# IDF Guide for Nurses

## Immunoglobulin Therapy for Primary Immunodeficiency Diseases

Fourth Edition

Immune Deficiency Foundation

**IDF GUIDE FOR NURSES**

IMMUNOGLOBULIN THERAPY FOR
PRIMARY IMMUNODEFICIENCY DISEASES

FOURTH EDITION



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# IDF Guide for Nurses

Immunoglobulin Therapy for
Primary Immunodeficiency Diseases

*Fourth Edition*

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## Immune Deficiency Foundation

The Immune Deficiency Foundation (IDF), founded in 1980, is the national non-profit patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases (PI) through advocacy, education and research. There are approximately 250,000 people who are diagnosed with PI in the U.S., and thousands more go undetected.

Primary immunodeficiency diseases are a group of more than 300 rare chronic disorders in which part of the body's immune system is missing or functions improperly. Because one of the most important functions of the normal immune system is to protect us against infection, patients with PI commonly have an increased vulnerability to infections, which can be recurrent, unusually severe or won't clear up. People with PI can face frequent health problems and often develop serious and debilitating illnesses.

While not contagious, these diseases are caused by hereditary or genetic defects, and although some disorders present at birth or in early childhood, the disorders can affect anyone, regardless of age or gender. Some affect a single part of the immune system; others may affect one or more components of the system. While the diseases may differ, they all share one common feature: each results from a defect in one of the functions of the body's normal immune system.

Individuals affected by PI often find it difficult to receive proper diagnosis, treatment and specialized healthcare. IDF estimates that the average length of time between onset of symptoms and diagnosis is between nine and 15 years. Patients also experience difficulties financing their healthcare, finding educational materials on the disease and locating others with whom to share their experiences. IDF helps individuals overcome these difficulties.

Thousands of individuals and families affected by PI depend on IDF for advocacy, education and empowerment. Years ago, a diagnosis of a PI meant extremely compromised lives, not just for the patients but for their families as well. Today, with early diagnosis and appropriate therapies, many patients diagnosed with a PI can live healthy, productive lives.

## IDF Nurse Advisory Committee

### A Resource for Nurses and Patients

The Immune Deficiency Foundation established the IDF Nurse Advisory Committee in 1999. This committee is comprised of nurse experts who have many years of managing and providing care for patients with PI. The goal of the committee is to improve the quality of healthcare received by patients with PI. This goal is achieved primarily by educating and providing resources for patients' caregivers. The Nurse Advisory Committee also increases awareness of PI through professional education and outreach on local, national and international levels. The committee is instrumental in increasing educational and peer support opportunities for individuals and families affected by these rare, chronic diseases.

Although there are many types of PI, the clinical and immunologic features of which differ by the affected component of the immune system; antibody disorders (B-cell) comprise 55% of all PI[1]. Immunoglobulin (Ig) replacement therapy is the treatment indicated for patients with antibody disorders. The IDF Nurse Advisory Committee is proud to offer this guide to help nurses administer this therapy, safely and effectively, thus to improve the treatment experience and provide an improved quality of life for individuals living with PI.

The IDF Nurse Advisory Committee is a resource for those nurses who provide therapy for or treat patients with PI.

Many of the activities of IDF Nurse Advisory Committee are made possible by an unrestricted educational grant by CSL Behring.

# INTRODUCTION TO PRIMARY IMMUNODEFICIENCY DISEASES

Primary immunodeficiency diseases (PI) are a group of more than 300 disorders in which part of the body's immune system is missing or functions improperly. Some are relatively common; others are quite rare. These diseases are often lifelong, debilitating and costly. However, much progress has been made since the original description of a PI in 1952. Great strides have been made in understanding the genetics, characteristics and treatment of PI. Some types affect a single cell type within the immune system; others may involve more than one component of the system. PI is typically classified according to the part of the major components of the immune system involved, either the adaptive or innate components of the immune system. Each system has a specific function and works in concert with the other ***(See Table 1)***.

Regardless of whether the problem is with the adaptive or innate system, patients affected with PI are susceptible to infection and at risk for infection from virtually any pathogen. Even organisms that are not pathogenic in immunocompetent hosts can be pathogenic for people with immunodeficiencies. These infections can be unusually severe or recurrent and are often difficult to treat with conventional therapy. Occasionally, recurrent infections are not the predominant symptom at presentation. Some patients with immunodeficiencies present with autoimmune disease or a lymphoreticular cancer. As these disorders are considered rare, they may not be included in the differential diagnosis and may go unrecognized. IDF estimates that the average length of time between onset of symptoms and diagnosis is between nine and 15 years, although certain diagnoses will present much earlier in life than others.

Some types of PI are caused by a problem with a single gene; others are caused by defects in multiple genes. There can be a clear inheritance pattern, such as with those immunodeficiencies that are x-linked diseases. For other diseases, the inheritance pattern is less clear. It is believed that some types of PI develop over time and may be the result of a combination of genetic and environmental factors. Therefore, PI may present and be diagnosed at any age. PI may have overlapping features or be caused by combined immune defects. Similarly, there can be tremendous phenotypic and immunologic variability among individuals with the same diagnosis[2].

| Table 1: Comparison of the Innate vs. Adaptive Immune Systems[3] | | |
|---|---|---|
| | **Innate immunity** | **Adaptive immunity** |
| Components | ▪ Physical barriers, e.g., skin.<br>▪ Chemical barriers.<br>▪ Phagocytic cells, e.g., leukocytes.<br>▪ Natural killer cells, e.g., NK cells.<br>▪ Complementary proteins. | ▪ Humoral immunity, consisting of B cells and plasma cells.<br>▪ Cell mediated immunity, consisting of T cells, which mature into helper T cells (CD4 cells), suppressor T cells and cytotoxic T cells (CD8 cells). |
| Activity type | Cells of innate immunity are active all the time and are ready to combat pathogen as soon as a foreign body enters the human system.<br>These cells are active since birth. | Cells of adaptive immunity are normally in silent mode and become active only when the antigen is identified.<br>The cells of adaptive immunity develop over time. |
| Response | The response comes immediately, hence this process is also referred to as immediate immunity. | The initial response takes place after a week or two; it is also called delayed response type immunity. |
| Potency | Although the response is immediate, the effectiveness and potency is limited. | The potency and effectiveness levels are extremely high because the combat cells are highly specialized and powerful. |
| Time span | The immune response is directed towards the active infection, and becomes quiescent once the infection resolves. | Developed immunity can be lifelong or short-lived. Once activated against a specific type of antigen, the immunity remains throughout the life. |
| Inheritance | Innate immunity is generally inherited from parents and passed to offspring. | Adaptive immunity is not passed from the parents to offspring, hence it cannot be inherited. |
| Specificity | All types of pathogens are recognized including viruses, bacteria and fungi. | The cells are highly specific. |
| Memory | A same response is produced every time pathogen invades. | Memory cells are present, which lead to fast responses on subsequent exposure to the same antigen. |
| Diversity of response | The diversity among the response produced is very low. | Diversity is very high. |

Clinical presentation of PI is broad and highly variable. Patients may present with recurrent sinopulmonary infections[4]. In some patients, GI disorders may be the most prominent or only presenting complaint[5]. GI symptoms may overshadow respiratory disease and cause diagnostic delay. Autoimmune phenomena/disease (such as cytopenias) are relatively common and are seen in over 20% of patients[6] with Common Variable Immune Deficiency and can also mask the underlying diagnosis. Many patients with PI have significant co-morbidities. For example, a patient with recurrent pneumonias may have irreversible lung damage (bronchiectasis) because of the infections. However, co-morbidity is not limited to infection; in fact, noninfectious complications can be the most threatening and difficult to treat[7]. It is also known that patients with some PI's have a predisposition to autoimmune diseases such as rheumatoid arthritis. Sometimes the immunodeficiency is diagnosed after a presentation of autoimmune disease. With some types of PI, there is a higher risk of lymphoreticular malignancy, such as lymphoma, compared to that risk in the general population[6]. So a lymphoreticular malignancy can sometimes be the initial presentation of an immunodeficiency.

Diagnosis of a PI includes careful evaluation of the patient's family history, details of the clinical presentation and screening tests. Genetic testing may be ordered to determine a definitive diagnosis[8].

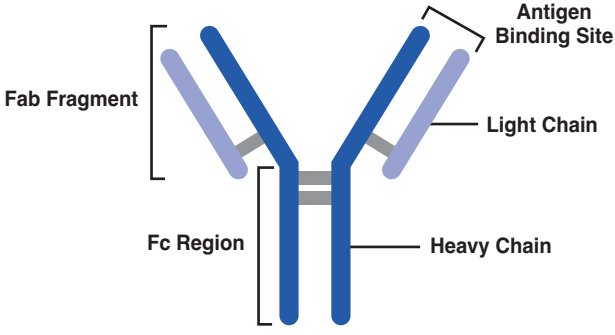
Patients with antibody disorders are the largest group of people with PI as approximately 55-60% of immundeficiencies are antibody disorders. These include patients with selective IgA deficiency—by far the most common PI—patients with hypogammaglobulinemia and impaired antibody responses, and patients with combined B and T cell problems. For some patients with these diagnoses, but not all, immunoglobulin (Ig) replacement therapy is the standard of care. This therapy provides replacement antibodies to patients who do not have adequate quantities and diversity of antibodies (deficient) or to those patients with antibodies of limited diversity that do not cover all types of infections.

# IMMUNOGLOBULIN

Immunoglobulin (Ig) is a solution of antibodies derived from pooled human plasma. All Ig preparations currently available in the U.S. are manufactured using donor pools from 10,000 to 60,000 units of donated human plasma. All contain IgG antibodies against a broad spectrum of vaccine antigens and infectious agents. All preparations contain ≥ 96% IgG. All products also contain some IgA and trace amounts of other plasma proteins. Brand differences exist in the manufacturing processes, viral inactivation and safety, as well stabilizing agents.

The FDA has established guidelines for Ig manufacturers that ensure all Ig products are safe and effective. Safety is demonstrated by rigorous monitoring of adverse reactions during the initial drug trials. Efficacy is demonstrated by rigorous monitoring of serious bacterial infections along with any other infections in those subjects participating in the trial[9]. Ig therapy affects many different pathways to modulate the immune and inflammatory responses. One mechanism of action of Ig is to neutralize antigens of infectious agents by providing antibodies to a wide range of bacterial and viral pathogens. Antigen binding is mediated by the Fab portion of the Ig molecule, whereas the effector functions include complement activation, complement binding and interaction with various Fc receptors *(See Figure 1)*. There have been a number of mechanisms described for immune modulation and anti-inflammatory actions including receptor blockades, complement inhibition, effects on regulatory T cells, up or down regulation of cytokines and more that have not been totally elucidated.

**Figure 1: Ig Molecule**



The use of immunoglobulin as replacement therapy for PI was first described by Dr. Ogden Bruton in 1952 when he treated a boy he diagnosed with X-linked agammaglobulinemia with subcutaneous injections of Ig which had been isolated from human plasma.

Initially Ig was given predominantly via intramuscular injections. These injections were painful and dose limited due to route and volume. In the early 1980's, preparations that could be safely given by the intravenous route were developed and licensed in the U.S. Intravenous immunoglobulin replacement therapy or IVIG, also referred to as IGIV, was generally well tolerated by most patients and became the standard of care for treatment of patients with humoral primary immunodeficiencies. Larger therapeutic doses of Ig could be given intravenously compared to those doses given via intramuscular injections. Dosing frequency varied from 3-4 weeks, but adequate replacement could be achieved resulting in better infection prophylaxis.

In 2006, the first commercial preparation for subcutaneous immunoglobulin replacement therapy (SCIG) was approved by the FDA. SCIG is administered more frequently and in smaller doses than IVIG. SCIG provides very stable, consistent levels of IgG as opposed to the peaks and troughs associated with the intravenous route that is administered in large doses much less frequently. Additionally, several 10% IVIG preparations have been FDA approved for subcutaneous administration. In 2014, FDA approved a 10% Ig preparation to be infused subcutaneously and facilitated by prior infusion of recombinant human hyaluronidase.

Ig therapy is indicated as replacement therapy for primary and secondary immunodeficiencies in those patients who do not make sufficient amounts and/or types of specific antibodies to adequately protect themselves from infectious diseases. The goal of the therapy is to prevent frequent and/or severe infections. Two examples of PI requiring replacement therapy are Agammaglobulinemia (either x-linked or autosomal recessive) and Common Variable Immune Deficiency (CVID). Examples of secondary immunodeficiencies include hypogammaglobulinemia with impaired antibody responses caused by chemotherapy, monoclonal antibody therapy and/or immunosuppressive therapies.

In addition to antibody replacement, Ig also has anti-inflammatory and/or immunomodulatory effects. As such, it is sometimes used to treat patients with a variety of conditions other than PI. Ig therapy has been demonstrated to be efficacious in the treatment of such diseases as idiopathic thrombocytopenia purpura (ITP), Kawasaki disease and neuromuscular diseases. However, some of the uses are experimental and/or "off-label," which means that the FDA has not approved the use of Ig for those particular conditions.

| Table 2: FDA Approved Uses of Immunoglobulin (Ig) | |
|---|---|
| **Clinical Condition** | **Ig Indication** |
| Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) | Improve neurological symptoms. |
| Primary Humoral Immunodeficiency | Antibody replacement therapy. |
| Kawasaki Disease | Prevent coronary artery aneurysms. |
| Idiopathic Thrombocytopenia Purpura (ITP) | Increase platelets counts to prevent and control bleeding. |
| B-cell Chronic Lymphocytic Leukemia | Prevent recurrent bacterial infections. |

| Table 3: Immunodeficiencies that ALWAYS Require Ig Replacement Therapy |
|---|
| Agammaglobulinemia (X-linked, autosomal, or acquired) |
| Common Variable Immune Deficiency |
| Hyper IgM Syndrome |
| Severe Combined Immunodeficiency (SCID) before and sometimes after bone marrow transplantation |

| Table 4: Immunodeficiencies that MAY Require Ig Replacement Therapy |
|---|
| Selective Antibody Disorder |
| Wiskott Aldrich Syndrome |
| DiGeorge (22q11 deletion) Syndrome |
| Ataxia-Telangiectasia |
| Pediatric HIV |

## PRODUCT SELECTION AND CHARACTERISTICS

There are many brands of immunoglobulin (Ig) currently licensed for use in the U.S. Ig is derived from plasma. All manufacturing must be done in FDA approved facilities. All Ig products available in the U.S. are made solely from plasma collected from carefully screened and tested U.S. donors, and all of the manufacturing procedures include steps which have been shown to inactivate and/or partition multiple types of viruses[10].

These processes vary from manufacturer to manufacturer but include such steps as cold alcohol fractionation, low pH incubation, nanofiltration, chromatography and solvent/detergent treatment. There is no evidence to suggest that the risk of acquiring blood borne viruses or prions varies with subcutaneous vs. intravenous administration. There are no reported cases of disease transmission by SCIG, and none with IVIG since 1994[11]. None of the Ig preparations currently available in the U.S. contains thimerosal or other mercury-compound preservatives. However, contraindications, precautions and warnings can differ among products.

The main component of all Ig products is IgG (> 96%). Products vary in concentration, pH, stabilizing agents, osmolality, as well as sodium content. There is variability in galenic form (liquid or lyophilized) shelf life, storage (room temp vs refrigerated) approved means of administration (intravenous and/or subcutaneous) and recommended rate of infusion. These factors should be carefully considered when choosing a product for a particular patient. *(See Table 5.)*

| Table 5: Examples of Factors to Consider in Choosing an Immunoglobulin Product[12,13,14] | | | | | | |
|---|---|---|---|---|---|---|
| Potential Patient Risk Factors | Potential Immunoglobulin Risk Factors | | | | | |
| | Volume Load | Sugar Content | Sodium Content | Osmolality | pH | IgA Content |
| Cardiac Impairment | ■ | | | ■ | ■ | |
| Renal Dysfunction | ■ | ■ | ■ | | | |
| Anti IgA Antibodies | | | | | | ■ |
| Thromboembolic Risk | ■ | | ■ | ■ | | |
| (Pre) Diabetes | | ■ | | | | |
| Elderly Patients | ■ | ■ | ■ | ■ | | |
| Infants/Children | ■ | | ■ | ■ | ■ | |

All products, regardless of route of administration, carry warnings for:

- Hypersensitivity (previous reactions to IG or IgA)
- Thrombosis
- Renal Dysfunction/Failure
- Hemolysis
- Transfusion Related Acute Lung Injury (TRALI)
- Transmittable Infectious Agents

Some products carry additional warnings, and all manufacturer prescribing information should be reviewed prior to infusion.

## Preparations

Ig products are supplied as liquids or lyophilized (freeze dried powder that requires reconstitution) products. Some liquids require refrigeration; others are stored at room temperature. It is important to follow the manufacturer's specifications regarding storage. Any liquid which has been frozen, even if it has thawed, should be discarded, as freezing deactivates the product. Refrigerated products should be allowed to warm naturally to room temperature before administration, as adverse reactions can be associated with the administration of products that are too cold.

Lyophilized products can be stored at room temperature before reconstitution. It is possible for these products to be prepared at more than one concentration depending on the amount of diluent added. Possibilities for different concentrations are specified in the manufacturer's prescribing data. Nurses may be asked to reconstitute lyophilized products in the home or the infusion clinic. It is critically important to be aware of and to follow manufacturer's guidelines, prescriber's orders and aseptic technique when reconstituting these products.

Additionally, Ig products should be infused using a separate infusion line and not mixed with other drugs. Manufacturers' instructions and guidelines regarding flushing and pooling should be consulted and followed.

## Stabilizers

The range of stabilizers that are used in Ig include carbohydrates or proteins (amino acids). Stabilizers are added to Ig products to prevent them from aggregating. Patient risk factors should be considered regarding selection of stabilizers. For example, products containing glucose as a stabilizer used for diabetic patients may affect insulin needs; similarly, maltose stabilized products used for diabetics may distort serum glucose levels. Also, patients at risk for renal disease should avoid sucrose stabilized products as these products have been implicated in renal insufficiency[15].

## IgA Levels

There are small amounts of IgA in all Ig products. Although all Ig products (IVIG and SCIG) carry the same warning related to use in patients with IgA deficiency, it should be emphasized that anaphylaxis by any mechanism is a very rare event with any form of Ig therapy, including patients with IgA deficiency. This is a potential concern only in patients with absent IgA (i.e., below the limit of detection or < 5-7 mg/dL) and who have high levels of IgE anti-IgA antibody[16,17]. Patients with low or undetectable levels of IgA may be able to tolerate all Ig products without problems; however, these patients (particularly the patients with CVID) should be carefully monitored. The first IVIG infusion should be administered in a controlled setting where emergency treatment can be administered immediately should problems occur. If the infusion is tolerated, the patient is not likely to have subsequent problems with IgA-containing products and can receive home infusions. There are no reports of anaphylaxis with SCIG in patients with IgA deficiency. In fact, patients who have had reactions with IVIG (whatever the mechanism may have been) have tolerated SCIG[16-18].

## Product Integrity

All products should be carefully inspected before administration. Both outer and inner packaging as well as the individual vials should be examined closely. Any evidence of tampering should be reported to the supplier and/or manufacturer and the product should not be used.

Reconstituted and liquid products should not be given if there is particulate matter, visible precipitate, crystals or fibers in it. Products that have been frozen, even if they have thawed should not be administered. Each manufacturer states the range of color for the product in the label and it can vary per manufacturer. Typically, Ig should be a clear or slightly opalescent, colorless to pale yellow solution. The product should not be used if the solution is cloudy, turbid or if it contains particulate matter. If the nurse or patient has any doubts at all about the integrity of the product, it should not be administered[19].

## Documentation

All Ig infusions should be carefully documented. Documentation should include:

- The patient's current health status and any changes in this status in the period between infusions.
- The brand name and dose of the product along with lot numbers of the vials used.
- Any pre-medications that were given.
- Total time of infusion and specific rate of infusion titrations.
- Any problems the patient experienced during the infusion and what the response to these problems was.
- Patient teaching and response to teaching.

## Risk Stratification for IVIG and SCIG

Ig products are not generic drugs. There are significant differences in manufacturing, stabilizers, content such as sodium and sugar. The appropriate product for each patient should be selected based upon individualized assessment and stratification of risk factors. All IVIG brands carry the same-class black box warnings for renal insufficiency and thrombotic events. All SCIG brands carry a black box warning for thrombotic events. The nurse should adhere to individual manufacturer's recommendations in patients with identified risk factors who may be at increased risk with rapid infusion rates and require careful administration, monitoring and follow up. A rapid infusion rate is defined as a rate of administration greater than 4 mg/kg/min (0.04 mL/kg/min).

| Table 6: Adverse Effects and Patients at Risk | |
|---|---|
| Renal Insufficiency | Diabetes mellitus, advanced age (>65), sepsis, volume depletion, paraproteinemia, nephrotoxic medication. |
| Thrombotic Events | Advanced age, history of atherosclerosis, multiple cardiovascular risk factors, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, known or suspected hyperviscosity, such as patients with monoclonal gammopathies or high triglycerides, oral contraceptives. Rajabally recommends a maximum dose 35 grams/per day[20,21]. |
| Hemolysis | Risk factors include high dose, ongoing inflammatory process; non O blood group, and rapid infusion rates. |
| Aseptic Meningitis | Suspected risk is history of migraine. |
| B-cell Chronic Lymphocytic Leukemia | Prevent recurrent bacterial infections. |

Other risk factors include naïve patients (patient who have never received Ig), patients who have had more than 6-8 weeks between infusions, patients with a history of sensitivity and previous reactions to IVIG, and patients with poor hydration status.

## Hydration status

The patient should be evaluated for dehydration to determine if pre-hydration may be necessary. Evaluation for dehydration involves taking a history for proper fluid intake / output and several other tests described below:

- *Use the skin pinch test.* Skin turgor is the skin's ability to resist a change in shape and use elasticity to return to normal. Nurses will often use skin turgor to assess dehydration. The skin pinch test involves pinching the skin on the back of the lower arm or abdomen so that it tents up. Hold the skin together for a few seconds and release. Skin with normal turgor snaps rapidly back to its normal position. Skin with decreased turgor will slowly return to normal and is indicative of dehydration. Turgor also decreases with age, so the skin for older adults will return to normal less rapidly (within 2-5 seconds) even when hydrated.
- *Use the capillary nail refill test.* Apply pressure to the nail bed by pinching a finger or thumb for several seconds. The nail bed will turn white because the blood has been forced from the tissue. Remove the pressure and observe how quickly the blood refills the nail bed. A pink color should return within 2 seconds. If it takes longer, this could indicate dehydration.
- *Use the urine color test.* One of the best checks for dehydration is urine color. Clear or light-colored urine indicates proper hydration. Dark yellow or amber urine usually signals dehydration.
- *Check for other signs of dehydration.* Other common symptoms for dehydration include a dry mouth, tacky mucous membranes, sleepiness, thirst, decreased urine output, headaches, dizziness and a lack of sweat or tears[22].

## Nursing Responsibilities

Whether the nurse is administering an intravenous infusion or teaching patients to administer their own subcutaneous infusions, safety should always be the first priority. The prescriber's orders should be carefully followed and any problems with the orders should be addressed and resolved before the infusion. Communication of potential issues and problems so that they can be proactively addressed is critical. The following are broad guidelines for nursing interventions prior to, during and after administration of immunoglobulin (Ig) replacement therapy[19]. The nurse should be able to recognize any predisposing factors to prevent avoidable reactions. These guidelines are offered to help infusion nurses minimize problems and adverse reactions, and safely provide a successful infusion experience for the patient.

### Key Pre-Infusion Assessments

- Review patient history and risk assessment to ensure an appropriate product has been selected. Communicate potential problems to the prescriber. It is important to be aware of the differences between the various products that are available. As previously discussed, the qualities of a particular product may affect the tolerability and success of an infusion. Any patient who has had an interruption in therapy (more than 6 weeks between infusions) should be treated as a naïve patient. The first dose of any product is best administered in a controlled setting, where emergency equipment and treatment is readily available. The transition to home infusions can take place after it has been demonstrated that a particular product and infusion protocol is tolerated. Should it be necessary to change products, the first infusion of the new product should, again, be monitored.
- Assess product integrity. If the protective seals are not intact, the dispensing pharmacy should be notified immediately and the product should not be given.
- Assess product temperature. The immunoglobulin should be at room temperature before the infusion. Solutions should be allowed to come to room temperature naturally. Product integrity may be compromised (denatured) by freezing or heating. NEVER put product into the microwave for warming.

## Key Pre-Infusion Assessments *(continued)*

- Assess level of patient's understanding of therapy. Patients should be informed that Ig is a plasma product, and many institutions will obtain signed consent before receiving Ig. The consent form used in the practitioner's institution or local hospital for other blood products is usually satisfactory for Ig products. The patient must be informed of the benefits as well as the risk associated with Ig replacement therapy. All IVIG and SCIG products have similar warnings and contraindications, such as potential for renal failure, thrombotic events, aseptic meningitis, hemolysis and anaphylactic reactions. Facilitated SCIG, the monthly SCIG which combines hyaluronidase and SCIG, has different warnings as stated in the prescribing information, and the patient should be informed before starting therapy[23].
- Assess the patient's general health and hydration status. It is important to document and inform the prescriber of any changes in health status or new health problems which may have arisen since the last infusion. Any new medications should be noted as these may have an impact on prescribed therapy. If the patient is poorly hydrated, pre infusion hydration should be considered, either enterally or parenterally.
- Assess any weight loss or gain. Ig replacement therapy is prescribed based on weight. Any significant change (greater or less than 10%) may warrant a dose adjustment. However, dosing should be individualized and based on clinical outcomes[24].
- Assess heart rate and respiratory status. Patients with congestive heart failure or who are at risk of fluid overload should be assessed carefully before beginning the infusion. Total volume infused and the characteristics of the fluid (osmolality, sodium content) could exacerbate these problems; avoid use of products with lower IVIG concentrations[19] for these patients. Patients should be monitored frequently during the infusion for any change in respiratory status, which could indicate fluid overload. Diuretics may be prescribed before, during or after the infusion to prevent or relieve respiratory distress and/or complications associated with fluid volumes in these patients.

## Key Pre-Infusion Assessments *(continued)*

- Assess for fever prior to the start of infusion. If fever is present, the prescriber should be notified for directions in proceeding with or deferring the infusion. If the patient has an acute febrile illness or if there are other indications of an infection are present, the infusion may need to be postponed until the patient is treated with antibiotics and/or the fever subsides. Administration of intravenous immunoglobulin when the patient has an acute infection may lead to adverse effects due to the formation of immune complexes[25].
- Assess the need for pre-medication. Review prior infusion history for any adverse reaction to determine tolerability. If tolerability problems have occurred with previous infusions, discuss potential pre-medication/hydration with the prescriber[26]. Pre-medications may be indicated to diminish the risk of infusion-related adverse events. Examples of pre-medications include antihistamines, anti-emetics, acetaminophen, NSAIDs and/or systemic corticosteroids.
- Assess the need for localized anesthesia and obtain an order as necessary. Children, especially, may prefer to have topical anesthesia, such as lidocaine/prilocaine cream, applied in advance of needle insertion in order to numb the sites into which needles or intravenous catheters will be placed.
- Assess preparedness for emergency situations. Emergency equipment should be readily available during the infusion but may vary according to route of administration. Emergency medications may include epinephrine, diphenhydramine and parenteral fluids; these should be checked to ensure that they have not expired. If the site of care is the home, a phone to call 911 should always be available. A protocol for communicating with the prescriber for both routine and emergency issues should be in place.
- Assess routine monitoring and need for laboratory blood work prior to start of infusion. For patients receiving intravenous immunoglobulin, trough levels of IgG should be drawn immediately before beginning an infusion. The nurse should review the results of previous lab work with the patient and communicate with the prescriber to ensure that routine monitoring labs are done as ordered. For subcutaneous infusion, lab work can be drawn at any time.

## Key Pre-Infusion Assessments *(continued)*

- Assess the overall well-being of the patient and their experiences with previous infusions. It is important for the nurse to listen to any patient concerns and ensure that established routines are followed to avoid causing undue stress. Children, in particular, may have routines in place to assist them in dealing with both the physical and psychological impacts of infusions. Changes to the established routine could cause undue stress.

## Key Intra-Infusion Assessments

- Assess and observe the patient to monitor tolerability and adverse reactions. The nurse should listen carefully to any complaints and be sensitive to any alteration in the patient's baseline status. Vital signs should be assessed as ordered and more frequently, as indicated.
    - Adverse reactions which may occur include headache, fever/chills/flushing, cough, wheezing, chest tightness or SOB, urticarial or hives, nausea/vomiting, abdominal pain, lower back pain or generalized myalgia.

## Key Post-Infusion Assessments

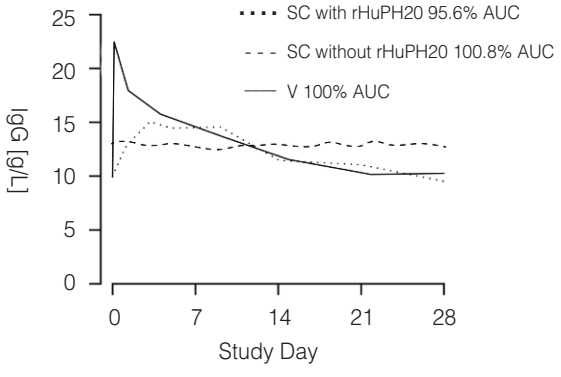
- Assess for any problems occurring after the infusion which may be infusion related. These can include headaches, myalgias, fever, arthralgias, rashes or a subjective feeling of general "unwellness." If these problems are postulated to be infusion related, alterations to the infusion protocol including infusion titration changes and the addition of pre-medication may be necessary with the next and subsequent infusions.
- Assess the patient understanding about upcoming infusions. It is important for the patient to know timing, site of care, brand, dose and what his/her responsibilities regarding this infusion are.
- Patients should be given adequate written instructions regarding post infusion symptoms and when to contact their healthcare provider, as well as acceptable medications that can be used for headache or myalagias.

## Routes of Administration: Intravenous vs Subcutaneous

Ig replacement therapy can be administered intravenously (IVIG) or subcutaneously (SCIG). There are multiple factors to consider when choosing the route of administration; careful consideration of these factors and their relationship to the individual patient is critical to ensuring success. The patient's input should be considered, thus ensuring a collaborative approach for therapy. Factors to consider include:

- *Efficacy of Therapy:* All FDA-approved Ig products meet a standard of efficacy. In the U.S., efficacy is judged by the incidence of acute serious bacterial infections (SBI) per patient per year (eight)[9]. The FDA has defined rigorous criteria for diagnosing the infections fitting into this classification, which include bacteremia/sepsis, pneumonia, visceral abscess, osteomyelitis/septic arthritis and bacterial meningitis. The minimal acceptable criterion for licensing of a new Ig product in the U.S. is that the annual incidence of these infections in patients with XLA and/or CVID must be <1 (in most trials it is much lower). However, the pharmacokinetics between the routes are dissimilar, resulting in different Ig levels. IVIG and facilitated SCIG infusions are usually given every 3 to 4 weeks, with an initial peak in the IgG level when the infusion is given; the IgG level then decreases over the dosing interval to a trough. With traditional SCIG infusions, the drug is given more frequently resulting in a steady serum level during the entire month without the fluctuations characteristic of IVIG or facilitated SCIG which are given every 3 or 4 weeks. *(See Figure 2.)*

**Figure 2: Kinetics of Serum IgG Levels[27]**



Depending on the subcutaneous product chosen, infusions can be given daily up to every two weeks (biweekly). This consistency of level, i.e., lack of a peak and a trough, may be therapeutically important for patients with conditions such as protein losing enteropathies or for patients currently receiving IVIG or facilitated SCIG who have frequent breakthrough infections, especially when their IgG level is at trough.

- *Time Factor:* IVIG and facilitated SCIG infusions generally require 3 to 4 hours for infusion. SCIG infusions require less time and are typically given weekly; however, frequency can vary from every day up to every 14 days or any frequency in between (every 2 days, every 3 days, every 4 days, every 5 days, etc.) depending on the label and patient preference.
- *Adverse Reactions:* There has been a greater incidence of systemic adverse reactions reported with IVIG than by the subcutaneous route. Systemic reactions are rare with SCIG and local site reactions are more common. Patients receiving facilitated SCIG also experienced systemic reactions at a rate higher than that of patients receiving traditional SCIG but lower than that of patients receiving IVIG. Patients who experience adverse reactions with IVIG and need pre-medication for their infusions may not experience these problems with SCIG[28].
- *Cost of Therapy:* In addition to the cost of drugs, there are costs associated with nursing administration, patient teaching, ancillary supplies, including needles, tubing and pumps. For those patients who receive IVIG in an infusion suite, there may be facility costs. The patient's insurance benefits and out-of-pocket costs need to be investigated to ascertain the patient's fiscal responsibility. Additionally, information should be provided to the patient regarding resources that can help defer costs. Financial assistance may be available through manufacturer, home health agency or specialty pharmacy assistance programs.
- *Patient Compliance and QOL:* There are many life/socioeconomic factors that should be considered when choosing the route of administration, all of which can impact compliance and quality of life. Some of these include: patient/family preference; distance from/accessibility of infusion center; patient/family schedule; availability of home nursing services; ability to learn and perform infusions; availability of partner/parent/infusion buddy; home environment; and individual

reliability. Decisions for treatment options should be individualized based on each patient's medical condition(s) as well as patient input. Full involvement of patients in their treatment decisions has the potential to improve compliance and adherence resulting in improved quality of life and patient outcomes[29]. It has been shown that engaging the patient and empowering patient choice without preconceived opinions resulted in a high rate of compliance[29,30].

- *Comorbidities:* Patients with PI often have other coexisting disease or comorbidities as discussed in the earlier section. Some of these co-morbidities, such as cardiac and renal disease, may sometimes be better managed with SCIG (smaller doses administered more frequently). Patients with protein losing enteropathies may benefit from frequent doses of small, slowly absorbed amounts of Ig, which can be achieved with SCIG.
- *IV Access Issues:* The American Academy of Allergy, Asthma and Immunology (AAAAI) strongly discourages the use of permanent indwelling ports or central venous lines in antibody deficient patients due to the risk of systemic infection (sepsis) and thrombotic events[8]. If peripheral access is consistently difficult, SCIG may be a viable option.

**Table 7: Features of IVIG and SCIG Therapy**

| Intravenous Immunoglobulin (IVIG) | Subcutaneous Immunoglobulin (SCIG) |
|---|---|
| Must be administered with trained healthcare personnel present. | Self-administration at home (after appropriate training). |
| Given once every 3-4 weeks. | Flexible dosing schedule, from daily up to once every 3-4 weeks. |
| Wider fluctuation in serum IgG levels, with peaks and troughs. | Keeps serum IgG levels consistent week to week. |
| Venous access required. | Venous access not required |
| Reduces the incidence of serious bacterial infections (SBIs)*. | Reduces the incidence of serious bacterial infections (SBIs)*. |
| Systemic AEs more common. | Low rate of systemic AEs. |
| Slight risk of local skin damage at infusion site. | Mild local site reactions can be expected. |

**SBIs defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis and visceral abscess[28].*

# INTRAVENOUS IMMUNOGLOBULIN THERAPY

Intravenous immunoglobulin replacement therapy (IVIG) is typically administered every 3 to 4 weeks at a dose range of approximately 400-800 mg/kg/dose. Dosing is individualized and based on the patient's clinical status and outcomes. It is generally well tolerated by a majority of patients, but it is important to note that—just as each patient may require a different immunoglobulin product—each may also require an individualized infusion regimen. Once a successful regimen has been established, it should be carefully followed with every infusion. This includes the rate of the infusion, any necessary pre-medications and brand consistency.

## Nurse's Role

### Administration

Different products vary in their compatibility with normal saline, sterile water or D5W, and manufacturer's guidelines should be followed carefully. Administration of concomitant medications through the same IV line should be avoided. Should medications be required prior to or during an infusion, it is recommended that the line be flushed with at least 5-10 ml of compatible fluid prior to administering the medication. Some medications will precipitate when in contact with IVIG, especially furosemide or diazepam. No medications should be directly administered into the same line simultaneously with the IVIG. If multiple medications are required, a second IV line should be placed so as not to interfere with the infusion. Another option is to piggyback the IVIG into the closest port in a line where a compatible fluid is already running. The compatible fluid can then be used as a flush if necessary. Check the manufacturer prescribing information for specifics with each Ig product[19].

### Intra-infusion Assessments

- Assess the rate of infusion. Prescriber's orders and manufacturer's recommended rates of infusion should determine the length of time for an infusion. Generally, a ramp-up procedure is used for IVIG rates of infusion. The infusion is started slowly and the rate increased incrementally, every 15 to 30 minutes, as tolerated, until the patient's maximum rate of infusion is reached. There is large inter-patient variability for infusion rate tolerance. However, it should be noted that patient

risk factors override tolerability. Patients at risk for renal insufficiency, thrombotic events, hemolysis, etc. should be administered at the lowest dose/lowest rate[14,25,31-33]. If a product change is necessary, the process for assessment of tolerability and potential rate increases must again be taken slowly.

- Assess vital signs prior to each rate change to ensure that the infusion is being tolerated. Hyper- or hypotension, increased heart rate, increased respiratory rate or effort, and fever could all be signs of problems. It is important to assess the clinical relevance of any alterations in vital signs. For example, if a comfortable patient falls asleep, their blood pressure, heart rate and respiratory rate may decrease and these decreases may not represent a pathologic concern. Similar findings in another patient may be signs of significant problems with the infusion.
- Assess the need for comfort measures during the infusion, particularly if adverse reactions occur. Both pharmacologic and non-pharmacologic interventions (supplying blankets or pillows, heating pads and encouraging the use of relaxation techniques) may be indicated.
- Assess for signs of anaphylaxis. Although true IgE medicated anaphylaxis in patients with antibody deficiencies is extremely rare, if a patient has difficulty breathing, signs of tongue or throat swelling, a feeling that the throat is closing, stridor, wheezing and/or chest tightness, generalized urticaria, or extreme anxiety, the infusion should be stopped and immediate emergency treatment, including calling 911, should be initiated. First infusions should always be given cautiously in a setting prepared to treat anaphylaxis if it occurs.

## Adverse Reactions

Although most patients tolerate IVIG well, systemic adverse reactions have been reported with every licensing trial. It is estimated that 15-30% of patients experience some kind of reaction to their IVIG infusions. These reactions can range from mild to severe. Most reactions occur during the initial 30 to 60 minutes of the infusion and are mild, transient self-limited and rate related. Most do not require discontinuation of therapy but do require rate adjustment. These reactions include headaches, nausea, fever, chills, flushing, wheezing, vomiting, abdominal pain, backache, chest tightness; allergic reactions like rash and hives. Some rare

but serious adverse reactions that can occur are renal failure, thromboembolic events, hemolysis, aseptic meningitis and anaphylaxis. Reactions are more frequent with patients who are therapy naïve, when therapy is given with a different product than the patient has previously been using, or those who have been off of therapy for a period of time. Regardless of the severity of a reaction, managing these problems requires timely interventions on the nurse's part. A nursing policy and orders should be in place for dealing with these issues.

As previously stated, risk factors should be identified in order to appropriately manage the infusion rate regimen. It is advisable to read the specific package insert for the IVIG product used, as the incidence and types of adverse events varies from product to product.

## Types of Adverse Reactions

- *Febrile Reactions:* These reactions are marked by a significant rise in temperature and are usually accompanied by other systemic symptoms. Fever is the most common side effect in children. Management of acute febrile reactions includes the use of antipyretic medications, such as acetaminophen or ibuprofen. Persons who repeatedly experience temperature elevations during administration of IVIG may benefit from pre-medication with an antipyretic/anti-inflammatory, such as acetaminophen or ibuprofen, 30 to 60 minutes prior to initiation of the infusion[26].
- *Allergic Reactions:* True IgE mediated allergic reactions are extremely rare in patients with antibody deficiencies; however, they can occur. In some cases, anaphylactoid reactions to IVIG mimic those of true IgE mediated allergy but are actually due to activation of complement or other mediator systems. Allergic reactions can lead to acute anaphylaxis and shock. If these reactions occur, future use of IVIG is not precluded but, of course, must be investigated as to the primary cause. These allergic reactions may often begin with a generalized nonspecific feeling of unease. Patients may describe an uncomfortable feeling, such as a tightening around the neck, chest or abdomen and "a sense of impending doom." There may be difficulty swallowing, a choking sensation or difficulty breathing. Other symptoms may include wheezing, flushing, hives, rapid or weak pulse, hypotension, sweating or an upset stomach with or without nausea, vomiting or diarrhea.

- *Vasomotor Symptoms:* These can occur with or without additional cardiac manifestations. Blood pressure can either increase or decrease, and may be accompanied by flushing or tachycardia. Patients experiencing such reactions may report feeling faint, shortness of breath or tightness in the chest.
- *Anaphylactoid Reactions:* These reactions most commonly include headache, dizziness or lightheadedness. Patients can also experience chills sometimes progressing to rigors, nausea and/or vomiting, back or hip pain, malaise, myalgias and arthralgias. Frequently the patient reports anxiety. The most frequent cause of these reactions is infusion at an excessively rapid rate, infusion of a drug which is colder than room temperature or immune complexes that occur in an infected patient. Often, the patient will have elevated blood pressure rather than hypotension.

## Potential Post-Infusion Reactions

Post-infusion reactions can occur immediately or as long as 72 hours following the infusion. Symptoms associated with post-infusion reactions are usually less severe in nature but can interfere with a patient's quality of life. Common post-infusion reactions may include headache, low-grade fever, nausea, arthralgias and/or generalized malaise. Often patients describe fatigue and a "flu-like" feeling. These reactions are generally managed with over-the-counter analgesics. Some patients may require a short course of corticosteroids[26].

Headaches are more frequent in patients who have a history of migraine or cluster headaches, or are dehydrated. Some patients, particularly those with histories of migraines at other times, may have severe headaches and/or typical migraines up to 72 hours after their infusion. Over-the-counter analgesics are usually effective in treating these headaches but some affected patients may require the addition of a short burst of oral steroids. Severe, persistent posterior occipital headaches may be a sign of aseptic meningitis, which has been reported in some patients after IVIG infusion. Patients with this complaint should be seen by their prescriber or in the Emergency Room.

*Table 8 (page 28)* presents common adverse reactions and potential nursing interventions. It is important to follow the prescriber's orders when dealing with any infusion reaction. The prescriber should always be notified that a reaction has occurred and may wish to change immunoglobulin products or route of administration or order pre-medications for future infusions. Reactions to IVIG can diminish with subsequent infusions, so the use of pre-medication should be reassessed periodically.

| Table 8: Potential Nursing Interventions for Dealing with Adverse Reactions to IVIG[26] | |
|---|---|
| **Reaction** | **Nursing Interventions** |
| Chills / Rigors | ▪ Stop infusion.<br>▪ Administer prescribed medications.<br>▪ When symptoms resolve, restart the infusion at the rate the patient was tolerating before the symptoms occurred. |
| Headache | ▪ Administer acetaminophen or NSAID as prescribed.<br>▪ The patient's hydration status may affect the development of headaches; the patient should make sure he/she is adequately hydrated on the day of the infusion.<br>▪ Consider IV or oral hydration (500ml- 1000ml)[26]. |
| Migraine Headache *(patients with a history of and under treatment for headache problems)* | Pharmacologic:<br>▪ Administer prescribed anti-migraine medications as soon as the first signs of a migraine occur. Pre-medication with anti-migraine medications may also be considered.<br>▪ Oral or IV steroids may help decrease the intensity of the headache and should be given if ordered[26].<br>Non-pharmacologic:<br>▪ Include comfort measures, such as reducing auditory and visual stimuli, and applying cold compresses to the head or back of the neck. |
| Malaise/Flu-like Symptoms | ▪ Resting after an infusion may help to minimize muscle aches or pain and to decrease excessive fatigue.<br>▪ Acetaminophen or NSAIDS and ensuring adequate pre-infusion hydration may help with this problem. |
| Urticaria | ▪ Stop the infusion.<br>▪ Contact the prescriber.<br>▪ Administer prescribed antihistamines and/or steroids.<br>▪ Observe for signs of true anaphylaxis; if they occur administer epinephrine and activate the emergency response system (911). |

| Table 8: Potential Nursing Interventions for Dealing with Adverse Reactions to IVIG[26] *(continued)* | |
|---|---|
| **Reaction** | **Nursing Interventions** |
| Vasomotor Symptoms *(Hypotension, Hypertension, Flushing or Tachycardia)* | ▪ Stop infusion.<br>▪ Follow the prescriber's order for fluid bolus, diuretics or other interventions as indicated. |
| Nausea/Vomiting | ▪ Stop the infusion.<br>▪ Administer prescribed antiemetic medications.<br>▪ Provide comfort measures. |
| Back Pain / Hip Pain / Arthralgias / Myalgias | ▪ Stop or slow the infusion.<br>▪ Administer acetaminophen or NSAIDS for the discomfort.<br>▪ The use of a heating pad may be beneficial. |

## Serious Adverse Reactions

- *Thrombotic Events:* Thrombotic (vascular occlusive) events have been reported in association with IVIG. The mechanisms for these episodes may include increased blood viscosity after high-dose IgG and/or the presence of procoagulant proteins in the IVIG preparation. These episodes have been noted with increased frequency in patients following rapid infusion protocols or patients with risk factors such as prior thromboembolic events, thrombocytosis, or immobility. Thrombotic events are serious in nature and include chest pain, myocardial infarction, congestive cardiac failure, transient (cerebral) ischemic attack (TIA) and stroke. Patients with risk factors for thrombotic events should follow a conservative infusion protocol, with incremental increases in the rate of infusion to a maximum of 4 ml per kg of body weight per hour. Patients should be given clear instructions regarding what post-infusion symptoms should be reported immediately to their prescriber[34].
- *Renal Adverse Events:* Potential adverse effects involving the kidneys include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. There have been rare reports of increased serum creatinine, oliguria and

acute renal failure occurring from one to seven days after IVIG administration. Hyperosmolality and the presence of sucrose have been implicated as factors contributing to renal adverse events. Patients who are not adequately hydrated prior to onset of the infusion, who have diabetes mellitus or any pre-existing renal insufficiency, those receiving nephrotoxic antibiotics, those who have paraproteinemia and/or those who are over age 65 are at the greatest risk for these problems. Renal function (serum creatinine and BUN) and urine output should be carefully monitored in patients at risk for developing renal adverse events. Using slow infusion rates during administration of IVIG and assuring adequate hydration are advised for such at-risk patients or consideration should be given to changing the route of administration. As with patients at greater risk for thrombotic problems, patients with the potential for renal adverse events should be given clear instructions regarding what post-infusion symptoms should be reported immediately to their prescriber.

- *Aseptic Meningitis:* Cases of aseptic meningitis with headache and positive meningeal signs have been reported with the use of IVIG in both standard replacement therapy dosing and high dose therapy. The symptoms may occur during the infusion, but more typically they usually develop within 24 hours of the infusion. A previous history of migraine headaches has been noted to be a risk factor. A neurologic exam is indicated for these patients to rule out bacterial or viral meningitis. Patients with aseptic meningitis have a pleocytosis but no organisms in their cerebrospinal fluid. Treatment is symptomatic. The development of aseptic meningitis is an indication for a change in the immunoglobulin product or route of administration used for future infusions. Pre-medication with corticosteroids is also indicated for those with a previous history of infusion related aseptic meningitis.
- *Transfusion-related Acute Lung Injury (TRALI):* TRALI is a rare but potentially devastating complication of blood component therapy characterized by severe respiratory distress, hypotension, fever, dyspnea and tachycardia. Patients exhibit pulmonary edema, hypoxemia, abnormal left ventricular function and fever with a typical onset within 1 to 6 hours after infusion of the product. Pulmonary embolism and lung dysfunction due to “transfusion related acute lung injury” have also been observed during or immediately after IVIG infusions. Patients with TRALI

may be managed using oxygen therapy and appropriate ventilatory support; symptoms usually resolve within 96 hours. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum.

- *Hemolysis:* Hemolysis is a rare but serious adverse reaction associated with IVIG. IVIG may contain blood group antibodies that can act as hemolysins and induce coating of red blood cells (RBCs) with immunoglobulin causing a positive direct antiglobulin test (DAT, Coombs' test) result and hemolysis. Patients should be monitored for clinical signs and symptoms of hemolysis and be evaluated for positive DAT. Risk factors include patients with blood group A, B, or AB, those receiving high-dose IgG regimens, such as those used for ITP or autoimmune/inflammatory disease and those receiving high cumulative dose of IgG (>100g). Another postulated risk factor includes underlying systemic inflammatory state[35].

# SUBCUTANEOUS IMMUNOGLOBULIN THERAPY

In 1952 Dr. Bruton began treatment of his patient with an antibody deficiency using an intramuscular immunoglobulin (IMIG) product via a subcutaneous route. Intramuscular Ig continued until IVIG was introduced. The subcutaneous route continued to be used in Europe, Great Britain and Scandinavia. In January 2006, the FDA approved a 16% preparation of SCIG for use in the U.S. Currently the only FDA approved indication for SCIG is as antibody replacement therapy although clinical trials for SCIG use for other indications are ongoing. At this time, products for subcutaneous infusions are available in concentrations of 10 or 20%.

## Subcutaneous Immunoglobulin Therapy

For the majority of patients, IVIG and SCIG are equally effective. However, there are differences between the therapies in pharmacokinetics and tolerability. While IVIG is usually given as a single large infusion every 3 to 4 weeks, SCIG involves giving smaller doses more often, from daily to biweekly, depending on the product used. Fractionating the total monthly dose into more frequent smaller doses provides a steady state Ig serum level which differs from the peaks and troughs of less frequent, higher dose IVIG regimens. SCIG has a lower reported incidence of systemic adverse reactions as it allows more even distribution of doses over time. The steady state levels help avoid “wear-off” effects associated with IVIG such as malaise, fatigue, arthralgias/myalgias[36,37] and decreased susceptibility to infections towards the end of each dosing interva[24,38,39].

SCIG is typically administered by the patient or a caregiver. Depending on the volume of drug to be infused, multiple sites can be used simultaneously. The drug can be administered via a small syringe driver pump or via a manual push[40]. Many studies have demonstrated that patients can tolerate relatively rapid infusions and those patients who deliver their infusions via a manual push can easily do so.

Subcutaneous administration offers a great deal of flexibility in the regimen. Parameters to be considered include the number of sites, duration of the infusion and frequency of infusions. Because of these multiple options, the patient can collaborate with the

healthcare provider to design a regimen which "works" for him/her; that is, one with which he/she can be compliant. For example, a SCIG dose of 10 grams/week if given with a 20% solution would have a volume of 50 ml. The typical adult could receive this dose via a once weekly infusion, using two needles connected to bifurcated tubing and a pump; the infusion could take approximately 45 to 55 minutes, although it could be adjusted to infuse faster or slower based on the patient's tolerability. Similarly, this dose could be split into two infusions during a week (e.g., Monday and Thursday) each using a single needle. This regimen would deliver 25 mls to one site twice a week. Some patients could even choose to administer 10 cc on five days every week. This flexibility in "custom designing" a regimen can be very attractive to patients who seek greater control over their illness and treatment. Deciding how, where and when the infusion occurs may help to minimize time lost from work or school, and allow greater freedom for patients who travel frequently[41].

## Facilitated Subcutaneous Immunoglobulin Therapy

In September 2014, the FDA approved a new subcutaneous Ig product which combines 10% Ig with recombinant human hyaluronidase (rHuPH20) for replacement therapy for adults.

Hyaluronidase is administered prior to the Ig infusion in order to increase the subcutaneous space by depolymerizing hyaluronanan in the subcutaneous tissue. Facilitated SCIG (fSCIG) is used in regimens more similar to IVIG as it is administered every 3 to 4 weeks. The pharmacokinetics of facilitated SCIG lies between IVIG and SCIG with a blunted broad early peak of concentration and a trough similar to IVIG ***(see Figure 3)***. Efficacy data for facilitated subcutaneous therapy is equivalent to that of IVIG and traditional SCIG.

There is a recommended ramp up for the initiation of fSCIG administration over the first seven weeks ***(see Figure 3)***. With each infusion, the rHuPH20 is administered first, after the subcutaneous needle or needles have been placed at an initial rate of 1-2 mL per minute per site. Within 10 minutes, the 10% Ig is then infused with a rate ramp up similar to IVIG ***(see Figure 4)***, thus administration requires an infusion pump capable of high infusion rates.

### Figure 3: fSCIG Initial Treatment Interval / Dosage Ramp-Up Schedule[23]

| Week | Infusion Number | Dose Interval | Example for 30 grams per 4 weeks |
|---|---|---|---|
| 1 | 1st infusion | 1-week-dose | 7.5 grams |
| 2 | 2nd infusion | 2-week-dose | 15 grams |
| 3 | No infusion | | |
| 4 | 3rd infusion | 3-week-dose | 22.5 grams |
| 5 | No infusion | | |
| 6 | No infusion | | |
| 7 | 4th infusion (if required) | 4-week-dose | 30 grams |

### Figure 4: fSCIG Infusion Rates[23]

| | First 2 Infusions | | Subsequent 2 or 3 Infusions | |
|---|---|---|---|---|
| | **Subjects < 40 kg** *(< 88lbs)* | **Subjects ≥ 40 kg** *(≥ 88lbs)* | **Subjects < 40 kg** *(< 88lbs)* | **Subjects ≥ 40 kg** *(≥ 88lbs)* |
| **Intervals** *Minutes* | **Rate per site** *mL per hour* | **Rate per site** *mL per hour* | **Rate per site** *mL per hour* | **Rate per site** *mL per hour* |
| 5 - 15 | 5 | 10 | 10 | 10 |
| 5 - 15 | 10 | 30 | 20 | 30 |
| 5 - 15 | 20 | 60 | 40 | 120 |
| 5 - 15 | 40 | 120 | 80 | 240 |
| Remainder of infusion | 80 | 240 | 160 | 300 |

## Nurse's Role

### Educator and Facilitator

The nursing role in SCIG is primarily one of an educator and facilitator. The goal for care is to help the patient/caregiver become independent. Patients and/or caregivers will need to be taught the skills necessary to administer their infusions in a safe and aseptic manner. A systematic, step-wise teaching approach is usually effective. This starts with the nurse first demonstrating the procedure, then allowing the patient to practice the skill, and finally allowing the patient to teach an infusion back to demonstrate mastery: the "See one, Do one, Teach one" approach. After the patient is independent, follow up and support are critical in managing issues and/or problems. There may be a need to adjust ancillary supplies to optimize the SCIG infusion. These might include changing the gauge or length of the needle, a recommendation about using different sites, or changing the volume per site or rate of the infusion.

The most critical factors in assuring the success of subcutaneous therapy are teaching and follow up support. The nurse should develop a teaching plan that takes into consideration: the patient's capacity to learn, as well as the manner in which learning is achieved; independence; self-motivation; compliance; ability to read and/or follow instructions; physical limitations, especially regarding manual dexterity; and presence of someone to assist or actually perform the infusion, if necessary[42].

Much of the education for SCIG administration includes basic nursing, i.e., hand washing and aseptic technique. A systematic approach to setting up the equipment and drawing up the product, inserting the needle(s), monitoring local effects, discontinuing the infusion and safely discarding the used equipment and needles needs to be developed.

### Specific topics that need to be covered:

- Storage and handling of medication
- Traveling with medication, supplies and pumps
- Using aseptic technique for drawing up and administering the drug
- Priming tubing

- Subcutaneous sites selection and preparation
- Insertion, securing and removal of needles, including the importance of dry needle insertion
- Checking needle placement to ensure that they have not been inadvertently placed in the intravascular space
- Setting up the pump, if a pump is going to be used
- Anticipating and troubleshooting infusion problems
- Discontinuing infusion
- Comfort measures and site care
- Appropriate waste disposal

Another important teaching topic is ensuring that the patient understands adverse reactions and/or complications, as well as how to initiate the appropriate action should something untoward occur. Expectations regarding site reactions and management should be discussed. The patient must be taught the signs of anaphylaxis and what to do should they occur. EpiPen training should be provided when an EpiPen has been prescribed[42].

Documentation of the patient's mastery of skills is important. The number of sessions required for the patient to master all of these steps may vary widely depending on the individual's capacity for learning, coupled with their anxiety level.

## Adverse Reactions

The black box warnings differ between the 20% SCIG and IVIG products. There are also some noteworthy differences between SCIG and the 10% Ig combination with hyaluronidase. However, both IVIG and SCIG products have similar warnings and contraindications with regard to thrombotic events, aseptic meningitis, hemolysis and anaphylactic reactions. It is prudent to check the prescribing information so the patient can be correctly educated before starting therapy

Systemic symptoms are less frequent in patients receiving SCIG[43]. The relative freedom from systemic effects of subcutaneously administered Ig is likely due in part, to the slower absorption and equilibration of the Ig into the circulation[28,44]. However, the incidence of local reactions at the infusion sites commonly occurs

when patients first begin to use the subcutaneous route. Local reactions are higher with initial therapy and decrease within 1-2 months of continued weekly subcutaneous treatments.

Local reactions often include swelling, which in some cases may seem to be bigger than the volume of Ig infused depending on distribution of subcutaneous tissue, and erythema. Sometimes there can be a sensation of burning or itching. These are rarely considered painful or serious. Some patients may experience swelling without erythema, or vice versa. Often, adjustment of ancillary supplies will mitigate site reactions. The swelling and erythema deceases as the drug is absorbed, usually within 24 hours. In most cases, by 72 hours, it is difficult to identify the site at which SCIG was given.

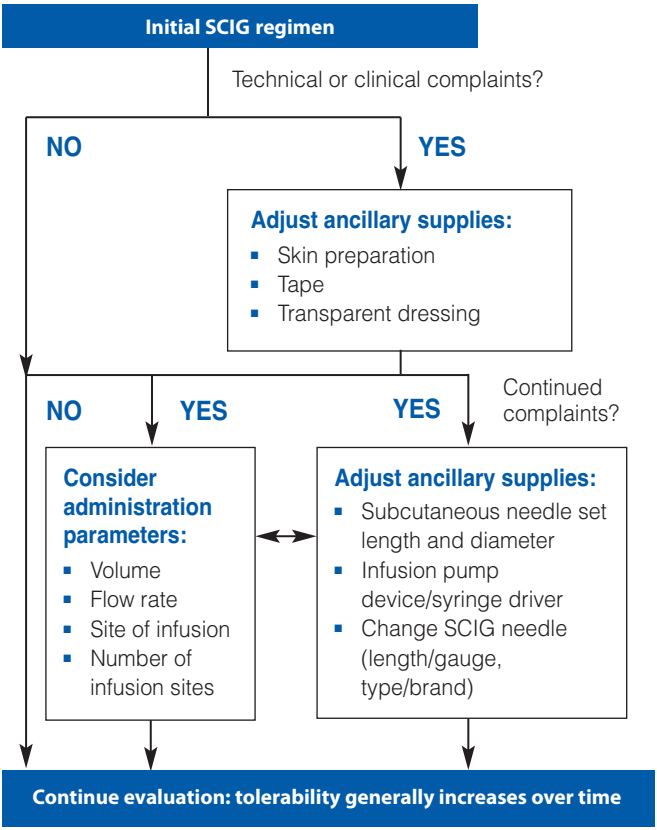
As fSCIG combines features of IVIG (large single dose) with traditional SCIG (slow absorption rate), systemic side effects seen with IVIG and local side effects seen with SCIG can both occur. Refer to ***Table 9 (page 39)*** for potential nursing interventions for adverse reactions seen with facilitated SCIG.

In addition to adverse reactions and effects in common with other means of Ig administration, fSCIG has additional warnings and precautions related to the hyaluronidase. It is possible for patients to develop auto antibodies to rHuPH20. It is not known if these antibodies interfere with human fertilization or have any clinical significance, at all.

Infusion into or around an infected area can spread a local infection into the system. The manufacturers of fSCIG caution that neither the rHuPH20 nor Ig should be infused into areas where an infection is present[23].

Local site reactions can be managed with adjustments to the infusion regimen, gentle massage, warm or cold compresses and/or mild pain medications such as ibuprofen or acetaminophen[45]. Patients who experience itching may get relief by applying hydrocortisone cream or ointment to the sites.

**Figure 5: Algorithm for Troubleshooting SCIG Local Site Reactions[43]**




As with IVIG, true anaphylaxis with SCIG is extremely rare and has not been reported to date in patients with IgA deficiency. In fact, patients who have had anaphylactic-like reactions with IVIG (whatever the mechanism may have been) have tolerated SCIG[16,17]. Patients should be educated regarding signs and symptoms of potential adverse reactions and appropriate actions to initiate. Many prescribers order an Epi-pen for their patients receiving SCIG. Patients need education regarding indications for use and administration of the epinephrine.

| Table 9: Potential Nursing Interventions for Dealing with Adverse Reactions to SCIG | |
|---|---|
| **Reaction** | **Nursing Interventions** |
| Local Itching | ▪ Ensure that a dry needle insertion technique has been used.<br>▪ Apply cold compress (do not apply cold pack directly to skin).<br>▪ Over-the-counter topical steroid.<br>For future infusions, consider:<br>▪ Use of a longer needle.<br>▪ Decrease volume per site and work up to desired site volume gradually. |
| Redness | ▪ Apply cold compress.<br>▪ Consider irritation from tape or adhesive and change this product.<br>▪ Assure patient that redness should decrease with each subsequent infusion. |
| Burning | ▪ Clamp off catheter for 5-10 minutes, if desired.<br>▪ Slow the rate of infusion.<br>▪ Cold compress.<br>▪ Consider changing the site or volume.<br>▪ Assess needle placement as the needle may be partially intramuscular instead of subcutaneous. Consider the use of a shorter needle.<br>▪ Assess antiseptic used for skin prep. |
| Swelling<br>*There will always be some degree of swelling as the patient is infusing fluid subcutaneously, under the skin. Thinner patients may have more pronounced swelling* | ▪ Warm compresses for 5-10 minutes.<br>▪ If using a heating pad, use low setting.<br>▪ Gentle massage.<br>▪ Adjust volume / consider alternate site. |
| Urticaria/Hives | ▪ Stop infusion.<br>▪ Contact prescriber for instructions and to determine if infusion should continue.<br>▪ Antihistamine. |

*(continued on next page)*

| Table 9: Potential Nursing Interventions for Dealing with Adverse Reactions to SCIG *(continued)* | |
|---|---|
| **Reaction** | **Nursing Interventions** |
| Rash | ▪ Assess if local or systemic; stop SCIG if systemic.<br>▪ Contact prescriber for instructions and to determine if infusion should continue.<br>▪ Consider the possibility of tape or latex sensitivity. |
| Discomfort | ▪ Slow infusion.<br>▪ If intolerable pain, needle may be intramuscular, remove the needle and change sites.<br>▪ Warm compresses.<br>▪ Gentle massage.<br>▪ Over-the-counter analgesics can be used but are rarely necessary. |

## Serious Adverse Reactions

As with IVIG, FDA requires the prescribing information of SCIG products to include the "Warnings and Precautions" about the risks of aseptic meningitis syndrome, acute hemolysis and hemolytic anemia, thrombosis and transfusion-associated acute lung injury. In addition, IgA deficiency is considered a risk factor for severe hypersensitivity and true anaphylactic reactions. These reactions have been discussed in the previous section for adverse reactions with IVIG.

The overall incidence of systemic adverse reactions due to SCIG is low when compared with IVIG. However, there may be some reported differences in warnings; those would be stated in the product prescribing monograph[38,46,47].

# THE HEALTHCARE TEAM: A MULTI-DISCIPLINED APPROACH

The nurse, the prescriber, the patient and/or the caregiver should form a collaborative team to optimize care delivery. Each has a unique role that overlap to some degree but hinge on solid communication. Other team members, such as the specialty pharmacy, consulting medical specialists, etc., may be involved as well, but these are key in directing care

## Prescriber

The prescriber's responsibility begins with making a diagnosis and educating the patient about the diagnosis and treatment. Decisions for therapy should be made collaboratively. The prescriber should explain available options for therapy including rationale for each option and practicalities involving each treatment. The prescriber should communicate the immediate and long term plans for managing the diagnosis, such as follow up care and sick visits, referrals to other providers and laboratory monitoring.

## Patients and Caregivers

Patients and caregivers should be encouraged and empowered to assume an active role in their care. They are responsible for asking questions and communicating their concerns. Many times a new diagnosis and treatment are overwhelming, and patients may rely on a close family member or friend as a patient advocate. The Immune Deficiency Foundation (IDF) provides the opportunity for these connections as well: www.primaryimmune.org/ask-idf. Patients are in the unique position to understand and communicate their need for education and/or concerns, especially potential barriers to care (i.e., financial, social, mental) in a timely manner. These interactions help determine patient choices and allow appropriate interventions for support. Ultimately, it is the patient who establishes the boundaries for the partnerships in this interdependent collaboration with nurse and prescriber.

## Nurse

The nurse's responsibility includes both education and delivery of the prescribed therapy. The nurse should provide patient with clear, detailed, written instructions and guidance regarding the intended

treatment. To fully appreciate the level of patient understanding, the patient should be able to demonstrate what is being taught or communicated. A printed instruction list with relevant contact information is useful as a reference guide in the patient's home[48]. Other nurse responsibilities may include compliance monitoring, documentation and advocacy.

## Compliance Monitoring

The nurse may oversee the establishment of monitoring parameters for infusions and infusion related issues, including patient compliance. Compliance monitoring begins with clear instructions for the patient regarding his/her therapy. The patient should know the name and dose of the drug being administered. The patient should be able to record specifics of each infusion in a paper or digital diary or infusion log. Information that should be recorded includes:

- Expiration dates and lot numbers of drug, the site(s) used.
- Length of time for infusion to be complete.
- Adverse events.
- Any other pertinent information.

Patients can use IDF ePHR, the Immune Deficiency Foundation's online electronic personal health record developed specifically for the PI community and available at no cost to users: www.idfephr.org. IDF ePHR can keep all medical history, current medications, infusions logs and more all in one place. This is extremely important as the patient's records reflect lot numbers and dosages in the rare event that the FDA recalls a product and/or specific lot numbers. Patients have a right to know if there is a potential problem and to seek appropriate help if there is a concern. Patients can enroll in a patient notification system for information on product withdrawals and recalls at: www.patientnotificationsystem.org.

## Documentation

Documentation is another key nurse responsibility. As with all blood products, the nurse needs to keep a record of the product, lot number(s) and expiration date(s). These data need to be readily

retrievable in the event of a product recall or if a reportable patient problem occurs. Other infusion related data including dose, duration of the infusion and assessments of the patient should also be carefully recorded. These data are important when trending information about the patient's replacement therapy and his/her overall health status and determining adjustments/changes to improve care.

## Communication

The nurse has a critical role in establishing parameters for communication between all members of the healthcare team. Variables to be determined regarding communication include the mode (telephone, e-mail, written), what needs to be communicated to whom, to whom specific problems should be communicated and communication in the event of emergency.

## Education and Advocacy

The nurse plays a critical role in patient education and advocacy. Assessment of the patient's knowledge about the disease state and treatment will guide the plan of care. There is a multitude of resources available to meet educational needs.

IDF has patient education materials readily available: www.primaryimmune.org/idf-publications. Through IDF, patients can also connect with other patients. Additionally, IDF has frequent outreach programs for patients and families. Information about new modalities of treatment, legislative initiatives and insurance issues can be valuable. For a complete list of resources available through IDF, see Appendix B.

The nurse may also provide ongoing information and referrals for resources for such diverse issues as insurance problems, pediatric patients' transition to adulthood and assumption of their own care, attending school/college, concerns regarding traveling and vacations, pregnancy and any other life cycle changes. Nurses should provide patients with information about their product manufacturer's patient assistance program. Much of this information can be found on the IDF website: www.primaryimmune.org.

Patient advocacy is a key role for nurses. Nurses naturally raise any patient issues to the prescriber that may have an impact on the patients' care or quality of life. The ultimate goal should be to empower patients to have an active role in their own care, in order for the patient to achieve the highest quality of life possible.

# APPENDIX A: QUICK NURSE'S GUIDE FOR TROUBLESHOOTING SCIG ADMINISTRATION

## Leaking at the site

- Assess catheter: is it fixed securely?
- Assess placement: may be in a location that is subject to movement, advise regarding selection of site, assess amount of subcutaneous tissue vs. muscle.
- Assess length of catheter: may be too short, can suggest catheter brand change.
- Assess volume that is being infused: may be too much volume per individual site.

## Local irritation, i.e. redness, swelling, itching

- Assure that this is normal reaction, should diminish in 24-48 hours, definitely by 4 days.
- Assess size: mosquito bite, raised wheel, quarter, plum, peach or grapefruit? Size should be consistent with volume being infused and amount of subcutaneous tissue on patients; thinner patients may have more prominent raised area and may need to decrease amount of volume per site.
- Assess length of catheter: may be too short, can suggest longer catheter length or brand change to avoid.
- Advise use of gentle massage or warm compress post-infusion.
- Assess if tape allergy: change to paper/hypo-allergenic tape.
- Assess if rotating sites appropriately, may decrease frequency of rotation.
- Decrease volume per site and/or increase infusion time.
- When priming the subcutaneous needle sets, do not allow excessive drops of IgG to cover needle or prime dry leaving a small amount of air before needle. It has been suggested that the IgG tracked through the intradermal space can cause site reactions such as redness and itching in some patients.
- Apply topical Benadryl cream to site during and after infusion.

## Extreme discomfort with needle

- Assess length: may be too long and irritating abdominal wall.
- Try catheter that allows introducer needle to be removed.
- Try topical anesthetic prior to insertion.

## Blood return observed

- In single-site tubing, remove and discard. Use new set. Notify supplier of need for replacement sets.
- In multi-site sets, clamp off the tubing that shows the blood return and then remove the catheter from that site. Check with prescribing physician regarding selecting alternative for accommodating fewer sites:
    - Infuse the drug with the remaining appropriately located sites, thus increasing volume per site. May need to recalculate to a slower rate of infusion if appropriate. Consider previous history of site reaction and other factors.
    - Infuse the original amount of volume per site with the sites that are in place. When completed, repeat the infusion session with new site to accommodate the remaining volume from the site that had blood return.
- Change entire set up and start over.

## Long infusion times

- Assess technique for infusion: solution brought to room temperature?
- Check patency of tubing, number of sites and volume per site. Decrease volume per site.
- Assess infusion rate settings, correct selection of tubing size and length to match infusion rates, check pump function, battery function, etc.
- Arrange observation of patient technique (SPP or office visit).

### Needle contaminated by touching, dropping, etc.

- Discard in appropriate waste container and use new one.

### Infusion pump stops during the infusion

- Check battery or for any line occlusion. Do not override occlusion alarm and increase psi delivered.
- Check sets for down line occlusion. Multi-site sets may cause occlusion alarm due to co-dependence of lines.
- Change catheter brands or use single independent lines that equally connected off a multi extension pigtail.
- Use 24-gauge catheter needle.
- Change type of infusion pump to simple syringe driver.
- Contact SPP or supplier for further information.
- If necessary, maintaining a closed system (leaving all connections intact), remove syringe, leave tubing attached to site and manually push plunger forward slowly to deliver remaining volume. Depending on volume, this may take some time.

### Difficulty with manipulating syringes for filling

- Lubricate the barrel of syringe for easy manipulation by aseptically pulling back on the syringe, and moving it up and down before drawing up solution or filling with air.
- Pull back the amount of air to be infused into the vial and then attach the needle aseptically to the syringe.
- Mark the level of cc to which the syringe should be drawn back by placing tape on the outside barrel at the necessary level.

# APPENDIX B: IMMUNE DEFICIENCY FOUNDATION RESOURCES

## Services for Healthcare Professionals

The Immune Deficiency Foundation (IDF) actively promotes and develops medical education and resources to improve the diagnosis, treatment and care of primary immunodeficiency diseases (PI). IDF programs for healthcare professionals promote the recognition and management of PI. All services and resources can be found at: www.primaryimmune.org/healthcare-professionals.

- *IDF Healthcare Professionals Publications* – A Full Spectrum of Educational Publications

  IDF publications are developed by world renowned immunologists and healthcare professionals. Resources are available for clinicians to learn more about PI: www.primaryimmune.org/product-category/healthcare-professionals.

- *IDF Consulting Immunologist Program* – Free Consult for Physicians

  The IDF Consulting Immunologist Program provides physicians the opportunity to consult with expert clinical immunologists about patient specific questions and obtain valuable diagnostic, treatment and disease management information. For complete details, visit www.primaryimmune.org/consult.

- *IDF Online Continuing Education Course for Nurses* – Free U.S. Accredited Course on PI

  This free, accredited course enhances the knowledge of the nurse clinician by providing an update on PI, immunoglobulin therapies and the nurse's role with these therapies: www.primaryimmune.org/healthcare-professionals/continuing-education-course-for-nurses.

- *United States Immunodeficiency Network (USIDNET)* – Patient Registry and Research Consortium

  USIDNET, funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH), is a research consortium established to advance scientific research in the field of PI. The current focus of this initiative is on the patient-consented registry, and education and mentoring for

young investigators. Find out how you can be a participant by encouraging your patients to register with USIDNET and using the registry as a resource for research. Learn more at: www.usidnet.org.

- *IDF & USIDNET LeBien Visiting Professor Program* – Promote Improved Knowledge about PI

  The IDF & USIDNET LeBien Visiting Professor Program promotes improved knowledge by providing faculty at teaching hospitals with a Visiting Professor with expertise in PI. Teaching hospitals throughout the U.S. may request a leading clinical immunologist to lead Grand Rounds or present at other educational activities. For more information, go to: www.primaryimmune.org/healthcare-professionals/lebien-visiting-professor-program.

- *IDF Communications* – Information and Resources for All Ages

  IDF communications include monthly e-newsletters, newsletters published three times a year, blogs, video channels and more! Sign up for the latest IDF communications at: www.primaryimmune.org/sign-up.

## Resources for Patients and Families

- *IDF Website* – Information Gateway for the PI Community

  Features the latest information about diagnosis, treatment, programs, services and much more: www.primaryimmune.org.

- *Patient Meetings* – Local & National Patient Educational Meetings for all Ages

  Education Meetings, retreats and conferences held across the country. For regularly updated information on all educational meetings, visit www.primaryimmune.org/events-calendar.

- *Educational Publications* – Heralded as Best Patient Resources for PI in the World

  IDF publications developed by world renowned immunologists and healthcare professionals. To download or order copies, visit www.primaryimmune.org/idf-publications.

- *Ask IDF* – Individualized Assistance for All Living with PI

  IDF offers help with the unique aspects of living with PI. Patients can use Ask IDF to answer their questions, receive peer support, help them locate a specialist in their area, and assist them with insurance issues. Go to: www.primaryimmune.org/ask-idf.

- *Join the PI Community* – Learn and Share with Others in the Community

  - IDF Social Networks – IDF Friends, www.idffriends.org, and IDF Common Ground, www.idfcommonground.org, are two exclusive social networks for patients living with PI.

  - IDF Get Connected Groups – Individuals and families can meet others living with PI in their local area. To find an upcoming meeting, visit www.primaryimmune.org/events-calendar.

  - IDF Advocacy Center - Monitor public policy issues that are critical to patients at national and state levels. Learn more at www.primaryimmune.org/idf-advocacy-center.

- *IDF Walk for Primary Immunodeficiency* – An Extraordinary Experience to Support the PI Community

  IDF Walk for Primary Immunodeficiency unites people touched by primary immunodeficiency diseases (PI) to help create better lives for individuals living with these rare, chronic disorders. The walks provide a unique opportunity to for the PI community to come together to raise funds for critical materials, programs, and research for thousands of people who are searching for answers and support. Visit: www.walkforpi.org for more information.

- *Valuable Tools* – Improving Health, Powering Research

  IDF ePHR, www.idfephr.org, is the electronic personal health record for people with PI to track their health and the opportunity to consent into PI CONNECT, the IDF Patient-Powered Research Network, www.idfpiconnect.org, which transforms research by bringing together patient data with clinical data.

- *Volunteering Opportunities* – A Robust Volunteer Network

  IDF Volunteers help assist with educational meetings, advocate for public policy, visit plasma centers and help organize fundraising events throughout the country. Learn more at: www.primaryimmune.org/volunteer.

## Additional Resources

- *Patient Notification System*
  www.patientnotificationsystem.org
  888-UPDATE-U (888-873-2838)

  The Patient Notification System is a program developed by the Plasma Protein Therapeutics Association (PPTA) to notify patients who receive plasma products, such as intravenous immunoglobulin (IVIG), about product recalls.

- *Product Information*

  Information regarding the immunoglobulin (Ig) products currently licensed in the U.S. is available from each specific manufacturer via the individual corporate websites. The manufacturers of Ig often provide up-to-date information and added financial resources for individuals and families living with PI on their websites. The resources vary over time and between manufacturers. Check IDF website: www.primaryimmune.org/treatment-information.

**Immune Deficiency Foundation**
www.primaryimmune.org
800-296-4433
idf@primaryimmune.org

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