Case Management of the Challenging IgG Patient: Clinical Considerations for the Most Effective and Safe Therapy

By Jerry Siegel, PharmD, FASHP
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Introduction

In a normally functioning immune system, immunoglobulins (Ig) are the most prevalent class of antibodies, defending the host from foreign invaders including bacteria, viruses, fungi, and other non-host particles. Immunoglobulin G (IgG) antibodies are the most abundant of the five types (A, D, E, G, and M), triggering action of the complement system and providing a critical cornerstone of the body’s immunological defense.

When the immune system is not functioning normally, IgG therapy, derived from the plasma of more than 1,000 individual donors, has proven to be a revolutionary treatment. There are two primary reasons why IgG therapy is administered: replacement therapy for patients with IgG deficiency, and immunomodulation for patients with immune-mediated disorders. Several mechanisms of action have been proposed for the immunomodulatory effects of IgG, depending on the underlying cause of the disorder being treated, but the exact mechanism of action remains elusive. The discovery and utilization of immunoglobulins has been evolving since the 1940s, with much still to be learned.

History and Indications

From 1944, when immune globulins were first identified, until the late-1970s, IgG could only be administered via intramuscular injection. Intramuscular immune globulin (IMIG) was used to treat primary immune deficiency disease (PID) and afforded young PID patients a great deal of freedom and quality of life—they were no longer required to live in sterile “the boy in the bubble” environments. However, the standard treatment of multiple (eight to 12), simultaneous injections was cumbersome to administer and extremely painful for the patient to receive. The ethanol-fractionization process used to isolate IgG from pooled plasma also led to aggregation of the IgG molecules. These aggregates in IgG acted as antigens when administered intravenously, triggering the complement cascade and leading to severe anaphylactoid-like infusion reactions.

Understandably, the advent of intravenous immune globulins (IVIG) in 1979 was a welcome development. New Ig preparations, isolated at low pH (e.g., pH 4) in the presence of traces of pepsin to inhibit re-aggregation, were well tolerated when administered intravenously. Thus a new era of treatment and prophylaxis of disease using IVIG was launched. The IVIG preparations revolutionized the management of virtually all immunodeficiency syndromes characterized by failure of antibody responses. Amelioration of antibody deficiency secondary to certain chronic diseases or surgical trauma can also be achieved with these preparations.

But, while IV administration offered advantages, many clinical parameters were still unknown, including the threshold for and severity of adverse reactions. With mindfulness toward these issues, and other unknown side effects, clinicians cautiously began the process of learning how to safely...
administer IVIG. Some of those first infusions proceeded very slowly (over 24 hours) under extremely guarded conditions (in the hospital with a crash cart nearby).

It wasn’t long before IVIG was shown to be safe for administration outside the hospital; it is now administered in the home and alternate-site settings via intravenous infusion, and increasingly via subcutaneous infusion (SCIG). As IVIG and SCIG are used in a growing number of indications (see Exhibit 1), clinicians must remain vigilant in managing adverse reactions, and selecting the most clinically appropriate product for each patient.

**Adverse Reactions to IVIG**

Adverse reactions to IVIG are as individual as the patients who receive it. Every patient has his/her own tolerance based on a variety of physiological factors, including the underlying condition being treated. Clinicians must work with each patient to understand their tolerance while also seeking a maximum effective dose and efficient infusion rate.

Patients can experience a variety of adverse reactions to IVIG, most of which can be managed through proper dosing, product selection, infusion rate, administration route, and the administration of other drugs before and/or after the infusion. Exhibit 2 describes the four main variables of adverse reactions, how each can affect the patient, and some adjustments that can be made to avoid or mitigate reactions.

It’s important to note that these variables often work in concert, making the clinical adjustment process as much an art as it is a science. Clinical experience is as important as clinical knowledge in this area, which is why there is no substitute for a high-caliber home infusion team that interfaces well with the patient and prescribing physician. This case management approach has proven safe and effective over time.

**Managing Common Adverse Reactions**

A patient database collected by the author over 10 years shows an average adverse reaction rate of three percent. Overall, less than one-third of patients (29%) experienced an adverse reaction, and less than 10 percent (7.6%) of all infusions resulted in a reaction. Because the patients who experienced reactions didn’t experience them with every infusion they received, the overall average is quite low. Many patients don’t have a reaction at all, or only experience a reaction when their infusion rate is increased.

The three most common reactions are chills, headache, and fever. Much less common, but more severe, are thromboembolic events—such as pulmonary embolism, deep vein thrombosis, myocardial infarction, hemolytic anemia, renal complications, and anaphylactoid reactions. For the more severe reactions, prevention is the best management. Clinicians should exercise caution when considering IVIG therapy in patients with pre-existing renal problems, diabetes, volume depletion, concomitant nephrotoxic medications, paraproteinemia, sepsis, or who are over age 65. Consider using lower concentrations, minimize sugars and saline, and administer slowly. For a complete listing of the pharmaceutical aspects of IVIG products, refer to Exhibit 3.

Following is a brief listing of IVIG reactions, categorized as “expected” or “unexpected,” why they occur, and some basic steps for managing them:

**EXPECTED IVIG ADVERSE EVENTS:**

- **Hypotension.** Changes in blood pressure occur during the infusion and are usually related to the infusion rate. Hypertension is fairly easily managed by reducing the rate of infusion. Hypotension during an infusion is more troublesome because it can indicate another problem. In cases where the patient’s blood pressure drops rapidly, it is suggested that the infusion be stopped.
**Exhibit 2**
**IVIG Administration Variables and How They Work**

<table>
<thead>
<tr>
<th>Variable</th>
<th>How it Works</th>
<th>Clinical Adjustments</th>
</tr>
</thead>
</table>
| **Infusion Rate** | As IVIG is being processed by the body, the antibodies are looking for antigens to fight. If infused too rapidly, they can set off the complement cascade, causing a host of adverse reactions ranging from headache, fever, and chills to shortness of breath, back and chest pain, and nausea and vomiting. | • Rate is everything. Each patient has a maximum infusion rate that s/he can tolerate—this may differ between brands.  
• Start new patients with slow infusions and gradually increase the rate to find tolerability—reducing the rate if signs of a reaction are observed.  
• If reactions persist with one brand, consider switching to another formulation (see below). |
| **Dosing**        | Original doses (100 – 150 mg/kg) were for replacement therapy with the goal of achieving an IgG level of >600 mg/dL. Dosing levels vary depending on the underlying disease and the purpose of the therapy (replacement vs. immunomodulation). Doses should be rounded up or down to the nearest vial size. Doses should also be adjusted for morbid obesity. Licensing studies for IVIG products were all done with actual body weight on patients with normal body mass index (BMI); however many patients exceed these parameters. Dosing for actual body weight can cause complications, such as kidney failure and thrombosis; dosing for ideal body weight can be ineffective. | • Split the difference between actual and ideal body weight—don’t forget to adjust the infusion rate for the new volume.  
• Make kinetic adjustments, looking to approach the maximum dose tolerated by the patient—each patient is different.  
• Consider choosing IVIG products that are non-carbohydrate and have low osmolarity.  
See Case Study 1 for more. |
| **Product Selection** | IVIG products are considered identical in clinical effectiveness, but their pharmacologic profiles vary. Different brands have different side effect profiles that can also be patient-specific. IVIG product features that can affect tolerability include:  
- Osmolality  
- Sodium content  
- Sugar content  
- IgA content  
- pH | Finding the right match for the patient is a critical clinical concern.  
• Nephropathy and renal failure can occur as a result of the hyperosmolarity and hyperviscosity driven by a sucrose (or other carbohydrate) stabilizer. Consider an IVIG product with a non-carbohydrate stabilizer in patients with compromised renal function.  
• Thrombosis can also occur due to hyperosmolarity. For patients at increased risk, consider products with low osmolarity (300-400 mOsmol/L).  
• Anaphylaxis can occur in patients with IgA deficiency and anti-IgA antibodies. Choose an IVIG product with low IgA levels for identified patients.  
See Case Study 2 for more. |
| **Administration Route** | Most IVIG infusions are given every 21 days and dosed to compensate for the IgG half-life. This creates a curve with a peak dose and waning efficacy. By giving smaller doses more often via the subcutaneous route, a constant level of IgG can be sustained, eliminating malaise at the end of a treatment period and often avoiding infusion-related reactions. | Switch to weekly SCIG infusions. The best site for SCIG is in the abdomen or anterior thigh (limit 15 mL per site). Using a simple infuser pump and split tubing, SCIG can be delivered to multiple sites in 30-45 minutes (rate should be <20 mL/hr). Injection site swelling and mild inflammation is normal.  
See Case Study 3 for more. |
In both hyper and hypotension, most patients typically develop a tolerance and generally do not require pre-medication. It is recommended that blood pressure be monitored pre- and post-infusion at home until a tolerable infusion rate is reached. If the patient appears intolerant, consider switching brands of IVIG, as each has a different side-effect profile.

- **Headache.** Almost all IVIG patients experience headache at some point during IVIG infusion. The condition is typically transient and related to the rate of infusion. In most cases, patients develop a tolerance, and no pre-medications are needed. If a tolerance is not reached even with pre-medications, consider switching brands as mentioned above.

- **Post-infusion headache.** This type of headache typically occurs hours to days after the infusion, is severe, and is often associated with nausea and vomiting. In some cases, headache has occurred as many as five to seven days post-infusion. In these instances, when the patient doesn’t make the connection and seeks medical care, the headache can be attributed to aseptic meningitis.

Unfortunately, most treatments are ineffective once the headache develops. If the condition is intolerable, consider switching brands of IVIG or consider administering it differently—long-term infusion or SCIG, for example.

- **Flu-like symptoms.** When present, flu-like symptoms generally occur hours to days following IVIG infusion. They can be treated effectively with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, and sometimes methylprednisolone and diphenhydramine. Pre-treatment with these drugs can also prevent flu-like symptoms from developing.

If the condition persists, consider switching brands of IVIG or consider administering it differently—long-term infusion or SCIG, for example.

- **Rash.** Rashes can occur following IVIG infusion and can be treated effectively with methylprednisolone and diphenhydramine. Pre-treatment with these drugs can also prevent the rash from developing.

If the condition persists, consider switching brands of IVIG or consider administering it differently—long-term infusion or SCIG, for example.

- **Severe back and leg pain.** This reaction is unique to IVIG and is characterized by intense pain. It can be treated with a triad of medications: methylprednisolone, diphenhydramine, and narcotics, which are also effective in preventing the reaction when used as a pre-treatment. Back and leg pain usually diminishes with subsequent infusions. If it persists, use a pre-treatment or consider switching brands.

- **Rigors.** This amphotericin-like reaction is characterized by fever and shakes (rigors). It can be treated with a triad of medications: methylprednisolone, diphenhydramine, and narcotics, which are also effective in preventing the reaction when used as a pre-treatment.

### Exhibit 3
**Pharmaceutical Aspects of IVIG Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Sodium Content</th>
<th>Sugar Content</th>
<th>Osmolality</th>
<th>IgA mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flebogamma® 5% DIF (liquid, 5%)</td>
<td>&lt;3.3 mEq</td>
<td>Polyl (sugar alcohol)</td>
<td>342-350 mOsm/kg</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Gammmagard™ S/D, (Polygam® S/D, lyophilized- no longer manufactured)</td>
<td>0.85% (at 5% concentration)</td>
<td>2% Glucose</td>
<td>5%: 636 mOsm/L; 10%: 1250 mOsm/L</td>
<td>&lt;2.2 (5% concentration); &lt;1 (separate 5% solution)</td>
</tr>
<tr>
<td>Gammmagard™ Liquid (liquid, 10%)</td>
<td>Trace</td>
<td>No sugar (glycine-based)</td>
<td>240-300 mOsm/kg</td>
<td>37</td>
</tr>
<tr>
<td>Gammunex™ (liquid, 10%)</td>
<td>Trace</td>
<td>No sugar (glycine-based)</td>
<td>258 mOsm/kg</td>
<td>46</td>
</tr>
<tr>
<td>Privige™ (liquid, 10%)</td>
<td>Trace</td>
<td>No sugar (L-proline–based)</td>
<td>240-440 mOsm/L</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Carmine® NF, (Panglobulin®, lyophilized- no longer manufactured)</td>
<td>0%-0.9%, depending on diluent</td>
<td>10% Sucrose (at 6% concentration)</td>
<td>In water: 3%: 192 mOsm/L; 6%: 384 mOsm/L In saline: 6%: 690 mOsm/L; 12%: 1074 mOsm/L</td>
<td>Trace</td>
</tr>
<tr>
<td>Octagam® (liquid, 5%)</td>
<td>&lt;30 mmol/L</td>
<td>10% Maltose</td>
<td>310-380 mOsm/kg</td>
<td>&lt;200</td>
</tr>
</tbody>
</table>
and meperidine. Other opioids are preferred over meperidine in elderly or renally compromised patients. If it persists, use a pre-treatment (consider tramadol), consider switching brands of IVIG, or consider administering it differently—long-term infusion or SCIG, for example.

- **Anaphylactoid reactions.** The incidence of these reactions is really quiet low (about one in 3,333), and may be related to IgA deficiency with anti-IgE or anti-IgG antibodies against IgA. To treat anaphylactoid reactions, stop the infusion immediately. Methylprednisolone, diphenhydramine, and epinephrine can be administered to stabilize the patient, open airways, and suppress inflammation associated with anaphylaxis.

For patients who are IgA deficient, anaphylaxis may be prevented by selecting products with the lowest levels of IgA, such as Gammagard S/D™ and Flebogamma®. Clinicians may also want to consider administering IVIG over a longer period or switch to SCIG administration.

**EXPECTED IVIG ADVERSE EVENTS:**

- **Renal complications.** The mechanical insult of hyperosmolarity and hyperviscosity driven by the carbohydrate (sucrose) stabilizer in some IVIG products has led to nephropathy and acute renal failure in a small number of patients. While sucrose itself is not the sole culprit, it was much less damaging in earlier IVIG formulations that didn’t exceed more than 3% solution, and when doses stayed below 150 mg/kg. As doses and concentrations increased (12% and >1000mOsm/L), the sucrose stabilizer and the hyperosmolarity it creates as a potential source of renal failure became more of an issue. Patients at risk for renal complications should receive IVIG products with osmolarity below 400 mOsm.

- **Thromboembolic events.** Pulmonary embolism, deep vein thrombosis, myocardial infarction, and hemolytic anemia can occur following IVIG administration for a variety of reasons, including elevated levels of coagulation factor XI, increased plasma viscosity, patient risk factors, and patient reaction to IVIG salt and sugar content. With patients who are at risk of thromboembolic events, choose lower IVIG concentrations, minimize sugars and saline, and slow the rate of administration.

- **Viral transmission.** IVIG is a blood product, and in the past was susceptible to contamination from microorganisms present in the blood of donors. For example, in the mid-1990s, hundreds of PID patients inadvertently received the hepatitis C virus. Thanks to new manufacturing steps such as solvent detergent, pasteurization, and caprylate treatments, viral transmission through IVIG no longer poses the same threat.

- **Prion transmission.** As with viral transmission, there is the potential danger of transmitting prions, infectious protein particles, through plasma-based products such as IVIG. Of particular concern is the transmission of Creutzfeld-Jakob disease. In the early-2000s, manufacturers began using nanofiltration to remove viruses, prions, and other infectious agents that could be present in pooled plasma. Because this process sorts molecules by size allowing only the immunoglobulins through the filter, it has the added benefit of guarding against organisms that have yet to be identified as threats.

**Case Study-Based Application of Knowledge**

As you read the following case studies, reference the preceding information in choosing from the available options to provide the best, most appropriate patient care.

**Case Study 1**

A 65-year-old woman is admitted to the hospital with suspected Guillain-Barre’ syndrome. She weighs 120 kg and has a history of myocardial infarction; her serum creatinine level is 2.0 mg/dL. Dosing is an issue because too high a dose (based on actual body weight) could cause severe adverse reactions, such as kidney failure or thrombosis, but too low a dose (based on ideal body weight) would be ineffective.

First Question: Which treatment options would you select for Case Study Patient 1?

1. IVIG with high osmolarity and low volume
2. Sucrose-stabilized IVIG (high osmolarity)
3. Plasmaphoresis
4. IVIG with low osmolarity and non-carbohydrate stabilizers
5. 3 & 4 are the best choices

Answer: 5- Patient could receive plasmaphoresis if available. Or this patient could receive a product that has a low osmolarity and non-carbohydrate stabilizers, given the evidence of her renal insufficiency.

Second Question: Which IVIG dose and infusion guidelines would you recommend?

1. Actual body weight of 120 kg with dose 120 gm/day for 4 days with rapid infusion protocol
2. Ideal body weight dose of 60 kg and dose of 60 grams/day for 4 days
3. Adjusted dosing weight of 90 kg with dose of 45 grams for 4 days
4. Actual body weight of 120 kg with dose of 60 grams for 4 days

Answer: 3-The best dose and infusion guidelines for this patient is to use an adjusted dose that splits the difference between actual and ideal body weight (90 kg with a dose of 45 g for 4 days).

**Case Study 2**

A 65-year-old woman with chronic IgG deficiency has been receiving IVIG infused at 40 g/month (400 mg/kg). Clinicians have used the standard three-phase escalation infusion and reached a maximum rate of 150 mL/hr. The patient...
was receiving Panglobulin® NF, but that product was discontinued. She is now receiving Gammagard® Liquid. After the second dosing escalation, she developed severe rigors.

**First Question:** Which is the best choice to treat the rigors?
1. Slow the infusion of IVIG
2. Administer meperidine 50 mg IVP
3. Administer morphine 4 mg IVP
4. Administer diphenhydramine 100 mg IVP
5. 2, 3, and 4

**Answer:** 5—2, 3, and 4 are all reasonable choices. The infusion must be stopped—slowing the rate will not work. Merperdine is the classic treatment for rigors however production of the active metabolite normeperdine, which is cleared through the kidneys, can lead to seizures in patients with renal insufficiency.

**Second Question:** For future treatments, which considerations are important?
1. IVIG can no longer be given
2. Change brand to Carimune® NF
3. Use same product with very slow infusion rate
4. Change to SCIG administration
5. Use high dose methyl-prednisolone as a pre-medication
6. 2, 3, and 4 are reasonable choices

**Answer:** 6—2, 3, and 4 are all reasonable choices. While rigors is not usually product specific, it may be a prudent option to switch the patient to Carimune® NF, which is the same formulation as the brand she was taking before it was removed from the market. Begin the next infusion very slowly, and if these steps prove unsuccessful, consider switching to SCIG administration.

**Case Study 3**
A 12-year-old boy has been receiving IVIG at a medical center infusion clinic monthly for primary immune deficiency. It has become increasingly more difficult to infuse because he experiences fever, chills, and headaches following the infusions, as well as malaise. The patient has missed at least two days of school post-infusion due to adverse reactions. Clinicians have slowed the infusion rate several times; the infusion time is now longer than eight hours. In addition, they are struggling to maintain venous access, as the patient’s catheter had to be removed due to infection.

**Question:** What is the next best course of action for this patient?
1. Discontinue the use of IVIG
2. Give high-dose prednisone as pre-medication
3. Increase rate of infusion
4. Consider SCIG
5. Give smaller doses more often
6. Both 4 and 5

**Answer:** The patient was switched to weekly SCIG so he could receive smaller doses more frequently. This allowed him to avoid the side effects that accompanied IV administration of higher doses, and eliminated the need for venous access.

**Stability of IVIG**
Most manufacturers recommend that once reconstituted, IVIG be used “immediately.” Since the proteins are very stable, the remaining concern is over the possibility of microbial contamination. A study conducted at Ohio State University in 1994 indicates that, despite the presence of sugars and proteins, IVIG is not a very effective growth media for bacteria and fungi. The risk of microbial contamination was low because the pH and tonicity in IVIG are not conducive to growth. In fact, formulations with lower pH levels were bacteriocidal. The data from this study—and subsequent 14 years experience—support extending the stability of IVIG to 72 hours when refrigerated.

**Future of IVIG**
While there are many effective formulations of IVIG already on the market, manufacturers will continue to seek the “ideal” IVIG—one that can be administered over a short period of time with minimal to no side effects. At the same time, they will undoubtedly continue to make improvements to safeguard against the transmission of viruses, prions, and other pathogens as they are identified.

In the near future, we can probably expect to see liquid products with new purification processes and higher concentrations with low osmolality, which would contribute to faster and safer infusion rates. Further down the pipeline, clinicians may see improved precision and efficacy through combination therapies and monoclonal Ig targeting. The distant future may bring further developments in the clinical treatment of the underlying diseases for which IVIG is effective. More precise diagnostic criteria, better prognostic indicators, and gene therapy for permanent improvement are just a few of the promising areas currently under investigation.

**References**
About the Speaker
Jerry Siegel is Senior Director of Pharmaceutical Services at the Ohio State University Medical Center in Columbus, Ohio. He is also Clinical Associate Professor and Assistant Dean of the Ohio State University College of Pharmacy. Dr. Siegel received his B.S in Microbiology, B.S. Pharmacy and Pharm.D. from The Ohio State University. He practiced as a clinical pharmacist in transplant and hematology/oncology prior to his administrative responsibilities. In addition, he was a recognized as an American Society of Health System Pharmacy (ASHP) fellow in 1996 for his work in immunology.

Dr. Siegel is a member of many professional societies including ASHP and the Ohio Society of Health-System Pharmacists, where he served as president. Throughout his career, Dr. Siegel has been honored with several awards such as the Walter Frazier Award and the Latiolais Leadership Award presented at ASHP in 2003. Dr. Siegel has published in numerous journals and textbooks and has presented nationally and internationally on a broad range of pharmacy topics from immunology to management issues.

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