

Intravenous immunoglobulin: Adverse reactions and management

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The cold ethanol precipitation method developed by Cohn in the 1940s yields almost pure IgG suitable for intramuscular immunoglobulin or subcutaneous immunoglobulin (SCIG) administration with little modification other than inactivating or removing pathogens. These preparations are concentrated (16% wt/vol) and contain 5% to 10% of the IgG as large aggregates causing potentially fatal systemic anaphylactoid reactions if administered intravenously. Intravenous immunoglobulin (IVIG) products contain 1% or less of the total IgG in small aggregates and have a final concentration of 3% to 12%. IVIG products differ in their excipients (preservatives and inhibitors of IgG aggregation) and physical/chemical characteristics (eg, lyophilized powder or liquid and pH). Each product has a slightly different adverse reaction profile, although there are very few published comparisons of one product with another.

There are no clinical tests or predictors to guide selection of a particular IVIG product for individual patients. Some tolerate all products, some have symptoms with all products, and some tolerate only certain products. Unfortunately, third parties and availability often dictate choice of product, and therefore patients and physicians might be limited in their alternatives if adverse reactions are problematic.

ADVERSE REACTIONS TO IVIG

Adverse reactions to IVIG can be classified as systemic or organ specific. A systemic reaction leads to constitutional symptoms (eg, fatigue, malaise, fever, flushing, chills, anorexia, myalgia/arthritis, "flu-like" symptoms, and anaphylactoid symptoms; [Table I](#))¹ that might or might not be associated with effects on 1 or more organ systems. Generalized IVIG reactions vary in severity. Mild reactions do not require cessation of therapy, are not associated with significant vital sign changes, and respond promptly to symptomatic therapy. Severe reactions require stopping the infusion and resuscitation. Moderate reactions fall in between. Mild-to-moderate reactions occur in 5% to 15% of infusions overall, as stated in the manufacturers' prescribing information and reports of clinical trials. At some point during the course of therapy, 20% or more of patients experience such reactions.

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Abbreviations used

CVID: Common variable immunodeficiency

IVIG: Intravenous immunoglobulin

NSAID: Nonsteroidal anti-inflammatory drug

SCIG: Subcutaneous immunoglobulin

Severe reactions occur in less than 1% of patients. In one prospective audit of adverse reactions to IVIG over 2 years in almost 400 patients with immunodeficiency (>13,000 infusions), the overall reaction rate was very low (0.8%), and there were no events judged to be severe.² Thus absence of anaphylaxis in this audit indicates a rate of this complication of less than 0.007%. The reason for such a low rate compared with that reported by manufacturers is unclear. This could be due to a large fraction of these patients receiving medications before infusion; this is not permitted (at least initially) in tolerability assessment of IVIG products in clinical trials. IVIG reaction rates might be higher when larger doses of IVIG are used (eg, for autoimmunity), but this has not been measured in a large population.

The most common organ-specific IVIG reactions are neurologic. Headache is the most reported symptom, occurring in 5% to 20% of infusions and up to one third or more of patients overall ([Table I](#)). Most headaches begin during or within 1 day of the infusion and respond to nonprescription analgesics. Rarely, the headache is severe (migraine) or is part of an aseptic meningitis syndrome. This can begin any time within 72 hours after infusion and is associated with all of the clinical features of aseptic meningitis, including a lymphocytic cerebrospinal fluid pleocytosis. Other neurologic manifestations are rarer and idiosyncratic, including muscle or bone pain, dysesthesia, and subjective weakness.

Analysis of reports involving 52 patients experiencing renal failure after administration of IVIG showed that 58% had pre-existing renal insufficiency.³ Renal function should be monitored before and during therapy in all patients. Products containing sucrose had a higher rate of renal adverse effects, although they have been observed with many other IVIG formulations.

A variety of other organ systems can be affected after IVIG administration ([Table I](#)). Again, most symptoms are mild or moderate and easily controlled. Rare, recurring, troublesome, severe reactions require careful consideration of the costs and benefits of continued therapy.

Space does not permit a detailed discussion of anti-IgA antibodies. IgG anti-IgA antibodies have been associated anecdotally with anaphylactic IVIG reactions, mainly in patients with common variable immunodeficiency (CVID) having undetectable IgA; the mechanism is not established.⁴ The actual risk of such a reaction has not been determined. Note that 10% to 25% of patients with CVID have measurable IgG anti-IgA levels; patients with CVID represent a sizable fraction of those with immunodeficiency who receive IVIG, yet anaphylaxis is rare (see above).²

TABLE I. Symptoms and signs that can occur after IVIG infusion

System	Common (%)*	Rare
Constitutional or systemic (generalized)	Fatigue (5), malaise, fever (19), flushing, chills, anorexia, myalgia, arthralgia, joint swelling (7), "flu-like" symptoms (5), anaphylactoid symptoms (5)	Full-blown anaphylaxis
Neurologic	Headache (28), migraine (9), dizziness (4)	Aseptic meningitis, diffuse pain, dysesthesia, weakness
Respiratory	Shortness of breath (10), cough, bronchospasm	Pleural effusion, TRALI
Cardiovascular	Hypotension (5), hypertension (7), chest pain (5)	Arrhythmia, myocardial infarction
Gastrointestinal	Anorexia, nausea (14), vomiting (12), cramping, diarrhea	
Renal		Tubular damage, renal failure
Cutaneous	Urticaria (10), nonspecific macular or maculopapular eruption (8), pruritus (3)	Erythema multiforme
Hematologic	Hemolysis (not clinically significant)	Thrombotic phenomena (DVT, stroke), hyperviscosity, neutropenia

TRALI, Transfusion-related acute lung injury; DVT, deep vein thrombosis.

*Percentage of approximately 1500 patients with primary immunodeficiency receiving IVIG who reported in a survey at least 1 occurrence (over the course of their therapy and not per infusion) of each symptom.¹ Note that these are patient reported and not physician diagnosed. Entries without percentages are reported in the literature but are not included in the reference cited.

MANAGEMENT OF ADVERSE REACTIONS TO IVIG

Mechanisms of adverse reactions to IVIG are largely unknown. The small amount of aggregated IgG might be responsible in some patients. IVIG can interact with microbial antigens in the recipient, leading to immune complex phenomena. Plasma-derived vasoactive or hemodynamically active contaminants in IVIG can cause some adverse effects. Ingredients added during manufacturing can also contribute. Space does not permit further discussion of possible mechanisms. Because mechanistic knowledge is lacking, management of adverse effects is directed toward symptom prevention and relief.

Mild reactions rarely require abandoning the infusion, but the rate should be slowed or halted until symptoms have subsided. Subsequent infusions can be administered more slowly, or smaller doses can be administered more frequently. However, this might cause inconvenience for patients. Premedication with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) and H1 antihistamines is often sufficient (children: acetaminophen, 10-15 mg/kg; ibuprofen, 10 mg/kg; diphenhydramine, 1 mg/kg; adults: acetaminophen, 650-1000 mg, ibuprofen, 200-400 mg; diphenhydramine, 25-50 mg). In the author's experience, cyproheptadine (children: 2-4 mg; adults: 4-12 mg) can be particularly helpful for headache associated with IVIG. If necessary, additional doses are given after infusion to treat symptoms.

If maximum doses of NSAIDs and antihistamines are insufficient, one can add additional medications, such as H2 blockers (eg, 25-75 mg of ranitidine for children and 75-300 mg for adults) and glucocorticoids (children: hydrocortisone, 25-100 mg; prednisone, 5-20 mg; adults: hydrocortisone, 100-200 mg; prednisone, 20-40 mg). The latter are particularly effective for preventing adverse reactions, although there might be reluctance on the part of patients and prescribers to administer these regularly, especially in children. Prehydration (where cardiovascular and renal status allow) with 10 to 20 mL/kg of normal saline can also be beneficial for some patients.

Patients who tolerate IVIG regularly can still rarely have a generalized reaction. Several factors predispose patients to a higher rate of systemic reactions: presence of infection, initiation of therapy or its resumption after a hiatus, change in IVIG product, high-concentration product, and rapid infusion rate. Conversely, the likelihood of generalized reactions is minimized by using a single product on a regular schedule, adherence to a

maximum tolerated infusion rate for each patient, and use of premedication. It is almost never appropriate to delay IVIG infusion because of the presence of infection. Delaying IVIG therapy is counterproductive and not indicated.

Moderate symptoms, such as bronchospasm, wheezing, vomiting, or vital sign changes unresponsive to slowing the infusion, require stopping the infusion and providing specific treatment. System-specific medications, such as bronchodilators and antiemetic agents, can be included in premedication when necessary. However, regimens consisting solely of NSAIDs and antihistamines often prevent even these types of organ-specific symptoms.

If preinfusion and postinfusion medications and manipulations of the IVIG dosing regimen do not control adverse reactions, one should consider changing the IVIG product, if possible. Another alternative is to use SCIG replacement therapy. Note that any product with a concentration of at least 10% formulated for intravenous or intramuscular administration can also be administered subcutaneously.⁵ The occurrence of systemic adverse effects with SCIG is much lower in comparison with that seen with IVIG. SCIG can be associated with short-lived (24 hours) mild-to-moderate local (skin/subcutaneous tissue) erythema, swelling, and tenderness that most patients tolerate well. Although it has not been well studied, there is reasonable theoretic basis to consider that some rare, serious, organ-specific adverse effects (aseptic meningitis syndrome and cardiovascular, renal, and hematologic effects) might also be less common with SCIG. Finally, patients with anti-IgA antibodies who have had anaphylaxis with IVIG have tolerated SCIG.⁴

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