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Adverse Effects of Human Immunoglobulin Therapy

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ABSTRACT

Human immunoglobulin (IG) is used for IgG replacement therapy in primary and secondary immunodeficiency, for prevention and treatment of certain infections, and as an immunomodulatory agent for autoimmune and inflammatory disorders. IG has a wide spectrum of antibodies to microbial and human antigens. Several high-titered IGs are also available enriched in antibodies to specific viruses or bacterial toxins. IG can be given intravenously (IGIV), intramuscularly (IGIM) or by subcutaneous infusions (SCIG). Local adverse reactions such as persistent pain, bruising, swelling and erythema are rare with IGIV infusions but common (75%) with SCIG infusions. By contrast, adverse systemic reactions are rare with SCIG infusions but common with IGIV infusions, occurring as often as 20% to 50% of patients and 5% to 15% of all IGIV infusions. Systemic adverse reactions can be immediate (60% of reactions) occurring within 6 hours of an infusion, delayed (40% of reactions) occurring 6 hours–1 week after an infusion, and late (less than 1% of reactions), occurring weeks and months after an infusion. Immediate systemic reactions such as head and body aches, chills and fever are usually mild and readily treatable. Immediate anaphylactic and anaphylactoid reactions are uncommon. The most common delayed systemic reaction is persistent headache. Less common but more serious delayed reactions include aseptic meningitis, renal failure, thromboembolism, and hemolytic reactions. Late reactions are uncommon but often severe, and include lung disease, enteritis, dermatologic disorders and infectious diseases. The types, incidence, causes, prevention, and management of these reactions are discussed.

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ANTIBODY THERAPY FOR infections using animal serums and antitoxins has been available since the 1890 s, garnering Emil van Behring the first Nobel prize in Medicine in 1901. Human immunoglobulin (IG) was developed during World War II (1941–45) when a team headed by EJ Cohn and JL Oncley used alcohol fractionation of human plasma to develop concentrated albumin (for blood loss in war casualties) and gamma globulin (for prevention of infection) [1]. The gamma globulin fraction, termed Cohn fraction 2, is a concentrated 16% product for intramuscular injection (IGIM) and was used initially for prevention of hepatitis, measles, and polio [2,3].

Bruton in 1952 first used IG to treat the first patient identified with agammaglobulinemia [4]. Thereafter large painful weekly intramuscular IG injections became the standard therapy for immunodeficiency until the introduction of IGIV 40 years later. The IGIM preparations could not be tolerated if given by the intravenous route [5].

Single small doses of 16% IGIM continue to be used for prevention of infections (measles, polio, hepatitis B). High-titered 16% IGIMs from immunized or convalescing patients were subsequently developed for specific disorders (eg, tetanus, rabies, and hepatitis B) [6]. Systemic reactions to these injections are infrequent since the quantity of IG

given is small, its entry to the circulation gradual, and the injection is not usually repeated.

Five percent intravenous immunoglobulin (IGIV), free of high molecular weight complexes, was introduced in 1982 for patients with antibody immunodeficiency [7]. The intravenous route avoids painful large intramuscular injections, permits larger doses and results in rapid attainment of therapeutic serum IgG levels. The infusions are usually given every 3 to 4 weeks. Higher concentrations of IGIV (10–12%) were subsequently developed to decrease the volume and duration of the infusions. High-titered IGIVs for prevention and treatment of infectious disease including hepatitis B, varicella,¹ rabies, infantile botulism,² and cytomegalovirus are also available [6].

IGIV use greatly increased with the discovery that IGIV was effective in autoimmune and inflammatory diseases such as immune thrombocytopenic purpura [8], Kawasaki disease [9] and immune-mediated neurologic disorders [10]. The IGIV dose in these disorders is large, often repeated and given to high risk patients, mostly adults, all increasing the risk of adverse reactions.

Subcutaneous infusion of immunoglobulin (SCIG) for antibody deficiency was first used by Berger et al in 1980 in a pregnant woman

Conflict of Interest: None.

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¹ Varicella-zoster immune globulin is available as an investigation new drug by calling FFF enterprises at +1-800-843-7477.

² Botulism immune globulin intravenous is available through the California Department of Health Services by calling +1-510-231-7600.

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[11] and then by Ugazio et al and Roord et al in 1982 [12,13]. This route was first used regularly in Sweden for immunodeficiency in the late 1980s by Gardulf et al [14]. Many immunodeficiency patients now receive their immunoglobulin by slow subcutaneous infusion using a 10%, 16%, or 20% product, the latter developed especially for subcutaneous use. The subcutaneous route has the advantages of no need for intravenous access, steadier IgG levels, higher IgG trough levels with comparable doses, and, most importantly, considerably fewer systemic side effects than IGIV infusions [14–19].

This review will focus on the adverse effects of therapeutic human immunoglobulins, including the 5% and 10% products for intravenous use (IGIVs), and the 10% to 20% products for subcutaneous use (IGSCs). The hyperimmune IGIMs and IGIVs for specific infections have the same potential for adverse reactions. Several non-human immunoglobulins (eg, equine diphtheria antitoxin) and therapeutic monoclonal antibodies (eg, rituximab, infliximab) are also available, but their side effects are not discussed in this review.

General Considerations

Pre-infusion Considerations

The indication for use of immunoglobulin should be carefully considered because of its expense, infusion discomfort, and potential side effects. Indeed insurance companies are reluctant to pay for IG infusions unless their medical need is well established and alternative treatments have been considered or used without expected results. The cost of immunoglobulin is about \$100/g, plus additional costs for infusion. The hyperimmune immunoglobulins are even more costly. Many medical centers have a pharmacy committee that must approve the use of immunoglobulin for each patient.

After immunoglobulin use is approved, the route, the IG product to be used, and the dose must be considered. The location and the training of the personnel responsible for the infusion must be established. The patient's history should be explored for reactions to prior IG administration, known allergies, and the presence of conditions that may predispose to adverse reactions.

Laboratory studies recommended prior to the first infusion include a complete blood count, blood chemistries, tests for chronic viral disease (hepatitis B, hepatitis C), immunoglobulin levels, and if the patient is anemic, a direct Coombs' test. For immunodeficient patients vaccine antibody titers for diagnosis of immunodeficiency must be obtained prior to infusions since the IG given will elevate their titers and obscure the diagnosis of antibody deficiency. Many physicians save a serum sample before and after the first infusion for study if there is an adverse reaction.

The manufacturer, lot number and details of the infusion should be recorded including premedication given and adverse reactions. If one brand of IG has been tolerated, switching to another brand is discouraged [20].

Dosage

IGIM Dose

The dose for prevention of infection by 16% regular IGIM or the hyperimmune IGIMs or IGIVs is dependent on the patient's weight and is given in the package inserts or in the pediatric Red Book [21]. Large weekly doses of IGIM for immunodeficiency are no longer used because of the discomfort and painful local side effects of these injections [15,22].

IGIV Dose

The usual recommended dose of IGIV for immunodeficiency is 300 to 500 mg/kg given every 3 to 4 weeks. The usual initial rate of infusion is 0.01 mL/kg/minute, which provides 0.5 or 1 mg/kg/minute of IgG depending whether a 5% or a 10% IGIV is used, respectively. These

recommended doses and rates may vary slightly in the package inserts of various products. The infusion rate can be doubled every 20 to 30 minutes until a rate of 0.08 mL/kg is achieved. The infusion usually takes 2 to 4 hours. This may be longer if higher doses are given or shorter if the patient has tolerated a more rapid rate or shorter interval between doses.

Higher doses of IGIV are used for autoimmune and inflammatory diseases, typically 1 to 2 g/kg per dose, and repeated at regular intervals. I recommend that the daily dose of no more than 1 g/kg/day be given to most patients under age 60 and no more than 500 mg/kg/day be given to patients over age 60 or to high risk patients. Patients requiring higher doses can get 500 mg/kg on subsequent days. The maximal dose is usually based on a weight of 70 kg, regardless of the patient's actual weight.

SCIG Dose

The usual dose for SCIG is also 300 to 500 mg/kg/month, similar to the IGIV dose. Infusions are usually given weekly at 25% of the monthly dose. Thus a weekly dose of 100 mg/kg (400 mg/kg/month requires a subcutaneous infusion of 1.0 mL/kg of a 10% IG product or 0.5 mL/kg of a 20% IG product. This is usually given slowly using a portable infusion pump. Multiple sites on the abdominal wall, thighs or arms can be used so that no more than 5 to 30 mL is given at a single site, depending on the patient's weight. Because of the lessened risk of systemic side effects, SCIG can be given at home, often by self-infusion, and without premedication [14,18].

Pathogenesis of Adverse Events

Adverse reactions may be due to the antigenicity of the IgG itself, large molecular weight IgG aggregates, the presence of an antibody to a circulating microbial antigens or self antigens, complement activation or direct release of cytokines from mononuclear cells. The product may contain low molecular weight kinins or kallikreins or procoagulant factors not removed during fractionation.

The presence of these factors vary considerable from brand to brand and even lot to lot of the same product. The presence of factors in the product can sometimes be identified, eg, high levels of IgA causing anaphylactic reactions, erythrocyte antibodies causing hemolytic reactions, procoagulant activity causing thrombotic episodes (Table 1).

A search for the cause of a reaction is often unrewarding, although the product can be tested for erythrocyte antibodies, procoagulant activity and autoimmune antibodies. Post-infusion serum levels for tryptase, complement activation products or circulating immune complexes may help define the type of a reaction that has occurred. Adverse effects may occur with any IGIV product so that switching brands may not prevent another reaction.

Table 1

Factors in some IG products associated with adverse effects

Microbial contamination (viruses, bacteria, endotoxins)
Immune complexes
Trace amounts of IgA
Low pH
Sugars: glucose, maltose, sucrose
High osmolality
High levels of sodium
Procoagulants
Vasoactive enzymes; kallikreins, others
Erythrocyte antibodies; Anti-A, -B, -D, -Kell; others
Antibodies to human leukocyte antigens
Antibodies to neutrophil or platelet antigens
Pathogenic autoimmune antibodies (eg, antiphospholipid antibodies)
Procoagulant coagulation factors (Factor XIa)
Preservatives (thimerosal)

Adverse Reactions to IGIV Infusions

Adverse reactions to IG can be local (at the infusion site) or systemic, involving the body as a whole or a specific organ (eg, kidney, skin) or system (eg, nervous system, hematologic system). Adverse systemic reaction are immediate (60% of reactions), occurring during or within 6 hours of the infusion, delayed (40% of reactions) occurring 6 hours to 1 week after an infusion, or late (<1%) occurring greater than 1 week after an infusion (Table 2). Late reactions may occur weeks or months after an infusion.

Local adverse reactions to IGIV are rare and include pain, bleeding, or bruising at the needle site. Prolonged pain and swelling may occur when venous access is difficult or if there is fluid extravasation into the tissues.

Systemic adverse reactions to IGIV are common and varied (Table 2), occurring in 20–40% of patients at one time or another and in 5% to 15% of all infusions [23–27]. The most common immediate reactions are chills, fever, headache, and muscular pain [26–28,30,32]. These usually are mild and occur within an hour of starting an infusion and disappear within 6 hours. Reactions are more likely to occur with the first infusion, a fast infusion, a large infusion, a long interval since the prior infusion, a switch to a new product and the presence of intercurrent infection.

The reported rates of adverse events vary considerably depending on the type of patients studied and the brand of the immunoglobulin used. In a review of 9 different trials of new IGIV products in immunodeficient subjects, Schroeder et al reported that adverse systemic reactions occurred in 26% to 44% of all patients and 5% to 27% of all infusions [28].

Systemic adverse reactions are rare in immunodeficient patients receiving the same dose of a previously well tolerated brand given at the same interval from the prior infusion. Struff et al reported that among 1705 patients at 72 centers given 15,548 infusions of the same product, only 10 patients (0.6%) had an adverse systemic reaction with an overall rate per infusion of 0.064% [29]. In a similar study of 459 patients at 4 centers given 13,508 infusions, Brennan et al [30] reported 111 systemic reactions (0.8%) in 59 patients (13%) [30].

Higher rates of systemic reaction rates are reported in other patient groups. Chapel et al reported that adverse events occurred in

12% of 442 infusions given to 82 multiple myeloma patients [31]. Singh-Grewal et al reported an adverse event in 26% of 58 children and 25% of infusions. Delayed headache was particularly common, occurring in 34% of patients and 13% of infusions [32].

The highest rate of systemic adverse events occur in non-immunodeficient patients with autoimmune, neurologic or hematologic disease given high dose IGIV, eg, 1 to 2 g/kg. Donofrio et al reported that 18% of infusions and 55% of 113 patients with chronic inflammatory polyneuropathy developed systemic reactions to high dose IGIV [33]. Kishiyama et al found that 40% of asthmatic patients had an adverse reaction to high dose IGIV [34]. Sekul et al reported that 56% of 54 neurologic patents developed severe headaches (six developed aseptic meningitis) following high dose of IGIV [35]. Hommes et al reported that 71% of 159 patients with multiple sclerosis had a systemic reaction to high dose IGIV [36].

Many of these side effects can be minimized or prevented by oral premedication with an antihistaminic such as diphenhydramine and a non-steroidal anti-inflammatory agent such as acetaminophen. Oral or intravenous corticosteroids can be given if the patient has had a prior reaction or is high risk for a reaction. Treatment of most immediate reactions include slowing or stopping the infusion, giving additional non-steroidal anti-inflammatories, an antihistaminic or corticosteroids. Other drugs used occasionally include promethazine for nausea and vomiting, diazepam for muscle spasms, narcotics for severe pain, and antimigraine medications for prolonged headache.

Adverse Reactions to SCIG Infusions

Local reactions to SCIG infusions are common. The pain from the needle insertion is minimal because of the tiny needles used. Nearly 75% of patients have some discomfort associated with the swelling and redness at the site of the infusion [14,17]. The swelling usually subsides within 24 to 48 hours. These local effects may lessen with subsequent infusions, making it unnecessary to rotate sites; indeed site-specific tolerance may develop [17]. The volume of each infusion can also be reduced by giving smaller doses more frequently, sometimes even daily, without the use of a pump [39]. These local adverse effects are rarely severe, and do not usually deter patients continuing with this route.

Systemic reactions to SCIG infusions are rare. Gardulf et al reported 30 systemic reactions in 25 immunodeficient patients given 3232 infusions (0.93%) [14]. A subsequent report from their group reported only 106 adverse reactions in 33,000 subcutaneous infusions [17]. A direct comparison of reactions to SCIG and IGIV infusions in the same patients was conducted by Chapel et al in a crossover study in 40 immunodeficient patients receiving IGIV or SCIG for one year and then switched to the other route for a second year [15]. They recorded an adverse reaction in 51 of the 684 IVIG infusions (7.5%) and in 32 of the 1222 subcutaneous infusions (2.6%), a significant difference.

Because of the infrequency of these side effects, premedication is rarely necessary nor is close monitoring during the infusion. Other studies also confirm that systemic reactions are most unusual with SCIG infusions [18,19,37–40]. This low rate of systemic reactions makes close monitoring during SCIG infusion unnecessary and thus an ideal route for home use.

Less Common Specific Adverse Reactions

Anaphylactic/Anaphylactoid Reactions

Anaphylaxis with urticaria, itching, flushing, chest tightness, dyspnea and wheezing, acute anxiety and circulatory collapse is most uncommon. This usually occurs shortly after the start of the infusion. Anaphylaxis usually occurs in patients with some ability to make antibody, notably non-immunodeficient patients, or immunodeficient patients that can make some antibody, eg, selective IgA

Table 2

Adverse effects associated with human immunoglobulin use

Mild adverse effects (common, usually immediate*)
Infusion site pain, swelling, erythema *
Headache *
Myalgia, back pain, arthralgia *
Fever, chills, flushing *
Anxiety, malaise, fatigue *
Nausea, vomiting *
Hypotension, hypertension, tachycardia *
Hyponatremia **
Neutropenia **
Direct Coombs' positivity **
Moderate adverse effects (less common, usually delayed)**)
Persistent headache **
Aseptic meningitis **
Hemolytic anemia **
Serum sickness/arthritis **
Dermatologic complications **
Interference with vaccine effectiveness and/or immunodiagnosis ***
Severe adverse effects
Anaphylactic/anaphylactoid reaction *
Renal complications **
Pulmonary complications **
Thrombosis/embolism **
Colitis **
Blood borne Infectious diseases ***

* Immediate reaction—within 6 hours from onset of infusion.

** Delayed reaction—6 hours to 1 week after infusion.

*** Late reaction—weeks-months after infusion.

deficiency and common variable immunodeficiency. These reactions are treated with epinephrine, antihistamines, corticosteroids, fluids and oxygen as needed. No fatalities have been reported.

Anaphylactic reactions have not been reported with subcutaneous IGIV; indeed patients with anaphylactic reactions to IGIV may tolerate slow subcutaneous IGIV [40,41].

Anaphylactoid reactions resemble anaphylactic reactions but are not IgE mediated. They usually develop several hours after starting the infusion, and may not occur earlier or at all with subsequent infusions.

Serious side reactions are potentially life-threatening, and emphasize the necessity of close monitoring of patients during the infusions by trained personnel at a facility with emergency equipment and access to a facility near an emergency facility.

Anaphylaxis in IgA Deficient Patients

Anaphylaxis following IGIV infusions may occur in patients with anti-IgA antibodies that react to the trace quantities of IgA found in most IGIV products [42,43]. Anti-IgA antibodies commonly develop in individuals with complete IgA deficiency who are exposed to IgA in IGIV or other blood products. These persons have some antibody function; most have selective IgA deficiency or common variable immunodeficiency [44,45]. The anti-IgA antibodies are usually of the IgG class and only rarely of the IgE class and either class of antibodies has been associated with rare anaphylactic reactions to IGIV. Indeed most IGIV product brochures contain a warning of the risk of giving IGIV to patients with IgA deficiency. Note that IGIV therapy is not indicated as treatment for IgA deficiency without concomitant IgG antibody deficiency [45].

Rachid and Bonilla found that anti-IgA antibodies are commonly present in normal individuals (2–7%) but are present in up to 30% of IgA deficient individuals [40]. They identified only three reports of anaphylaxis associated with IgE anti-IgA antibodies but identified 23 reports of anaphylaxis associated with IgG anti-IgA antibodies. Four other IgA-deficient patients had non-anaphylactic moderate systemic reactions. They also identified reports of 49 IgA-deficient patients with IgG anti-IgA antibodies that tolerated IG products.

Based on these studies, the consensus is that it is unnecessary to check IgA levels prior to an initial IGIV infusion for most patients. Nor is it necessary to measure anti-IgA antibodies in patients with IgA deficiency prior to IGIV infusions. Similar to other patients receiving their first IGIV infusion, premedication and a slow infusion rate should be used. Tests for IgA deficiency and anti-IgA antibodies should be sent in patients who experience a severe adverse reaction to IGIV. These patients (as well as other patients with a serious adverse reaction to IGIV) may be switched to subcutaneous IG infusions [40,41]. IgA-deficient patients and other patients with anaphylactic reactions to IGIV generally tolerate subcutaneous IG infusions well [40,41].

Headaches/Aseptic Meningitis/Central Nervous System (CNS) Complications

Headaches are a common complaint during or shortly after IGIV infusions. They often persist for several hours or even days. They may also have a delayed onset 6 to 12 hours after an infusion. Headaches are particularly common with high dose IGIV therapy as used in neurologic or autoimmune diseases. Headaches usually subside within 24 hours and are responsive to analgesics. Occasionally however the headaches are associated with nausea and vomiting, muscle aches and prolonged malaise, and are refractory to non-narcotic analgesics.

Some headaches are persistent, severe, and accompanied by neck stiffness, photophobia, fever and severe myalgia. Spinal puncture in early cases disclosed cerebrospinal fluid pleocytosis (both granulocytic and lymphocytic), elevated cerebral spinal fluid protein, and sterile viral or bacterial cultures, indicating a syndrome of aseptic meningitis. The first case of aseptic meningitis following IGIV was

reported in 1988 [46]. The onset is usually 6 to 24 hours after the infusion [47]. Patients with a history of migraine headaches are more susceptible to this complication [35].

Aseptic meningitis is usually associated with high dose IGIV therapy (1–2 g/kg) for thrombocytopenia or neuromuscular diseases [25,26], but has occasionally been observed in immunodeficient patients given standard doses [48].

The cause of aseptic meningitis is not known but its occurrence with high dose suggests that the CNS inflammatory response may result from small quantities of IgG in the cerebrospinal fluid, causing inflammation and osmotic shifts of the meninges. Some IGIV brands are more likely to cause aseptic meningitis for unknown reasons. Jarius et al have suggested that antineutrophil antibodies in some IGIV products may activate neutrophils in the CNS [49].

Treatment consists of analgesics, anti-emetics, and anti-migraine therapy. Steroids or anti-TNF drugs can be used in severe cases. If IGIV must be continued, infusions should be given in smaller increments, with slower rates and with a different IGIV brand. Aseptic meningitis is very rare with subcutaneous IG [50].

Other neurologic adverse events following IGIV infusions include encephalopathy, vasospasm, cerebral thrombosis, embolism, infarction, and vasculitis [51–56].

Renal Complications

Renal insufficiency following IGIV is not uncommon, particularly in older individuals receiving high IGIV doses. Barton et al in 1987 first reported renal failure after IGIV in a 39-year-old woman with lymphoma and cryoglobulinemia [57]. They postulated that immune complexes caused glomerular necrosis. Jordan in 1989 observed hematuria and proteinuria in 3 patients with glomerulonephritis given IGIV [58]. Schifferli et al in 1991 observed an asymptomatic increase in serum creatinine in 8 patients with chronic renal disease given IGIV [59]. Other patients have severe renal failure requiring dialysis [60]. Eighty-eight reports of renal failure or other features of renal dysfunction were reported to the US Food and Drug Administration (FDA) from 1985 to 1998 [60]. Most occurred in patients with pre-existing renal disease receiving a sucrose-containing IGIV product.

The first manifestation of renal toxicity is an increase of the BUN or creatinine, followed by oliguria and renal failure, peaking 5 to 7 days following the infusions. This may be complicated by hemolysis, serum sickness, thrombosis, hyponatremia and hyperkalemia. The renal failure may require dialysis and renal transplantation [60,61].

Nearly all such complications are associated with high dose IGIV for hematologic or neurologic diseases in patients with pre-existing renal disease. Other risk factors include older age, diabetes, vascular disease, and dysproteinemias such as multiple myeloma or cryoglobulinemia.

Most cases are attributable to the sugar stabilizers with the IGIV, particularly sucrose; the latter accounts for up to 88% of these reactions [60]. Maltose in IGIV has also been implicated [62]. Sucrose is not metabolized in the kidney; it localizes in the proximal tubule and causes swelling, osmotic nephrosis, and injury to proximal renal tubules [62–64]. There is now an FDA black box warning on IGIV products containing sucrose.

Prevention and treatment includes checking renal function prior to treatment, prehydration, avoiding volume depletion by diuretics, using slow infusion rates, and limiting the IGIV dose to no more than 0.5 g/kg/day.

Thromboembolism

Thrombotic events associated with IGIV were first reported in 1986 by Woodruff et al in 4 adults treated with IGIV for autoimmune thrombocytopenia [65]. Since then multiple cases have

been identified. The exact incidence is not known but may be as high as 10% in certain high risk populations [66,67]. Patients receiving single IGIM injections, subcutaneous IG infusions, and 5% IGIV for immunodeficiency are less likely to be affected, mostly because they receive low doses. Fatalities have been observed due to heart attacks, CNS thrombosis, and veno-occlusive disease in transplant patients [55,65–67].

The thrombosis in 80% of reported cases is arterial (eg, heart attack, stroke) occurring within hours or days of an infusion [67–69]. Venous thrombosis (20% of cases) generally occurs days or weeks after an infusion (eg, deep vein thrombosis, pulmonary embolism). Local thrombosis at the site of infusion has been recorded [70]. CNS thromboses include cerebral sinus thrombosis and jugular vein thrombosis [51,53–55]. Thrombotic events have been listed as complications in several IGIV trials [71–74].

Possible mechanisms are hyperviscosity, increased platelet count or adhesiveness, autoimmune procoagulant antibodies, or coagulation factors in the IGIV not removed by fractionation [75–79]. Certain IGIV brands with a high risk for thromboembolism contain activated factor XI. Several IGIV lots and a 16% product for subcutaneous use have been withdrawn from the US market as a result of such procoagulant properties. New regulations may include routine testing for procoagulant properties.

Patient risk factors for thrombosis are multiple (Table 3). More than one risk factor multiplies the risk [66]. Preventive measures as listed in Table 4 include identifying high risk patients, performing screening tests, prehydration, and premedication such as aspirin and/or enoxaparin. Huang et al reduced the rate of thrombosis associated with IGIV use in renal transplant recipients from 9 in 275 infusions to none in 74 infusions using a protocol of pre-infusion hydration, aspirin/enoxaparin and slow infusion rate [69]. Tissue plasminogen activator has been used in the treatment of thrombotic events [80].

Hemolysis

IGIV administration may result in mild hemolytic reactions, usually due to the presence of anti-A or anti-B isoagglutinins or, less commonly, anti-D or anti-K antibodies [81–87]. These blood group antibodies often result in a slight degree of hemolysis, mild hyperbilirubinemia, and a positive direct Coombs' test. These events are usually subclinical and thus overlooked. Isoagglutinin levels are

Table 3
Risk factors for IG adverse effects

Infusion factors
1. Prior history of infusion reaction
2. First infusion
3. Large dose
4. Rapid dose
5. No pre-infusion or post-infusion hydration
Patient factors
1. Fever/infection at time of infusion
2. Autoimmunity
3. Older age
4. Immobility/air travel
5. Hypertension
6. Present or past cardiovascular disease
7. Diabetes
8. High lipids/cholesterol
9. Elevated serum proteins/gammopathy
10. Smoking
11. Prior/current thrombosis
12. Estrogen use
13. Hereditary hypercoagulable state (Factor V Leiden, prothrombin mutations, Protein C, S, or antithrombin III deficiencies)
14. Permanent indwelling venous catheter (ie, Portacath)

Table 4
Minimizing risk of thrombosis for IGIV infusions

1. Limit daily IGIV dose to 400–500 mg/kg. If larger dose is needed, give repeat dose(s) on a subsequent day(s).
2. Consider pre-/post-infusion hydration
3. Use slow infusion rate, eg, 50 mg/kg for first hour, 100 mg/kg/hour, thereafter
4. Avoid "as tolerated" dose escalation
5. Premedicate with ASA or heparin/enoxaparin in high risk patients
6. Test for hypercoagulable tests/viscosity/dysproteinemias
7. Do Doppler tests for clots in bedridden patients

variable in immunoglobulin preparations and are not routinely measured. Cross matching prior to IGIV is not usually done.

In some instances significant hemolysis may occur with a fall in hemoglobin of 1 to 5 g/dL. Daw et al recognized 16 cases of clinically significant hemolysis among 1000 IGIV-treated adults (1.6%) given IGIV [87]. The decrease in hemoglobin was from 0.8 to 5.2 g/dL and the cumulative dose of IGIV was 50 to 350 g. Three patients required transfusions. Contributing factors included non-group O blood, female sex, a large cumulative IGIV dose and underlying inflammatory disease. Other risk factors that may contribute to clinically significant hemolysis include non-secretor status (with absence of circulating A and or B substance) [87], high isoagglutinin titer in the IGIV product [87], and coadministration of products such as platelets or plasma containing additional isoagglutinins [87].

Renal failure due to hemolysis and hemoglobinuria was reported, necessitating hemodialysis [64]. Fatal disseminated intravascular coagulation due to Rh immune globulin use for immune thrombocytopenia has also been reported [88].

IGIV has also been used successfully for autoimmune hemolytic anemia, indicating its ability to result in a therapeutic Fc blockade overrides its potential for further hemolysis [89].

Neutropenia

Transient asymptomatic neutropenia has followed IGIV administration. It generally occurs 2 to 4 days after an infusion, and lasts for less than a week [90–92]. No infectious complications have been reported.

One possible mechanism is granulocyte activation with increased adhesive molecule expression with increased margination [93]. von Gunten et al identified anti-Siglec-9 autoantibodies (anti-sialic acid-binding Ig-like lectin 9) in some batches of IGIV and suggest that these antibodies, in conjunction with proinflammatory cytokines such as granulocyte macrophage-colony stimulating factor and interferon- γ , may induce neutrophil death [93].

Lassiter et al reported prolonged neutropenia (lasting three weeks) in a premature infant given four infusions of IGIV for allo-immune thrombocytopenia [94]. They attributed this to anti-neutrophil antibodies present in the IGIV.

Pulmonary Toxicity

Mild wheezing or dyspnea are not uncommon immediate reactions (Table 2). Serious but very rare pulmonary complications include pulmonary embolism, pulmonary edema, pleural effusion, and transfusion-related lung injury associated with fever and hypotension [95–97]. The latter complication may be associated with neutrophil antibodies or human leukocyte antigen antibodies resulting in leukocyte aggregation in the lung [97].

Hyponatremia

The plasma sodium may drop 10 to 20 mEq/L shortly after an IGIV infusion. This hyponatremia is usually dilutional and asymptomatic, and results from the large amount of sucrose or maltose

present in the IGIV [98,99]. This increases the osmolality of the blood and results in an influx of fluid to the extracellular compartment, with dilution of the plasma volume, and a subsequent drop in sodium concentration.

A similar fall in plasma sodium may result since the large amount of protein in the IGIV increases plasma volume, without affecting the aqueous concentration, ie, pseudohyponatremia [100]. In both dilutional hyponatremia and pseudohyponatremia, a true sodium deficiency does not exist so additional sodium is not necessary and possibly detrimental.

Enterocolitis

Necrotizing enterocolitis in premature infants following IGIV for hemolytic disease of the newborn has been reported [101,102]. The hemolysis may aggravate the hypercoagulability of premature blood.

One case of reversible ileitis in an adult given IGIV for renal transplant neglect has also been reported [103].

Infectious Diseases

Hepatitis C infection following IGIV infusions given in the early 1990s was reported from several countries involving several IGIV and anti-D products [104–108]. These occurred after the US FDA recommended that all donors positive for Hepatitis C antibody be excluded from the donor plasma pools. Thus the IGIV from these pools had no hepatitis C virus (HCV) antibodies to neutralize HCV in the HCV-antigen positive donors who escaped detection since they were in the seronegative window period during early infection. The hepatitis was of varying severity and sometimes fatal [108]. Other patients cleared their infection with or without antiviral agents [107,108]. Subsequently new viral inactivation processes (solvent-detergent, pasteurization) and polymerase chain reaction assays for HCV were adopted and there have been no cases of hepatitis C from IGIV since 1996 [109].

Parvovirus B19 is not destroyed by solvent-detergent or heat treatment, so may appear in IG preparations. The parvovirus antibodies in these preparations probably prevent most clinical infection, although two cases have been reported [110,111]. Chronic parvovirus infection causing anemia is often treated with IGIV [6].

Prion disease (eg, variant Krutzfeld-Jakob (mad cow) disease) has not been recorded as a result of immunoglobulin therapy. A theoretical risk remains based on a case of its transmission by blood transfusion [112]. Tests for prions are in development as are methods for their removal [113,114].

Ziegner et al [115] reported a series of immunodeficient patient with progressive neurodegeneration who had been exposed to immunoglobulin preparations. None had proven prion disease.

No cases of HIV have been transmitted by IG products, probably because the fractionation process removes or inactivates this very labile virus [110,113].

Dermatologic Complications

Rare dermatologic complications following IGIV have been reported including eczema [116–118], alopecia [119], erythema multiforme [120], dyshidrosis [121], and baboon syndrome [122].

Other Rare Events

Single reports of adverse events include uveitis [123], hypothermia [124], non-infectious hepatitis [125], and serum sickness with arthritis [126].

Interference with Immune Diagnosis, Vaccine Responsiveness, and Endogenous IgG Synthesis

Recent immunoglobulin therapy (within 3–4 months) may prevent an accurate assessment of baseline serum IgG levels (but not IgM, IgA, or IgE levels). The antibodies in the administered IGIV also prevent the use of serum antibody levels to determine the presence of past infections. Further the IGIV may interfere with the antibody response to administered vaccines, particularly live virus vaccines such as measles, varicella and shingles vaccines [127].

Long term administration of IG therapy inhibits endogenous IgG synthesis (if present initially) for several months after the IGIV is discontinued [128,129].

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