Clinical Focus on Primary Immune Deficiencies

Primary Humoral Immunodeficiency: Optimizing IgG Replacement Therapy
IGIVs (Immune Globulin Intravenous (Human)) are all manufactured differently—but how does that impact a product’s efficacy or tolerability?

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Primary immune deficiency diseases (PIDD) are naturally occurring defects of the immune system and comprise a diverse group of illnesses. In the last decade, incredible progress has been made in the diagnosis and treatment of these diseases. Concerns remain about under diagnosis but important educational advances have certainly contributed to a dramatic increase in awareness and suspicion of PIDD in the general medical community. Continuing efforts to ensure that patients are diagnosed and treated as early as possible remain a priority. Importantly, rapid advances in defining the genetic bases of the diseases, the potential for antenatal diagnosis, and even prospects for successful gene therapy have all been accomplished. To date, 150-200 genetic defects have been defined (1).

Among the patients with PIDD are a group of disorders in which the ability to produce antibody is reduced or absent (Table 1). Such problems can be caused by defects intrinsic to the B lymphocyte (e.g., X-linked agammaglobulinemia in which B lymphocytes fail to mature) and by problems intrinsic to the CD4 helper T lymphocyte (e.g., X-linked Hyper-IgM syndrome). Patients may have defective humoral immunity with normal cell-mediated immune function, or defects of both arms of the immune system.

Increased susceptibility to infection is common to all of the primary humoral immunodeficiencies, with the possible exception of asymptomatic IgA deficiency. With the rapid institution of antibiotics, it is rare today to see osteomyelitis, meningitis or consolidated pneumonia as the presenting feature. More commonly, recurrent upper respiratory tract infections, such as otitis media and sinusitis are seen. Less commonly, patients develop mastoiditis, failure to thrive and chronic/recurrent diarrhea. In some forms of antibody deficiency, such as the hyper-IgM syndrome, autoimmune cytopenias, or infection with unusual pathogens such as Pneumocystis carinii or Cryptosporidium parvum infection, and chronic inflammatory disorders (e.g., sclerosing cholangitis) may be features of the disease.
The most common offending organisms generally are encapsulated bacteria, such as Hemophilus influenzae and Streptococcus pneumoniae. Patients with humoral immunodeficiency also appear to be uniquely susceptible to systemic mycoplasma infection, especially Ureaplasma urealyticum, M. hominis and other species (2-4). Indeed, some of the arthritis and osteomyelitis seen in these patients may be secondary to mycoplasma infection (2, 5). Similarly, acute and chronic lung disease may also be due to these organisms (3, 4). Often, the mycoplasma infections are insidious, evoking only a low grade febrile and leukocyte response. These organisms are very difficult to culture and do not respond to the usual antibiotics instituted for infections caused by encapsulated organisms. Tetracyclines or quinolones are often required to eradicate these organisms (2, 5).

The foundation for therapy of the humoral immunodeficiency diseases is immunoglobulin (IgG) replacement. This form of therapy has evolved significantly over the last 50 years. Bruton, in 1952, first treated his patient with subcutaneous injections of gammaglobulin. Intramuscular injections prevailed for almost 30 years until Bayer Pharmaceuticals introduced the first ready-to-use liquid preparation of modified gammaglobulin suitable for intravenous infusion in North America in the early 1980’s. Intramuscular gammaglobulin was generally injected at 0.6 cc (100 mg)/kg body weight. These injections were painful and limited the amounts injected. Nonetheless, even at these doses, reports of benefit emerged with reduction in febrile episodes and the incidence of infection. With the introduction of intravenous gammaglobulin replacement (IGIV), therapeutic strategies also changed. The ability to administer IgG intravenously provided the possibility to administer larger amounts. Several studies demonstrated the benefit of higher doses (400-600 mg/kg body weight) in infection prophylaxis and improvement in lung function (6, 7). Furthermore, the higher doses were associated with elimination of mycoplasma (8). It appeared that maintenance of trough levels (4 weeks post-infusion) above 500 mg/dL resulted in a reduction of major and minor infections, and the need for hospitalization. These studies also revealed individual variations in time to achieve a stable plateau at trough and in catabolic rates. These findings highlight the need to tailor IGIV regimens to the requirements of the individual patient and that a single fixed dose regimen may not be applicable to all patients.

Despite almost five decades of use and more than two decades of IGIV therapy, there is little documentation, which specifically addresses the efficacy of IGIV in the prevention of significant infections, especially pneumonia, and long-term and progressive lung disease. There has been reasonable documentation of the overall effectiveness of IGIV in preventing acute respiratory infections, otitis, and sinusitis, but some patients still suffer from these and gastrointestinal problems and other infections, despite institution of IGIV prophylaxis. Replacement IgG therapy, at standard doses, may not interrupt the occurrence or progression of permanent lung damage (9). Acute pulmonary infections may be significantly prevented, but not permanent lung damage (10). Patients who present with significant lung disease, such as bronchiectasis, prior to initiation of IGIV therapy, may continue to suffer from progressive lung disease. In turn, a subset of patients, despite optimal IGIV dosing and maintenance of adequate trough levels, may also develop permanent lung damage for reasons that are not currently understood. Chronic lung disease in patients with primary humoral immunodeficiency remains a major factor affecting quality of life and longevity.

At present, it is not known why “therapeutic failures” continue to occur despite the many advances in treatment. Surprisingly, in a recent survey carried out by the Immune Deficiency Foundation (IDF), 40% of patients felt that their disease was not optimally controlled and recurrent infections persisted. Approximately 60% complained that the effects of
IGIV were wearing off prior to their next scheduled infusion, even two weeks after an infusion. There are several possibilities to explain these incomplete responses, suggesting the need to regularly re-evaluate our approach to these patients.

**Management Guidelines**

Although the data may not be at hand, it makes empirical sense that the earlier the diagnosis and institution of appropriate therapy, the better the likelihood of preventing permanent lung damage. It is unclear if there are significant numbers of primary humoral immunodeficiency patients who are undiagnosed, who warrant therapy or whose therapy has been delayed. It is not surprising that the diagnosis may be delayed given the usual findings today that these patients most often present with common infections, such as otitis media and sinusitis, and initially respond appropriately to routine antibiotics. Indeed, a common presenting symptom in adults may be fatigue with little in the way of significant infections.

Once the diagnosis of (antibody) immunodeficiency is made, it is important to establish, at baseline, the extent of lung damage. The most effective way is to perform a high-resolution computed tomography (CT) scan of the chest (9). If lung damage, e.g., bronchiectasis, is detected at presentation, then management may need to be modified. Follow-up CT lung scans should be considered every 12-24 months, depending on the presenting features. Similarly, an initial CT scan of the paranasal sinuses may aid in the long-term management of these patients (Table 2).

The recent IDF survey also identified that 71% of patients were followed by primary care physicians and not by an immunologist. Primary humoral immunodeficiency is a lifelong and chronic disease requiring close co-operation between the patient, the primary care physician and the specialist.

<table>
<thead>
<tr>
<th>Table 2: Guidelines for Managing Patients with Antibody Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An immunologist should direct life-long care of the patient</td>
</tr>
<tr>
<td>• Assess pulmonary status with high resolution computed tomography (CT) and spirometry at baseline and every 12-24 months</td>
</tr>
<tr>
<td>• IgG replacement therapy at doses of at least 400-mg/kg/month and higher doses in patients where infections persist, especially bronchiectasis</td>
</tr>
<tr>
<td>• Institute appropriate antibiotic therapy when indicated</td>
</tr>
</tbody>
</table>

**Antibiotics**

A mainstay of therapy of antibody deficiency disorders is appropriate use of antibiotics. As discussed, patients with antibody deficiency disorders are susceptible to the common encapsulated bacteria (H. influenzae, S. pneumoniae), but also are uniquely susceptible to mycoplasma. The former are easy to culture, the latter are not and the specific antibiotics for each are quite different. Because of the difficulty in isolating the mycoplasmas, empirical therapy (e.g., doxycycline) may be indicated in patients with chronic/recurrent infection, who fail to respond to usual antibiotics.

**IgG Replacement**

IGIV is the current standard of therapy with few if any indications currently for intramuscular injections. Most patients receive IgG replacement via the intravenous route although some patients receive subcutaneous infusions (11). Suboptimal clinical outcomes could reflect a number of possibilities. Although there are no obvious differences in efficacy, careful scrutiny must be exercised as route and frequency of administration could potentially affect outcome. For example, it is not clear whether more frequent infusions at lower doses are more or less effective than larger infusions every three to four weeks. After appropriate training and the absence...
of a history of adverse reactions, infusion by either route can be performed at home. If monitored carefully, home infusion programs can be as effective as monthly visits to a recognized center under physician supervision. Convenience, however, is not a substitute for good medical management and home infusion programs do not replace the requirement for regular patient follow-up with physicians.

From the IDF survey, it appears that a significant proportion of patients may be under-dosed. Many of the product package inserts recommend monthly doses of 100-200 mg/kg body weight, but numerous studies have convincingly shown how dose and trough levels affect outcome. In a double blind, randomized study in PIDD patients, doubling the dose of IGIV (from 300 to 600 mg/kg body weight in adults and 400 to 800 mg/kg body weight in children) significantly reduced the number and duration of infections (12). Appropriate dosing is essential and should not be determined by costs, longer infusion times, or concerns about convenience.

**Mechanism of Action of IgG Replacement**

It is interesting to speculate on how IgG replacement works in the antibody deficiency diseases. Is it simply replacement of missing antibodies or do other potentially important activities come into play? For many organisms, the levels of specific antibodies are surprisingly low (e.g., against common serotypes of S. pneumoniae) and are not standardized from batch-to-batch or brand-to-brand (see below). Interestingly, there are virtually no detectable antibodies to the mycoplasmas, yet IGIV appears to play a role in their elimination or containment.

IGIV has also been shown to have a number of anti-inflammatory and immunomodulatory activities (13). These include inhibition of the production of pro-inflammatory cytokines, neutralization of bacterial exotoxins, modulation of Fcg receptors, triggering of lymphocyte apoptosis and prevention of deposition of the complement membrane attack complex. Whether any of these or other activities of IGIV play a role in these patients beyond antibody replacement is an interesting possibility.

**Are All IGIVs the Same?**

When surveyed, patients express four major concerns about IGIV: safety, supply, tolerability/adverse events, and outcome. For the patients, their physicians and other healthcare personnel, there has been an assumption that all eight licensed products in the United States are equivalent in these and other parameters. This assumption has in large part been fostered by the absence of any significant comparison data. However, these products do differ in terms of donor pools, manufacturing and final formulation. It is possible that a number of these differences can affect tolerability, risk of adverse events, infusion rate and efficacy.

Differences in basic fractionation and the addition of various modifications for further purification, stabilization and virus inactivation/removal have yielded products clearly different from one to the other (Table 3). There are well-established differences in chemical structure, antibody content, subclass distribution and electrophoretic profile. Further, the composition of the final product also differs widely. Some attempts at standardization, for example by a WHO Expert Committee on Biologic Standardization (14), has mandated that the IgG be as unmodified as possible, maintain its biologic function (opsonic activity, complement fixation, Fc-receptor binding), contain certain levels of specific antibody and meet accepted safety standards.

Despite meeting these standards, it is possible that the different preparations and the modifications used to enable safe intravenous administration can induce alterations in the biologic activity of the IgG molecule (15, 16). Whereas most commercial preparations are screened for levels of antibodies to several viral and bacterial antigens to validate purification procedures, there is little routine evaluation of the relationship between antibody
<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>Polygam S/D</th>
<th>Panglobulin</th>
<th>Gammar-P I.V.</th>
<th>Gammagard S/D</th>
<th>Ivecgam EN</th>
<th>Gamunex</th>
<th>Venoglobulin-S</th>
<th>Carimune NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer or Distributor</td>
<td>American Red Cross</td>
<td>American Red Cross</td>
<td>Aventis Behring, LLC</td>
<td>Baxter Corporation/ BioScience Division</td>
<td>Baxter Corporation/ BioScience Division</td>
<td>Bayer HealthCare/ Biologic Products Division</td>
<td>Grifols</td>
<td>ZLB Bioplasma, Inc.</td>
</tr>
<tr>
<td>Method of Production (Including Viral Inactivation)</td>
<td>Cohn-Oncley fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment</td>
<td>Kistler Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration</td>
<td>Cohn-Oncley fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment</td>
<td>Cohn-Oncley fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment</td>
<td>Cold ethanol fractionation, PEG, trypsin treatment</td>
<td>Cohn-Oncley fractionation, caprylate/chromatography purification, cloth and depth filtration, final container low pH incubation</td>
<td>Cold alcohol fractionation, PEG/Bentonite fractionation, ion-exchange chromatography, solvent detergent treatment</td>
<td>Kistler Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration</td>
</tr>
<tr>
<td>Form</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Lyophilized</td>
</tr>
<tr>
<td>Shelf-Life</td>
<td>24 Months</td>
<td>24 Months</td>
<td>24 Months</td>
<td>24 Months</td>
<td>24 Months</td>
<td>36 Months</td>
<td>24 Months</td>
<td>24 Months</td>
</tr>
<tr>
<td>Reconstitution Time</td>
<td>&lt;5 minutes at room temperature &gt;20 minutes if cold</td>
<td>Several minutes</td>
<td>&lt;5 minutes at room temperature &gt;20 minutes if cold</td>
<td>&lt;10 minutes at room temperature</td>
<td>None (Liquid Solution)</td>
<td>None (Liquid Solution)</td>
<td>Several minutes</td>
<td></td>
</tr>
<tr>
<td>Available Concentrations</td>
<td>5% 10%</td>
<td>3 to 12%</td>
<td>5%</td>
<td>5% 10%</td>
<td>5%</td>
<td>10%</td>
<td>5% 10%</td>
<td>3 to 12%</td>
</tr>
<tr>
<td>Maximum Recommended Infusion Rate</td>
<td>4 mL/kg/hour 8 mL/kg/hour</td>
<td>&gt;2.5 mL/kg/hour 3.6 mL/kg/hour</td>
<td>4 mL/kg/hour 8 mL/kg/hour</td>
<td>1.8 mL/kg/hour</td>
<td>4.8 mL/kg/hour 4.8 mL/kg/hour 3.0 mL/kg/hour</td>
<td>&gt;2.5 mL/kg/hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to Infuse 35 gms</td>
<td>2.5 hours 0.6 hours</td>
<td>&lt;3.3 hours (6% solution) 2.8 hours</td>
<td>2.5 hours 0.6 hours</td>
<td>5.6 hours</td>
<td>1.0 hours 2.1 hours 1.7 hours</td>
<td>&lt;3.3 hours (6% Solution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar Content</td>
<td>20 mg/mL glucose 40 mg/mL glucose</td>
<td>1.67 gm sucrose per gram of protein</td>
<td>50 mg/mL sucrose 20 mg/mL glucose 40 mg/mL glucose</td>
<td>50 mg/mL glucose</td>
<td>None</td>
<td>50 mg/mL D-Sorbitol</td>
<td>1.67 gm sucrose per gram of protein</td>
<td></td>
</tr>
<tr>
<td>Sodium Content</td>
<td>8.5 mg/mL sodium chloride 17 mg/mL sodium chloride</td>
<td>&lt;20 mg sodium chloride per gram of protein</td>
<td>5 mg/mL sodium chloride 8.5 mg/mL sodium chloride 17 mg/mL sodium chloride</td>
<td>3 mg/mL sodium chloride Trace Amounts</td>
<td>&lt;1 mEq/L</td>
<td>&lt;20 mg sodium chloride per gram of protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolarity/Osmolality</td>
<td>636 mOsm/L 1250 mOsm/L</td>
<td>192 - 1074 mOsm/kg 309 mOsm/L</td>
<td>636 mOsm/L 1250 mOsm/L</td>
<td>≥240 mOsm/L 258 mOsm/kg 300 mOsm/L</td>
<td>330 mOsm/kg</td>
<td>192 - 1074 mOsm/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH</td>
<td>6.4 - 7.2</td>
<td>6.4 - 6.8</td>
<td>6.4 - 7.2</td>
<td>6.4 - 7.2</td>
<td>4.0 - 4.5</td>
<td>5.2 - 5.8</td>
<td>6.4 - 6.8</td>
<td></td>
</tr>
<tr>
<td>IgA Content</td>
<td>&lt;2.2 µg/mL in a 5% solution 720 µg/mL</td>
<td>&lt;25 µg/mL</td>
<td>&lt;2.2 µg/mL in a 5% solution</td>
<td>&lt;10 µg/mL</td>
<td>46 µg/mL</td>
<td>15.1 µg/mL</td>
<td>20 - 50 µg/mL</td>
<td>720 µg/mL</td>
</tr>
</tbody>
</table>

1 Gamunex will replace Gamimmune N, 10% during the first half of 2004.
2 0.5 gm/kg for a 70 kg adult = 35 gms; 5% Concentrations: 1g = 20 mL; 10% Concentrations: 1g = 10 mL
The time to infuse is based on the maximal infusion rate.
titer and antibody function. Evaluation by determinations of antibody avidity or affinity, opsonic activity or viral neutralization that may be affected by the purification steps, is rarely carried out.

Comparative studies have shown differences and lack of consistency (product-to-product/batch-to-batch) that affect (reduce) opsonic activity (17-19). These and other differences related to enzyme treatment, chemical modification and fractionation, underscore the need for concerns about biologic efficacy and not simply meeting the standards established for protein electrophoretic profile and subclass determinations. These differences have also been extended to the protective effects of IGIV in patients with antibody deficiency (20). Although the commercial preparations are different with varying biologic activities, no systematic evaluation of the clinical implication of this fact has been reported, making it difficult for the clinician to select the best preparation for a specific indication.

Is there an “ideal” IGIV? The concept of ideal may vary significantly depending on the constituency queried – manufacturers require product integrity, the clinician is primarily interested in efficacy, while the patient may identify safety as the critical feature. For pharmacists, often in a central decision-making position, the acquisition cost of a product may be the major determining factor in product selection. However, selection based on acquisition cost alone may be more costly in the long run if biologic function or efficacy is compromised or adverse events are higher and need to be managed. Given the paucity of comparative trials or data, what factors or criteria may be used to help the clinician choose among the many products available? The factors include manufacturing process, safety, composition of the final product, tolerability and efficacy. As a consequence, many of the defined functions may also differ, as may a large number of the unknowns that contribute to efficacy in the wide-ranging number of diseases now being treated with IGIV.

Production of IGIV

IGIVs are prepared from plasma pooled from thousands of donors. Most production processes begin with sequential precipitation and fractionation with ethanol to isolate IgG from other plasma proteins. The material is subjected to freeze-drying to remove the ethanol and produce stable intermediates. Freeze drying in the presence of ethanol promotes formation of insoluble IgG aggregates. The IgG concentrates from initial fractionation are then subjected to additional processing to produce material suitable for intravenous administration. This is where major differences exist among products and where biologic function is most susceptible to alteration. Treatment with proteolytic enzymes generally gave way to chemical modification in an attempt to preserve the integrity of the IgG molecule, reduce aggregate formation and eliminate anti-complementary activity. Further modifications led to improved products, higher purity, improved stability and normal IgG subclass distribution.

Because of the different modifications used, it is not surprising that the different products vary when the amounts of IgG monomer, dimer and polymers are assessed, fragment levels are examined and the levels of excipient proteins are quantified (e.g., albumin). While they can vary from lot to lot within a product, the manufacturer’s specifications must be met. It is not unreasonable to assume that longer process times, more suspension/precipitation steps, and harshness of the treatment procedures contribute to some loss of the integrity of the IgG molecules and biologic function as well as create the potential for differences in efficacy, incidence of adverse events and batch-to-batch variability.

A major goal in improving the available products would be to increase yield (to help overcome supply issues), reduce processing time, minimize the harshness of the modification procedures, and ensure purity while maintaining batch-to-batch consistency.
**Product Characteristics**

*Liquid vs. Lyophilized*

The manufacturing process also impacts other important features. The first is whether the final product is in liquid form or not. Liquid preparations have been accepted as more convenient, easier to use and may be associated with fewer adverse events. In ready-to-use form, the liquid preparations shorten preparation time and delays for patients. When there is concern for wastage for example, if the patient does not show up for an appointment, liquid products can be returned to inventory and used later. Concerns about wastage often mean that preparation of lyophilized products does not begin until the patient arrives.

**Product Concentration**

The second consequence of the manufacturing process is product concentration. Products that can be given at higher concentrations decrease volume load, an important aspect in certain patient populations. For example, a 40 kg patient receiving 0.5 gm IGIV/kg body weight would receive 200 mL of a 10% solution compared to 400 mL of a 5% solution. Simply concentrating certain products by reconstitution in a smaller volume will increase the osmolality of the final solution and may contribute to significant adverse events such as renal complications or thromboembolic episodes (see below).

**Viral Inactivation**

Minimizing the risk of transmission of an infectious disease is now required during the manufacturing of IGIV. Safety standards have been implemented with respect to viral pathogens, including documentation of the capacity of the manufacturing process to remove or inactivate viruses. Plasma testing, both of individual donations using serological tests and manufacturing pools using polymerase chain reaction tests, is the initial step in providing source material that is free of high levels of clinically significant viruses. Accepted viral inactivation or removal steps include treatment with solvent detergent, polyethylene glycol (PEG), enzyme treatment including pepsin or trypsin, pasteurization, caprylate, acidification, PEG Bentonite, nanofiltration and depth filtration. Traditional calculation of overall process reduction of viruses has been based on the sum of reductions determined for individual production steps (21). An important aspect is the selection of complementary safety steps for incorporation into the manufacturing process. If these steps act through independent mechanisms in the inactivation/removal of viruses, they can be considered additive, thereby increasing overall safety and providing the widest possible safety margin against known and unknown viruses. Further validation of the robustness of these viral reduction steps, under conditions outside standard operating conditions adds to the safety margin.

Recently, a new IGIV product has been licensed: Gamunex, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified. The production process for Gamunex includes viral inactivation with the use of caprylate (caprylic acid), a naturally occurring octanoic fatty acid. Caprylate has been shown to be an effective virus inactivator with rapid kinetics and robustness when evaluated at different pH, temperature and protein concentrations (22). The kinetics of virus inactivation are much faster than seen with solvent detergent under many conditions. As time in the manufacturing process is a critical variable for quality of the end product, introduction of caprylate may not only be less harsh to the IgG molecule than solvent detergent or pasteurization, but could markedly shorten processing time. This shorter processing time could impact the quality of the end product.

Advances have also been made in effective screening for prion contamination on an experimental basis. Once fully evaluated, these methods may permit direct testing of the inactivation steps for reduction or elimination of the potential for prion contamination.
Product Composition
As discussed in a NIH consensus conference on IGIV (23), the variety of manufacturing processes, as well as starting materials, leads to differences among preparations that may be clinically important. Choosing the preparation of IGIV must take into account specific differences that can significantly impact the outcome in recipients (Table 4).

Fluid Volumes
Issues related to fluid load were discussed above and are linked to the final concentration of the solution. The ability to deliver higher amounts of IgG in lower volumes has a major impact on recipients who may be intolerant of large fluid volumes, such as infants or patients with congestive heart failure or renal insufficiency. In addition, larger fluid volumes require longer infusion times, a factor that patients may like to minimize.

Sugar Content
Various sugars (Table 3), sorbitol, glucose and sucrose have been added to some preparations as a stabilizer, preventing aggregate formation. Some products contain no sugar. The major problem associated with sugar content is the incidence of significant adverse events, particularly acute renal failure or insufficiency. Although rare, the CDC reported that 90% of the IGIV-associated renal adverse events in the United States occurred with sucrose-containing IGIV preparations (24).

Sodium Content
In the commercially available preparations, sodium content varies widely from trace amounts to 0.85% concentrations (Table 3). Caution must be exercised when lyophilized preparations are reconstituted to higher concentrations in an attempt to reduce volume load. In some instances, concentrating a lyophilized product from 5% to 10% can create a nearly 2% saline solution. Concerns about increased salt concentrations and association with significant adverse events and thromboembolic complications have been raised.

Osmolality
In IGIV solutions, the major contributors to osmolality include sodium, sugars, and other excipient proteins. Physiologic osmolality is 280-296 mOsm/kg of water. Solutions of IGIV range from physiologic osmolality to solutions that far exceed these levels, greater than 1,000 mOsm. Some sugar-stabilized products have higher osmolalities than sugar-free preparations. In reconstituting lyophilized preparations, careful attention to osmolality is required as significant adverse events may occur with solutions exceeding the physiologic range. With some lyophilized preparations, reconstitution to higher concentrated solutions results in hyperosmolar solutions.

pH
The pH optimum for IGIV to prevent aggregation is 4.0-4.5. As a consequence, for preparations at higher pH, agents are added to maintain stability and prevent aggregation. There are scattered reports that low pH may be associated with phlebitis.

IgA Content
Patients with selective IgA deficiency and the ability to produce antibodies may be at risk for
developing IgE or IgG anti-IgA antibodies resulting in reactions. Although anaphylaxis is a theoretical risk, it is indeed very rare; so rare that the NIH consensus conference did not recommend screening for anti-IgA antibodies in IGIV recipients (23). The content of IgA in a given preparation, except in the rarest of circumstances, is not usually an important factor.

**Isohemagglutinin Titers**

Preparations of IGIV do contain low-titered anti-A, anti-B, and anti-Rh blood group antibodies and they may be detectable, transiently, in post-treatment direct and indirect antiglobulin tests (25). There are no known reports of these antibodies in (non-hyperimmune) IGIV preparations being associated with hemolysis. The European Union Pharmacopea mandates that anti-A and anti-B titers be less than 1:64 in IGIV preparations.

**Antibody Titers**

There are marked differences in the levels of some antibodies among different preparations. Levels of certain antibodies, e.g., to tetanus or to ubiquitous organisms, such as H. influenzae type b, may not differ significantly. However, realization of such differences has prompted screening of certain preparations for higher titers to treat specific diseases, as for example, chronic ECHO virus meningitis in antibody-deficient patients (26). Differences in antibody titers can influence clinical outcomes as was shown in clinical trials of low birth weight neonates treated with IGIV - here antibody levels against S. epidermidis were an important factor in determining success or failure (27). As antibody levels may also play a role in the mechanism of action of IGIV in PIDD or different autoimmune and allergic diseases (e.g., anti-idiotype, anti-exotoxin/superantigen, anti-cytokine levels, etc.), these differences in antibody content between preparations could significantly determine efficacy of intervention with IGIV.

**Tolerability**

Tolerability, the ability to receive IGIV without incident and at rates that reduce the need for burdensome and long infusion times, varies markedly among preparations. In patients with primary immune deficiency diseases, the incidence of adverse events ranges from <5-16%, whereas the incidence of adverse events is higher among patients with immune-mediated diseases, such as immune thrombocytopenia. This may be related to differences in IGIV dose that is generally 0.5 gm/kg for immunodeficiency, but 1-2 gm/kg for immune-mediated diseases. The reactions most commonly seen include headache, fever, myalgia, chills, nausea and vomiting. The cause(s) of these reactions is not known but may be the result of aggregate formation. Many patients and clinicians notice differences among products in tolerability related to headache, fever, chills and shortness of breath. Transient elevations of serum ALT and AST without clinical correlation have been seen in some patients following infusions of different preparations of IGIV (28,29). Issues related to tolerability were significant enough to trigger a switch to another product in 24% of patients, while another 18% either refused a product or delayed the infusion in the recent IDF survey.

An important issue in the administration of IGIV is the rate of infusion as this relates directly to patient acceptability. The incidence of adverse events, including thromboembolic events, has been tied to the rate of infusion (30, 31). Current recommended rates fall within the range of 0.03-0.13 mL/kg/min, depending on the preparation. There are in fact relatively few studies examining the tolerability of rapid infusion of IGIV. The concentration of the solution and the rate will dictate the length of time an infusion will take (Table 3). With a 10% solution at a rate of 0.08 mL/kg/min (8 mg/kg/min, 480 mg/kg/hr), an infusion of 0.5 gm/kg would require about one hour to complete compared to a 5% solution, which would require two hours. Some IGIV preparations have slower recommended rates of infusion.
**Efficacy**

Ultimately, efficacy is a key and primary concern dictating selection of a particular product. There have been few, if any, comprehensive comparisons of efficacy made in a controlled, clinical trial setting. Recently, a direct comparison between products was made. In PIDD patients, infusion of Gamimune N 10% at equivalent doses and frequency of infusions was compared to infusion of a new product, Gamunex 10%. This multi-center clinical trial was unprecedented in many ways. More than 170 patients were enrolled compared to many previous licensure-relevant trials that enrolled 15-50 patients. This trial had clearly defined and clinically relevant end-points. The new product was manufactured by an entirely new process, which deliberately avoided harsh detergents; shortened production time (by 70%); and increased the efficiency of the entire process. Caprylate was used for rapid virus inactivation and as an additional purification step. The trial was powered to demonstrate non-inferiority showing that Gamunex was at least as effective as Gamimune N 10%. Yet, Gamunex showed in virtually all end-points, including incidence of validated infections, surprising differences in efficacy that challenge current perceptions that all products are expected to provide similar clinical outcomes. In particular, the incidence of validated infections was reduced to a level not previously reported in antibody-deficient PIDD patients (32). Controlled trials such as this one suggest that some differences in preparation and formulation might affect clinical outcomes. Confirming studies are needed to learn more about this intriguing possibility. How these differences potentially affect functional activity of the IgG molecule, IgG circulating half-life or other biologic functions remains to be determined.

**Conclusions and Recommendations**

1. Early diagnosis and institution of appropriate antibiotic and IGIV therapy are necessary to minimize long-term sequelae in PIDD patients with antibody deficiency.

2. Education of primary care physicians, pediatricians, internists, and otolaryngologists is necessary to minimize delays in diagnosis.

3. An integrated team approach, including the primary physician, specialist, infusionist, pharmacist, and the patient is necessary to optimize care.

4. Management can be optimized by establishing the level of baseline lung and sinus disease with CT scans and lung function tests and establishing a plan for regular follow-up to prevent lung disease progression.

5. Prompt institution of appropriate antibiotic therapy, especially in patients with chronic or recurrent disease is an important part of treatment.

6. The importance of appropriate dosing regimens specific to the needs of the individual patient should be recognized.

7. Differences among IGIV products (tolerability, risk of adverse effects, recommended rates of infusion and potentially efficacy) must be coupled with the needs of the patient to optimize outcome.

8. Physicians should make an effort to learn more about the products that have been carefully and stringently tested.
A review of medical literature reveals a wide range of IGIV (Immune Globulin Intravenous (Human)) related side reactions.

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The Immune Deficiency Foundation (IDF) is the national non-profit health organization dedicated to improving the diagnosis and treatment of primary immune deficiency diseases through research, education and advocacy. IDF was established more than two decades ago by concerned families of patients and their physicians. Since its inception, IDF has expanded to offer medical education, fellowship and research opportunities and publications. IDF sponsors a biennial National Conference for patients, their families and healthcare professionals.

More information about primary immune deficiency diseases and IDF can be found at www.primaryimmune.org or by calling 1-800-296-4433.