) found that, in a rat model, the infusion of an IgM-enriched (to >50%) IVIG preparation enhanced anti-inflammatory and antibacterial effects through an improved complement inhibitory activity and opsonization.<sup>79</sup> In addition, IgM appears to neutralize autoanti-

bodies through anti-idiotypic interactions, again to a greater extent on a molar basis than IgG.<sup>80</sup> These characteristics may one day prove to be of value in treating diseases with prominent inflammatory and autoimmune features.

The FDA regulates immune globulin manufacture (21 CFR 640 (Title 13), 640.100-640.104). However, these regulations were originally written for IM preparations, and have not been revised or added to so as to be specific for IVIG. In particular, and in large part because of the variability inherent in each manufacturing protocol, the regulations do not specify the composition and characteristics of the final IVIG product. Instead, additional specifications are negotiated on a case-by-case process with each manufacturer before approval of their Biologics License Application. These manufacturer-tailored specifications take on the force of law after product licensure. Most manufacturers also follow criteria established by a WHO committee in 1982 for IVIG characteristics, especially because they reflect the interests of international markets and regulators.<sup>81</sup> In many instances, these criteria are synonymous with FDA regulations. The major WHO criteria include:

1. The lot should be prepared from a pool of at least 1000 donors.
2. The lot should contain at least 90 percent intact IgG and as little IgA and IgM as possible.
3. IgG subclasses should be present in a distribution similar to natural plasma (WHO reference plasma: IgG1 [60%]; IgG2 [29.4%]; IgG3 [6.5%]; IgG4 [4.1%]).
4. The level of antibody against at least two bacterial species and two viruses should be ascertained; additionally, the IVIG should have at least 0.1 IU of anti-HBs and an RIA titer of 1 to 1000 per mL of anti-HAV. Note that in the US, standards for immune globulin apply here, including requirements for anti-HBs of 1.0 IU per g of IgG, and minimum levels of antibodies to diphtheria, measles, and one type of polio.
5. The preparation should be free of fragments and aggregates, as well as prekallikrein activator, kinins, plasmin, accumulating preservatives, and other damaging contaminants.
6. The immunoglobulin should be modified biochemically as little as possible.
7. The immunoglobulin should retain opsonizing and complement-fixing activities and other natural biologic characteristics.

Testing for transfusion-transmissible infectious diseases is discussed below (infectious disease transmission and screening).

We have summarized available information on the manufacturing process and physical properties of the seven different IVIG preparations in use in the US in

Table 3. Note that some aspects of the manufacturing process are maintained as proprietary information by manufacturers.

## ADVERSE EFFECTS OF IVIG

Despite considerable improvement in the safety of IVIG, its use is still associated with a variety of adverse effects, with an incidence ranging between 1 and 15 percent.<sup>51,82</sup>

### IgG aggregates and complement activation

The symptom complex that includes headaches, fever, and flushing is typically mild and transient and is often related to the rate of IVIG infusion. Although the etiology remains uncertain, IgG aggregates, IgG dimers, and complement activation appear to be involved.

This problem was first noted when immunoglobulins were administered intramuscularly to patients with immunodeficiencies.<sup>83</sup> With this mode of administration, at one extreme, a dramatic but uncommon immediate anaphylactic picture occurred in 1 in 500 to 1000 injections. But more frequently, a constellation of symptoms developed in the hours after the injection, including fever, arthralgias, diarrhea, and urticaria. With the first trials of IV administration of gammaglobulins, a much larger proportion of recipients—the majority of patients with congenital hypogammaglobulinemia but also a small proportion of immunologically normal recipients—developed similar symptoms immediately after the start of the infusion. The picture was often even more striking, with a markedly elevated temperature, headache, facial flushing, back pain, nausea, chills, dyspnea, circulatory shock, and convulsions.<sup>9,84</sup>

Subsequent studies by Barandun et al.<sup>84</sup> revealed that the reactions to IVIG were correlated with the IV infusion of IgG dimers (idiotype-anti-idiotypic antibody pairs) and larger immunoglobulin aggregates. These complexes are not present in normal human serum or plasma; dimers are formed when donor plasma is pooled, and aggregates form during the process of plasma fractionation. The aggregates proved to be similar to immune complexes with one important distinction: aggregates in IVIG were able to activate and consume complement even in the absence of antigen. Antibody-deficient patients had frequent, and sometimes extreme (anaphylactoid), reactions, possibly due to the lack of protective action of tissue-bound immunoglobulins against anticomplementary IgG aggregates. The anaphylactoid type of reaction could be avoided by starting the IVIG infusion at low rate to achieve initial "desensitization."<sup>9</sup>

After recognition of the importance of IgG aggregates in these reactions, the WHO moved to standards requiring their removal from IVIG preparations. Techniques

**TABLE 3. Manufacturing processes and physical properties of seven IVIG preparations used in the US**

Product (form)	Manufacturer	Method of preparation	Viral inactivation steps	Stabilizing agent: sucrose	Stabilizing agent: other	Final pH	Osmolality (µg/kg)	IgA content (µg/mL)
<i>Sandoglobulin</i> (now called <i>Carimune</i> ) and <i>Panglobulin</i> (lyophilized)	ZLB Bioplasma AG	Kistler-Nitschmann	Pepsin (pH 4)	1.67 g/g Ig	0	5.5-7.5	Ranges from 192 (3% solution in H <sub>2</sub> O) to 1074 (12% solution in 0.9% NaCl)	<2400
<i>Polygam S/D</i> (lyophilized) and <i>Gammagard S/D</i> (lyophilized)	Baxter	Cohn-Oncley, ion-exchange, ultrafiltration chromatography	S/D treatment	0	albumin, glycine, glucose, PEG (5 g/100 ml)	6.4-7.2	5% solution 590-636, 10% solution 1179-1250	<3.7†
<i>Iveegam EN</i> (lyophilized)	Baxter	Cold ethanol	Immobilized trypsin, PEG precipitation, DEAE Sephadex	0	0	6.4-7.2	240	25
<i>Gammimune N</i> (5% or 10% liquid)	Bayer	Cohn-Oncley	Filtration, pH 4.25 and low salt, S/D treatment	0	5% solution-maltose (10%) 10% solution-glycine (0.16-0.24 M)	4.25	274	120
<i>Gammar-P I.V.</i> (lyophilized)	Aventis-Behring	Cohn-Oncley, ultrafiltration	Heat treatment (10 hr at 60°C)	1 g/g Ig	albumin	6.8	5% solution 330, 10% solution 600	<50
<i>Venoglobulin-S</i> (5% or 10% liquid)	Alpha Therapeutic	Cold alcohol fractionation, ion exchange chromatography	PEG/bentonite precipitation, S/D treatment	0	albumin, D-sorbitol (50 mg/ml, isoosmolar)	5.2-5.8	5% solution, 300 mOsm/L, 10% solution, 330 mOsm/L	5% solution, 15 10% solution, 20-50

\* Information in this table compiled from manufacturers' package inserts, communication with manufacturers, and Siegel.<sup>2,48</sup>

† Labelled for use in IgA-deficient patient.

developed by manufacturers include PEG precipitation<sup>86</sup> and pepsin treatment at pH 4 to remove the Fc portion of antibodies and also eliminate complement consumption.<sup>9</sup> These steps have reduced, but not completely eliminated, the incidence of this type of reaction. In many cases, changing the brand of IVIG used eliminates the symptoms. In addition to effects of residual immunoglobulin aggregates, other pathophysiology may be at play. For example, in individuals with chronic infections, who develop febrile reactions, "antigen overload" may lead to exuberant formation of immune complexes during rapid infusion of IVIG.<sup>9</sup> Pain at the IV site, flushing, and hypotension may result from the presence of prekallikrein activator and kallikrein,<sup>87</sup> and increased levels of the pro-inflammatory cytokine IL-6 and the vasoactive substance thromboxane-B2<sup>88</sup> may also contribute to the clinical picture.

### Hypotension

A sudden fall in blood pressure during IVIG infusion is rare, but it can occur even in a patient who has never previously had a reaction to IVIG. In a rat model of IVIG-induced hypotension, researchers found an association with the presence of IgG dimers in the preparations.<sup>82</sup> Dimers, in contrast to IgG aggregates, probably do not activate complement but can have substantial effects on blood pressure.<sup>85</sup> Dimer formation occurs even in products with little residual IgG aggregation and is related to the number of donors, with larger numbers increasing the likelihood that idiotype-anti-idiotype pairing will occur.<sup>85</sup> The IgG-dimer content of different IVIG preparations varies, ranging from 5 to 18 percent in one study. Another hypothesis attributes hypotension to the result of IVIG activation of macrophages, monocytes, and neutrophils, and subsequent release of a platelet-activating factor.<sup>82</sup>

### Renal failure

The FDA has received over 100 reports of IVIG-associated renal dysfunction and acute renal failure, including 17 fatalities.<sup>89</sup> Although the etiology is not completely understood, sucrose, which is added to some IVIG preparations as a stabilizing agent, has been incriminated. Evidence for this comes from renal biopsies of affected recipients; the pathology typically reveals osmotic injury to the proximal renal tubules, with swelling and vacuolization of proximal renal tubular epithelial cells.<sup>90,91</sup> This appearance is reminiscent of findings in another syndrome, "sucrose nephropathy," which occurs in patients after administration of hypertonic solutions of sucrose and is also associated with renal failure. Sucrose nephropathy is caused by the cellular uptake of this nonmetabolizable disaccharide. The high solute load leads to the creation of an osmotic gradient that results in accumulation of water.

In keeping with this hypothesis is data demonstrating that the majority of US cases of IVIG-associated renal dysfunction (91%) are reported after the use of sucrose-containing products, including Carimune (previously known as Sandoglobulin) and Panglobulin (together responsible for 69% of cases), and Gammar-PI.V. (22% of cases).<sup>89</sup> Underlying renal failure predisposes patients to this complication, possibly because kidney disease facilitates longer exposure of tubular cells to the sucrose, with more uptake.<sup>91,92</sup> Elderly patients (>65 years of age) and patients with diabetes mellitus, monoclonal gammopathies, or cryoglobulinemia, and those who are volume depleted, septic, or receiving nephrotoxic drugs, may also be more susceptible. To avoid this serious complication, the FDA recommends administration of sucrose-containing IVIG with caution to patients at an increased risk for developing acute renal failure and at a maximum infusion rate of 3 mg sucrose per kg per minute. In addition, all patients receiving IVIG should be well hydrated.

Other sugar stabilizers can create mischief as well. For example, maltose has also been implicated in the development of renal dysfunction, although with a lower incidence. Gamimune N (Bayer) uses maltose rather than sucrose in its 5-percent protein product and has had four cases; now glycine, which is already used in its 10-percent product, has been substituted for the maltose in the 5-percent product as well (personal communication, Brian Tevlin, Bayer, May 2001). Some IVIG products are stabilized with glucose (2-5 g/100 mL; see Table 3), and their administration at high doses to diabetic patients can alter insulin requirements or interfere with blood-glucose monitoring. By contrast, note that because sucrose is secreted unchanged by the kidneys, it does not interfere with diabetic care. The osmotic load of glucose present in IVIG has been linked to dilutional (true) hyponatremia in a patient with Guillain-Barré syndrome.<sup>93</sup> However, a laboratory artifact, pseudohyponatremia, is also seen with IVIG administration and is due to the protein in IVIG, rather than glucose. Gamma globulins increase the non-aqueous phase of plasma; because sodium is present, and its concentration is physiologically regulated only in the aqueous phase, the additional gamma globulin results in an increase in the total plasma volume denominator and an artifactual dilution of the sodium value.<sup>94</sup>

### Aseptic meningitis

Aseptic meningitis is a rare adverse effect of IVIG that is dose related and is more common in patients with a history of migraine.<sup>95</sup> Symptoms typically begin 6 to 48 hours after the infusion. Pleocytosis and elevated protein in the CSF are observed in the majority of cases; the pathophysiology remains unknown.<sup>96</sup> Other case reports of neurologic adverse effects include encephalopathy

with seizures,<sup>97</sup> recurrent migraines,<sup>98</sup> and reproducible hypothermia.<sup>99</sup>

### Thromboembolic events

A collection of reports of unusual and sometimes serious thromboembolic events have been reported in association with IVIG use,<sup>100,101</sup> including deep venous thrombosis of the arm proximal to the infusion site,<sup>102</sup> myocardial infarction,<sup>103-106</sup> pulmonary embolism,<sup>107,108</sup> central retinal vein occlusion,<sup>109,110</sup> cerebrovascular accidents,<sup>111-114</sup> and fatal hepatic veno-occlusive disease.<sup>115</sup> The pathophysiology may involve the consequences of plasma expansion and increased viscosity. Furthermore, IVIG appears to enhance platelet activation, and this effect may be amplified by a rising platelet count in patients being treated for ITP.<sup>111</sup> Of interest, IVIG contains procoagulant activity, and in particular FXIa, which even in small amounts could lead to thrombin generation.<sup>116</sup> Patients who may be at particular risk include the elderly, the overweight, and the immobilized, as well as those with hypertension or a history of vascular disease such as stroke or coronary artery disease, or thrombophilic disorder. Patients with dehydration or with borderline high serum viscosity, such as related to monoclonal gammopathy, are also at risk because small additional changes in plasma viscosity with IVIG use may affect capillary blood flow.<sup>107,117</sup> In letters to clinicians in 2002, several manufacturers have reported the potential association between IVIG administration and thromboembolic events. This may be related to the use of rapid infusion protocols and higher infusion concentrations in high-risk population. The FDA has more recently issued an interim statement acknowledging this possible relationship and the need for further investigation.<sup>118</sup>

### Anaphylaxis in IgA-deficient recipients

Severe anaphylactic reactions to IVIG have occurred in patients with IgA deficiency.<sup>119,120</sup> IVIG products vary in their IgA content (Table 3). Polygam and Gammagard are the only US-licensed IVIG products with levels of IgA sufficiently low (<3.7 µg/mL in a 5% IVIG solution) for use in IgA-deficient patients. However, even small amounts of IgA can lead to this potentially fatal reaction, especially in patients with IgE anti-IgA.<sup>121</sup> For this reason, for patients with a history of severe anaphylactic reactions, some manufacturers reserve lots of IVIG with very low IgA levels, below those found in implicated lots (personal communication, John Gross, American Red Cross, June 2001).

### Miscellaneous adverse events

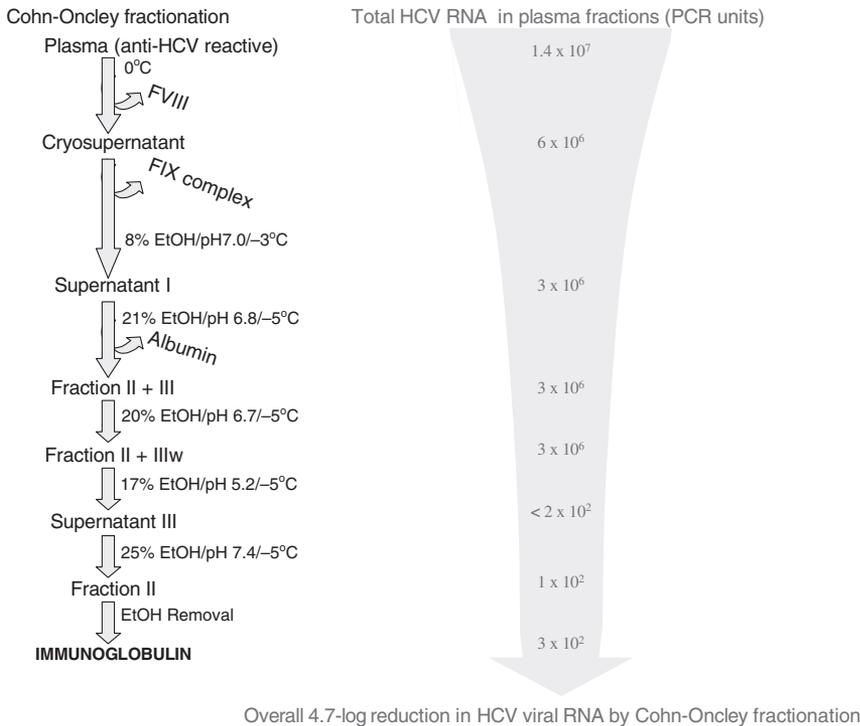
Pulmonary adverse effects of IVIG include fluid overload and pulmonary edema seen when large doses of IVIG are given to patients with pre-existing circulatory insufficiency or pulmonary capillary leakage.<sup>122</sup> A single case of

TRALI has been reported (and see discussion regarding neutrophil antibodies in IVIG, below).<sup>123</sup> Dermatologic adverse effects, including eczema, as well as arthritis, have been associated with IVIG use.<sup>122,124,125</sup>

## INFECTIOUS DISEASE TRANSMISSION AND SCREENING

Thousands of donors are used in the plasma pools that make up IVIG, and this poses a potentially substantial risk for viral transmission. Nonetheless, IVIG has always had a good safety record, even when it was produced in the absence of specific viral inactivation steps. This is in large part the result of the loss of virus through partitioning during the steps of the Cohn-Oncley fractionation protocol,<sup>126</sup> which results in the removal of a significant portion (5 log) of transfusion-transmissible viruses (Fig. 1).<sup>81,126-132</sup> Antibodies that form complexes with viruses may facilitate this partitioning. All manufacturers also add additional steps to ensure viral inactivation, such as use of a S/D procedure.<sup>127</sup> Finally, residual viruses that survive this process are probably neutralized by agent-specific antibodies present in the final IVIG product.<sup>51</sup>

For two notorious transfusion-transmissible viruses, HBV and HIV (as well as other retroviruses), case reports of infections after IVIG use are exceedingly rare.<sup>126-129,133</sup> HCV has a more checkered history. Although the overall incidence of disease transmission is small, a number of reports have documented HCV transmission by IVIG in the US and Europe, based on both epidemiology—the development of chronic HCV in recipients—and laboratory studies identifying HCV RNA in implicated IVIG preparations.<sup>134-142</sup> A notorious investigation involved Gammagard, manufactured by Baxter. This product was temporarily withdrawn from the market in 1994, after reports of over 200 cases worldwide of HCV transmission related to multiple lots.<sup>86</sup> The risk of transmission to recipients (11%) was striking.<sup>134</sup> Baxter was screening donors using an, at the time, new second-generation HCV antibody test, and the loss of donors with neutralizing and complexing antibodies to HCV could have resulted in a higher load of virus. In addition, all implicated IVIG preparations were lyophilized, which might have allowed greater stability of HCV virions.<sup>130</sup> Finally, the source of donor (paid for Gammagard vs. volunteer for Polygam) might have affected HCV infectivity in the pools.<sup>86</sup> A similar outbreak of HCV in Ireland and Germany after IM administration of Rh immune globulin pointed to the use of ion-exchange chromatography, which reduced viral clearance compared to the original Cohn fractionation protocol.<sup>86</sup> In the US, a series of increasingly stringent rules are used to prevent HCV transmission. After the Baxter outbreak, the FDA required all manufacturers of IVIG to validate viral clearance steps using models in which viruses were added, to demon-



**Fig. 1. Viral removal during Cohn-Oncley fractionation.** On the left is depicted a typical Cohn-Oncley fractionation protocol (adapted from Yei et al.<sup>132</sup>). On the right is the stepwise removal of HCV RNA during this fractionation method. An overall 4.7-log reduction in HCV occurs when the plasma pool contains anti-HCV.<sup>132</sup> Now that donor screening has eliminated anti-HCV from plasma, the log reduction of HCV attributable to the fractionation process is reduced, but additional steps are introduced to compensate for this. Viral reduction can be even higher when HIV is studied, with an overall reduction by Cohn-Oncley fractionation of 11 log in one study. The addition of PEG fractionation and S/D treatment yields an overall 23-log reduction.<sup>127</sup>

strate removal and inactivation. Many manufacturers have incorporated additional steps for HCV inactivation, including pasteurization and S/D treatment. Donor screening has also intensified.

Routine testing performed on the plasma donor in the US now includes HIV-1/2 antibodies, HIV-1 p24 antigen (manufacturers performing NAT testing can now ask for an exemption from this test), HBsAg, HCV antibodies, and NAT testing for HCV and HIV. ALT testing is not required by the FDA but is often performed because of international requirements. Of note, Source Plasma does not need to be tested for antibodies to HTLV-I/II because this infection is cell derived. Furthermore, Source Plasma from donors who test positive for syphilis can also be used for further manufacture into derivatives. Source plasma containing antibodies to HBc is not only allowed but actually considered advantageous because including such donors helps ensure adequate titers of anti-HBs, important when the plasma derivative is used to supply such antibodies. Thus, the presence of these antibodies in IVIG lots should not be a surprise.

In the case of other infectious agents, including HAV and CMV, the risk of disease transmission is minimal, screening is not performed, and the corresponding antibodies will be present in IVIG. In some situations, such as HGV, S/D treatment and possibly other maneuvers appears to reduce or eliminate the virus, but even when still present in the IVIG product, transmission to recipients has not been documented.<sup>143</sup> Parvovirus B19 is not destroyed by S/D treatment, and an interesting medical paradox exists here because the antibodies may be a marker for disease in a donor but are also valuable therapeutically. Parvovirus B19 antibodies present in IVIG are useful in the treatment of aplastic anemia, pure RBC aplasia, and vasculitis in infected patients.<sup>144-150</sup> However, the virus itself is detectable in IVIG using PCR and could theoretically pose an infectious threat to recipients.<sup>151</sup> A case of parvovirus B19 infection transmitted by heat-treated IVIG preparation that led to pure RBC aplasia has recently been reported,<sup>152</sup> as well as a possible superinfection with a new strain of parvovirus B19 in an already B19-infected IVIG recipient, based on a change in B19 DNA sequence after infusion.<sup>153</sup> The potential risk of B19 transmission by IVIG is foreshadowed by data in plasma and other derivatives.

Parvovirus is resistant to S/D treatment and partially resistant to heating, in either the wet or dry state; transmission has been documented after S/D- and heat-treated factor concentrates.<sup>154</sup> Transmission has also occurred after infusion to normal volunteers of pooled S/D-treated plasma with high concentrations of the virus ( $10^7$  geq/mL), although no recipient became clinically ill. At lower viral loads, transmission did not occur, presumably because parvovirus B19 antibodies in the plasma neutralized the virus.<sup>155</sup> The deferral of plasma donors with high-titer antibodies could result in diminished effectiveness of IVIG as a treatment for parvovirus B-19 infections, while at the same time possibly increasing its infectivity in IVIG. Thus, donors are not screened for this antibody, and manufacturers are implementing "in process" (postpooling) viral screening of their products using PCR.

### Prion disease risk

The risk of prion transmission, and specifically new variant CJD, is of great theoretical concern, and worries about

potential transmission were important factors in shortage of IVIG in 1997 and 1998, due to the withdrawal of numerous lots from the market based on postdonation medical histories in a few donors. Fortunately, prion transmission by IVIG is thought to be minuscule due to the low numbers of prions in blood and their inefficient transmission by blood as demonstrated in hamster studies.<sup>156</sup> In addition, several studies that used different strains of transmissible spongiform encephalopathy (TSE) agents have demonstrated the removal of infectivity by different steps used in the manufacture of IVIG.<sup>157,158</sup>

### PASSIVE TRANSFER OF ANTIBODIES ASSOCIATED WITH INFECTIOUS AGENTS

The presence in IVIG of antibodies to transfusion-transmissible viruses can lead to confusion regarding the corresponding infection in the IVIG recipient. Especially problematic in the past was the presence of anti-HCV in IVIG. Although the test protocols were developed for this antibody's detection in blood donors in 1990, the FDA did not immediately approve the use of screened plasma intended for IVIG production until it could be shown that removing anti-HCV did not jeopardize the safety of the product regarding HCV transmission.<sup>159</sup> Even then, the phase-in of testing by manufacturers was gradual. Thus, for a period of a few years, when the anti-HCV test was available but its testing in IVIG was not universal, anti-HCV in IVIG posed particular diagnostic problems for patients whose conditions could also have put them at risk for actual infection, including BMT recipients, other immunocompromised patients, and premature infants.<sup>160-163</sup>

Although IVIG now contains no anti-HIV or anti-HCV, other viral antibodies are, by nature of the product, present and desirable from the standpoint of treatment of immune deficiency disorders with a polyclonal assortment, and it is not surprising that many patients develop measurable titers of these after treatment with IVIG. Among such antibodies are anti-HBs, -HbC, -HAV, -HGV, -CMV, -VZV, and -parvovirus B19.<sup>145,150,155,164</sup> In one study of 165 lots of IVIG, 96 percent had anti-CMV, and 100 percent had anti-HBsAg, plus anti-HAV.<sup>160</sup> In some settings, the presence of these antibodies is advantageous above and beyond the needs of the immunodeficient recipient. For example, anti-HBs in the pooled product may be able to neutralize virus in the plasma pool from donors in the window period of infection. Furthermore, administration of IVIG with high titers of anti-HBs, as assayed by the authors, provided passive immunization to BMT recipients who could not receive hepatitis B immune globulin (HBIG) intramuscularly due to thrombocytopenia.<sup>165</sup> Titers of anti-HBs in the IVIG lots tested in this study ranged from 840 to 1890 IU per L and have been sufficient to lead to anti-HBs titers higher than 100 IU per L in four treated patients.

However, the passive transfer of antibody can also cause diagnostic confusion. For example, passive transfusion of treponemal antibodies was recently reported in a pregnant woman receiving IVIG to treat fetal alloimmune thrombocytopenia. Proof was established when one lot of IVIG tested positive for fluorescent treponemal antibody absorption test (FTA-ABS), and the patient's test became negative 6 weeks after the infusion of the lot. However, before the situation became clear, she was given antibiotics to treat syphilis.<sup>166</sup> Similarly, passive transfer of anti-*Borrelia burgdorferi* antibodies was demonstrated in a 5-year-old child with Guillain-Barré syndrome and led to an additional diagnostic work up to rule out neuroborreliosis.<sup>167</sup>

Thus, in the patient treated with IVIG, it remains important, when using serologic tests for viruses, to consider the possibility of passively transferred antibodies. Passive transfer, versus active infection, can be deduced by a comparison of pre- and posttreatment serologic results in the recipient, or to repeated postinfusion testing (the half life of most antibodies in IVIG is 21-24 days vs. endogenous antibodies, which should be sustained over time). More rigorous investigation could include demonstration of actual infection in the recipient, evidence for a higher incidence of infection in recipients of IVIG than in controls, detection of the virus in the implicated lot, and similarity of viral strains using molecular analysis.<sup>168</sup>

### PASSIVE TRANSFER OF BLOOD GROUP ANTIBODIES

Commercial immune globulins, including IVIG, have measurable levels of anti-A and -B (IgG class), as well as a variety of non-ABO antibodies.<sup>169,170</sup> Thus RBC antibodies have been found in 49 percent of 165 lots of IVIG, including anti-K, -C, and -Le<sup>b</sup>.<sup>160</sup> Most antibodies detected in IVIG are low titer (<1:16, using a saline method; <1:1024 using an antiglobulin method).<sup>171,172</sup> Nonetheless, positive antibody screens and DATs in patients treated with IVIG are seen, although limited in duration (2-5 days).<sup>173-175</sup> In one study of patients treated with IVIG after BMT, 49 percent of recipients developed positive DATs, and 25 percent had positive antibody screens, most often due to passively transfused anti-A, -B, -D, and -K.<sup>173</sup> However, examples have been reported of hemolytic anemias due to anti-D or anti-A.<sup>172,175-177</sup> This hemolysis presumably occurs because of direct antibody attack on RBCs; one group also reports that binding of IgG dimers and aggregates to CR1 (CD35) on RBCs can enhance extravascular reticuloendothelial system (RES) removal.<sup>178</sup>

ABO and Rh antibodies might be expected to be advantageous in treating ITP in patients with relevant blood groups in that RBC destruction could contribute to reticuloendothelial blockade. However, in one study of children with ITP, blood type appeared to be irrelevant,

perhaps because the amount of hemolysis that occurred was insufficient to matter biologically.<sup>179</sup>

Reports of hemolysis due to these antibodies have become much less frequent in the past decade, possibly reflecting manufacturers' attempts to lower the titers of antibodies. The FDA does not have global requirements for levels of blood-group antibodies in IVIG preparations but instead commits manufacturers to mutually agreed-upon specifications through a Biologics License Application. Reduction in titer of these antibodies can be achieved through additional chromatography steps.<sup>122</sup>

Transient neutropenia associated with IVIG therapy, while rare, has been described. Although the mechanism has not been conclusively established, it may be related to the presence of antineutrophil antibodies in the product.<sup>180-182</sup> In studies supporting an alternative mechanism, Telling et al.<sup>183</sup> demonstrated that IVIG antibodies, especially IgG dimers and polymers, interact directly with neutrophils via an interaction with neutrophil FcγRIIa augmented by macrophages. In a rat model, disappearance of neutrophils from the circulation was followed by tissue sequestration, especially in the lungs.<sup>184</sup> The authors caution that IVIG preparations with high dimer content may be harmful to patients with pre-existing clinical conditions that lead to neutrophil activation. Granulocyte antibodies may be able to cause pulmonary complications. A case of apparent TRALI, possibly related to infusion of IVIG, has been reported.<sup>123</sup>

## CONCLUSIONS

The development of IVIG has been a milestone in the history of blood products: lives have been saved and quality of life improved for patients with a variety of immunodeficiency diseases and conditions responsive to immunomodulation. However, the widening array of off-label conditions for which this product is administered cries out for more systematic evaluations of efficacy. This need is especially pressing because, despite an overall excellent safety record, IVIG can cause serious complications, including renal failure, myocardial infarction, and transmission of viral infections. Clinicians administering IVIG should carefully weigh risks and use appropriate precautions in susceptible patients. It is also prudent to keep records of lot numbers and manufacturers to be able to trace back lots in which problems are later reported and, similarly, to report suspected cases of infection transmitted by IVIG, or other complications, to the CDC, as well as the FDA (via MedWatch) and the product manufacturer.

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