Rare Adverse Effects of Human Immunoglobulin Therapy

Less-common adverse reactions to IG therapy are rare, but they are more severe.

By E Richard Stiehm, MD

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 (IVIG), intramuscularly (IGIM) or by subcutaneous infusions (SCIG).

Local adverse reactions such as persistent pain, bruising, swelling and erythema are rare with IVIG infusions but common (75 percent) with SCIG infusions. By contrast, adverse systemic reactions are rare with SCIG infusions but common with IVIG infusions, occurring in as often as 20 percent to 50 percent of patients and 5 percent to 15 percent of all IVIG infusions. Systemic adverse reactions can be immediate (60 percent of reactions) occurring within six hours of an infusion, delayed (40 percent of reactions) occurring six hours to one week after an infusion, and late (less than 1 percent 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.

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 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 considerably from brand to brand and even lot to lot of the same product. The presence of factors in the product can sometimes be identified, e.g., high levels of IgA causing anaphylactic reactions, erythrocyte antibodies causing hemolytic reactions, or 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 reaction that has occurred.

Adverse effects may occur with any IVIG product, so switching brands may not prevent another reaction.

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, e.g., selective IgA 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 SCIG; indeed, patients with anaphylactic reactions to IVIG may tolerate slow SCIG.[1,2]

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 IVIG infusions may occur in patients with anti-IgA antibodies that react to the trace quantities of IgA found in most IVIG products.[3,4] Anti-IgA antibodies commonly develop in individuals with complete IgA deficiency who are exposed to IgA in IVIG or other blood products. These persons have some

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 (e.g., antiphospholipid antibodies)
Procoagulant coagulation factors (Factor XIa)
Preservatives (thimerosal)

Table 2. 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 (i.e., Portacath)

antibody function; most have selective IgA deficiency or common variable immunodeficiency.[5,6] 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 IVIG. Indeed, most IVIG product brochures contain a warning of the risk of giving IVIG to patients with IgA deficiency. Note that IVIG therapy is not indicated as treatment for IgA deficiency without concomitant IgG antibody deficiency.[6]

Rachid and Bonilla found that anti-IgA antibodies are commonly present in normal individuals (2 percent to 7 percent) but are present in up to 30 percent of IgA-deficient individuals.[1] 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 who tolerated IG products.

Based on these studies, the consensus is that it is unnecessary to check IgA levels prior to an initial IVIG infusion for most patients. Nor is it necessary to measure anti-IgA antibodies in patients with IgA deficiency prior to IVIG infusions. Similar to other patients receiving their first IVIG 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 IVIG. These patients (as well as other patients with a serious adverse reaction to IVIG) may be switched to SCIG infusions.[1,2] IgA-deficient patients and other patients with anaphylactic reactions to IVIG generally tolerate SCIG infusions well.[1,2]

Headaches/aseptic meningitis/central nervous system (CNS) complications. Headaches are a common complaint during or shortly after IVIG infusions. They often persist for several hours or even days. They may also have a delayed onset six to 12 hours after an infusion. Headaches are particularly common with high-dose IVIG 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 IVIG was reported in 1988.[7] The onset is usually six hours to 24 hours after the infusion.[8] Patients with a history of migraine headaches are more susceptible to this complication.[9]

Aseptic meningitis is usually associated with high-dose IVIG therapy (1g/kg to 2 g/kg) for thrombocytopenia or neuromuscular diseases,[10,11] but has occasionally been observed in immunodeficient patients given standard doses.[12]

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 IVIG brands are more likely to cause aseptic meningitis for unknown reasons.

Jarius et al. have suggested that antineutrophil antibodies in some IVIG products may activate neutrophils in the CNS.[13]

Treatment consists of analgesics, antiemetics, and antimigraine therapy. Steroids or anti-TNF drugs can be used in severe cases. If IVIG must be continued, infusions should be given in smaller increments, with slower rates and with a different IVIG brand. Aseptic meningitis is very rare with SCIG.[14]

Other neurologic adverse events following IVIG infusions include encephalopathy, vasospasm, cerebral thrombosis, embolism, infarction and vasculitis.[15-20]

Renal complications. Renal insufficiency following IVIG is not uncommon, particularly in older individuals receiving high IVIG doses. Barton et al. in 1987 first reported renal failure after IVIG in a 39-year-old woman with lymphoma and cryoglobulinemia.[21] They postulated that immune complexes caused glomerular necrosis. Jordan in 1989 observed hematuria and proteinuria in three patients with glomerulonephritis given IVIG.[22] Schifferli et al. in 1991 observed an asymptomatic increase in serum creatinine in eight patients with chronic renal disease given IVIG.[23] Other patients have severe renal failure requiring dialysis.[24] Eighty-eight reports of renal failure or other features of renal dysfunction were reported to the U.S. Food and Drug Administration (FDA) from 1985 to 1998.[24] Most occurred in patients with pre-existing renal disease receiving a sucrose-containing IVIG product.

The first manifestation of renal toxicity is an increase of the BUN or creatinine, followed by oliguria and renal failure, peaking five to seven 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.[24,25]

Nearly all such complications are associated with high-dose IVIG 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 IVIG, particularly sucrose; the latter accounts for up to 88 percent of these reactions.[24] Maltose in IVIG has also been implicated.[26] Sucrose is not metabolized in the kidney; it localizes in the proximal tubule and causes swelling, osmotic nephrosis and injury to proximal renal tubules.[26-28] There is now an FDA black box warning on IVIG products containing sucrose.

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

Thromboembolism. Thrombotic events associated with IVIG were first reported in 1986 by Woodruff et al. in four adults treated with IVIG for autoimmune thrombocytopenia.[29] Since then, multiple cases have been identified. The exact incidence is not known but may be as high as 10 percent in certain high-risk populations.[30,31] Patients receiving single IGIM injections, SCIG infusions and 5% IVIG 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.[19,29-31]

Table 3. Minimizing Risk of Thrombosis for IVIG Infusions

1. Limit daily IVIG dose to 400 mg/kg to 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, e.g., 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

The thrombosis in 80 percent of reported cases is arterial (e.g., heart attack, stroke) occurring within hours or days of an infusion.[31-33]

Venous thrombosis (20 percent of cases) generally occurs days or weeks after an infusion (e.g., deep vein thrombosis, pulmonary embolism).

Local thrombosis at the site of infusion has been recorded.[34] CNS thromboses include cerebral sinus thrombosis and jugular vein thrombosis.[15,17-19] Thrombotic events have been listed as complications in several IVIG trials.[35-38]

Possible mechanisms are hyperviscosity, increased platelet count or adhesiveness, autoimmune procoagulant antibodies, or coagulation factors in the IVIG not removed by fractionation.[39-43] Certain IVIG brands with a high risk for thromboembolism contain activated factor XI. Several IVIG lots and a 16% product for subcutaneous use have been withdrawn from the U.S. 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 2). More than one risk factor multiplies the risk.[30] Preventive measures as listed in Table 3 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 IVIG use in renal transplant recipients from nine in 275 infusions to none in 74 infusions using a protocol of pre-infusion hydration, aspirin/enoxaparin and slow infusion rate.[33] Tissue

plasminogen activator has been used in the treatment of thrombotic events.[44]

Hemolysis. IVIG 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.[45-51] 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 variable in immunoglobulin preparations and are not routinely measured. Cross matching prior to IVIG 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 1,000 IVIG-treated adults (1.6 percent) given IVIG.[51] The decrease in hemoglobin was from 0.8 g/dL to 5.2 g/dL, and the cumulative dose of IVIG was 50 g to 350 g. Three patients required transfusions. Contributing factors included non-group O blood, female sex, a large cumulative IVIG 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),[51] high isoagglutinin titer in the IVIG product ,[51] and coadministration of products such as platelets or plasma containing additional isoagglutinins.[51]

Renal failure due to hemolysis and hemoglobinuria was reported, necessitating hemodialysis.[28] Fatal disseminated intravascular coagulation due to Rh immune globulin use for immune thrombocytopenia has also been reported.[52]

IVIG 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.[53]

Neutropenia. Transient asymptomatic neutropenia has followed IVIG administration. It generally occurs two to four days after an infusion, and lasts for less than a week.[54-56] No infectious complications have been reported.

One possible mechanism is granulocyte activation with increased adhesive molecule expression with increased margination.[57] Von Gunten et al. identified anti-Siglec-9 autoantibodies (anti-sialic acid-binding Ig-like lectin 9) in some batches of IVIG and suggest that these antibodies, in conjunction with proinflammatory cytokines such as granulocyte macrophage-colony stimulating factor and interferon-γ, may induce neutrophil death.[57]

Lassiter et al. reported prolonged neutropenia (lasting three weeks) in a premature infant given four infusions of IVIG for alloimmune thrombocytopenia.[58] They attributed this to anti-neutrophil antibodies present in the IVIG.

Pulmonary toxicity. Mild wheezing or dyspnea are not uncommon immediate reactions (Table 4). Serious but very rare pulmonary complications include pulmonary embolism, pulmonary edema, pleural effusion and transfusion-related lung injury associated with fever and hypotension.[59-61] The latter complication may be associated with neutrophil antibodies or human leukocyte antigen antibodies resulting in leukocyte aggregation in the lung.[61]

Hyponatremia. The plasma sodium may drop 10 mEq/L to 20 mEq/L shortly after an IVIG infusion. This hyponatremia is

Table 4. 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 **
Bloodborne infectious diseases ***

* Immediate reaction—within six hours from onset of infusion
** Delayed reaction—six hours to one week after infusion
*** Late reaction—weeks to months after infusion

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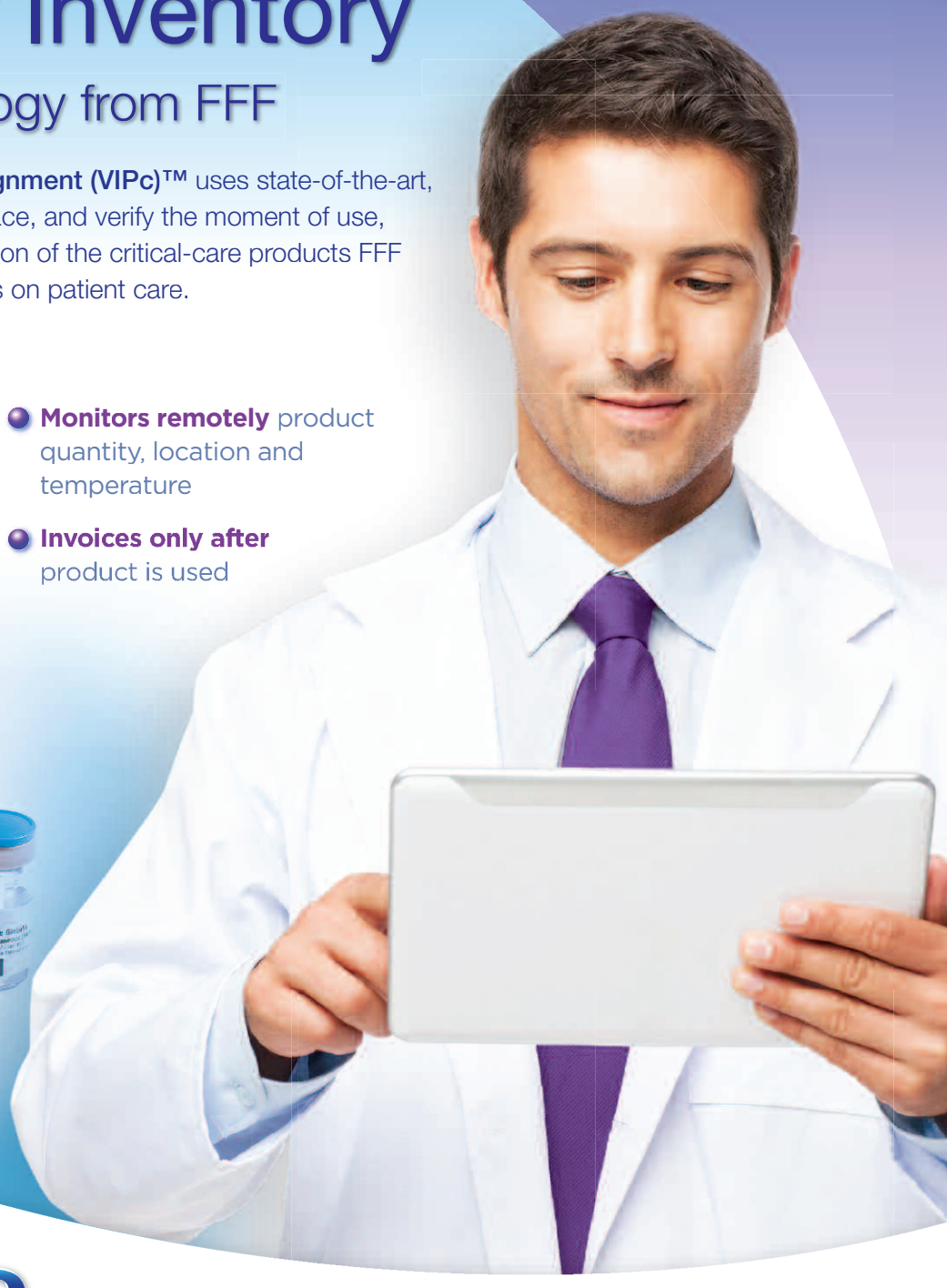

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usually dilutional and asymptomatic, and results from the large amount of sucrose or maltose present in the IVIG.[62,63] This increases the osmolality of the blood and results in an influx of fluid to the extracellular compartment, with dilution of the plasma volume, and a subsequent drop in sodium concentration.

The search for the cause of a reaction is often unrewarding, although the product can be tested for erythrocyte antibodies, procoagulant activity and autoimmune antibodies.

A similar fall in plasma sodium may result since the large amount of protein in the IVIG increases plasma volume without affecting the aqueous concentration, i.e., pseudohyponatremia.[64] 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 IVIG for hemolytic disease of the newborn has been reported.[65,66] The hemolysis may aggravate the hypercoagulability of premature blood.

One case of reversible ileitis in an adult given IVIG for renal transplant neglect has also been reported.[67]

Infectious diseases. Hepatitis C infection following IVIG infusions given in the early 1990s was reported from several countries involving several IVIG and anti-D products.[68-72] These occurred after the FDA recommended that all donors positive for hepatitis C antibody be excluded from the donor plasma pools. Thus, the IVIG 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.[72] Other patients cleared their infection with or without antiviral agents.[71,72] 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 IVIG since 1996.[73]

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.[74,75] Chronic parvovirus infection causing anemia is often treated with IVIG.[76]

Prion disease (e.g., variant Creutzfeldt-Jakob [mad cow] disease) has not been recorded as a result of IG therapy. A theoretical risk remains based on a case of its transmission by blood transfusion.[77] Tests for prions are in development, as are methods for their removal.[78,79]

Ziegner et al.[80] reported a series of immunodeficient patients with progressive neurodegeneration who had been exposed to IG 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.[74,78]

Dermatologic complications. Rare dermatologic complications following IVIG have been reported, including eczema,[81-83] alopecia,[84] erythema multiforme,[85] dyshidrosis,[86] and baboon syndrome.[87]

Other rare events. Single reports of adverse events include uveitis,[88] hypothermia,[89] non-infectious hepatitis[90] and serum sickness with arthritis.[91]

Interference with Immune Diagnosis, Vaccine Responsiveness and Endogenous IgG Synthesis

Recent IG therapy (within three to four months) may prevent an accurate assessment of baseline serum IgG levels (but not IgM, IgA or IgE levels). The antibodies in the administered IVIG also prevent the use of serum antibody levels to determine the presence of past infections. Further, the IVIG may interfere with the antibody response to administered vaccines, particularly live virus vaccines such as measles, varicella and shingles vaccines.[92]

Long-term administration of IG therapy inhibits endogenous IgG synthesis (if present initially) for several months after the IVIG is discontinued.[93,94] ❖

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References available upon request.

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