IDF Guide to Ig Therapy

Immunoglobulin Replacement Therapy for People Living with Primary Immunodeficiency Diseases

Immune Deficiency Foundation

This publication contains general medical information that cannot be applied safely to any individual case. Medical knowledge and practice can change rapidly. Therefore, this publication should not be used as a substitute for professional medical advice. In all cases, patients and caregivers should consult their healthcare providers. Each patient's condition and treatment are unique.

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Immune Deficiency Foundation Guide to Immunoglobulin Replacement Therapy for People Living with Primary Immunodeficiency Diseases

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Introduction

Immunoglobulin (Ig) replacement therapy is one of the most important and successful therapies for people with primary immunodeficiency diseases (PI), specifically for those who are antibody deficient. The therapy is both lifesaving and lifelong, and it plays a huge role in the lives of many people with PI.

This guide was developed for patients and caregivers to help increase understanding of Ig replacement therapy. An increased understanding puts patients and caregivers in a better position to make informed decisions regarding care. Education about the therapy can also build confidence and create a level of understanding that can reduce a patient's anxiety about a treatment that can be frightening. If a patient and/or caregiver is well educated about the treatment, they will understand the goals they need to work towards in order to improve health and be more motivated to reach those goals, which will in turn improve their overall health.

Chapter 1

About Immunoglobulin Replacement Therapy

What Are Primary Immunodeficiency Diseases?

Primary immunodeficiency diseases (PI) are a group of disorders caused by basic defects in immune function of the cells and proteins of the immune system. There are more than 350 types of PI. Some are relatively common, while others are quite rare. Some affect a single cell or protein of the immune system and others may affect two or more components of the immune system. Although PI may differ from one another in many ways, they share one important feature. They all result from a defect in one or more of the elements or functions of the normal immune system.

What Is Immunoglobulin Replacement Therapy?

There are several specific medical therapies available for people with PI with antibody deficiency that account for more than 50% of the primary immunodeficiencies. These illnesses, such as Common Variable Immune Deficiency (CVID), X-Linked Agammaglobulinemia (XLA) and other disorders, are characterized by a lack of and/or impaired antibody function.

Immunoglobulin (Ig), also known as gamma globulin or immune globulin, refers to the component of blood plasma that contains immunoglobulins or antibodies. These antibodies are used in the body to neutralize bacteria and viruses. They are large, Y-shaped proteins produced by specialized lymphocytes called plasma cells.

The immunoglobulins in the serum or plasma are IgG, IgM, IgA, IgD and IgE. Individuals who are unable to produce adequate amounts of antibodies may benefit from Ig replacement therapy. Only the IgG is purified from the plasma to produce therapeutic Ig products, so Ig used for treatment contains 95-98% pure IgG with small amounts of other plasma proteins including some IgA.

Ig replacement therapy reduces the susceptibility to infections, can optimize patient health and improve their quality of life. For all of these therapies, individual risks and benefits should be discussed with a healthcare provider.

History of Immunoglobulin Replacement Therapy

Gamma globulin derived from human plasma was first introduced as a treatment option in 1952 when gamma globulin was injected intramuscularly (IM) to treat patients with recurrent infections who had antibody immune deficiencies[1]. Dosing was very difficult because only small amounts of gamma globulin could be given in each painful shot. Much scientific investigation in the 1960s and 1970s finally led to a suitable gamma globulin product that could be used intravenously. People with PI have been treated with intravenous immunoglobulin replacement therapy (IVIG) for over 30 years. IVIG has greatly reduced the complications of bacterial infections in people affected by antibody deficiencies.

With the discovery of well-tolerated preparations of IVIG in the 1980s, the suboptimal, painful IM administration was no longer used[2]. This shift to IVIG changed the face of PI treatment.

Uses of Immunoglobulin Replacement Therapy

Human immunoglobulin was originally used as antibody replacement therapy in primary and secondary antibody deficiencies. Patients with primary antibody deficiencies are susceptible to bacterial infections and require lifelong Ig replacement therapy. In primary or secondary hypogammaglobulinemia (low IgG), Ig replacement protects against infections by providing an adequate amount of IgG in the blood[3].

Human immunoglobulin plays an important role in the treatment of many diseases, including diseases for which there is no other alternative treatment[3,4]. Currently, more than 100 inflammatory and autoimmune disorders are treated with IVIG.

Route of Administration

Today, Ig replacement therapy is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). The patient or caregiver and the prescriber should have a discussion about which route of administration is most appropriate for each patient.

IVIG has allowed infusion of higher doses over a short time and has been the standard route of administration. It must be administered by a medical professional, and the procedure must be scheduled. More details about this therapy can be found in Chapter 2.

SCIG was utilized as early as the 1970s[5], but it did not gain approval from the Food & Drug Administration (FDA) in the U.S. until 2006. This therapy does not require venous access and is associated with the slow release of Ig from the subcutaneous tissues into the blood, which enables IgG levels to remain high and stable between infusions[6]. Additional details about this therapy can be found in Chapter 3.

Currently among those receiving Ig replacement therapy, approximately 50% use IVIG and 50% use SCIG. The patient or caregiver and the prescriber need to make a decision on the route of therapy that is best for the patient. Both options are effective but must be individualized.

Manufacturing

All Ig products are produced from donated human plasma. There are more than 25 different Ig preparations available worldwide[7]. The preparations vary in a number of ways, including the distribution of IgG subclasses, stabilizers, and infusion details. All Ig preparations are made from human plasma, which is pooled from thousands of plasma donations. The product contains at least 90% intact IgG molecules. Each Ig manufacturer has a unique product that varies in its function and application. All Ig products licensed in the U.S. are made from plasma collected in the U.S.

Safety

There are multiple safety steps in the production of Ig. Donor screening, viral removal and inactivation of viruses are both crucial to safe manufacturing.

All plasma donors undergo a very rigorous screening process and cannot give their plasma unless they pass this screening. Donors are asked specific questions about risk factors that could affect the safety of the donation and are deferred from donation if risk factors are identified. Plasma centers can look at the donation history for each donor. The FDA also requires blood centers to maintain lists of unsuitable donors to prevent further donations from these rejected donors. As an added protection, donors must return to donate within a set timeframe for rescreening. If a donor does not return within that timeframe, their prior plasma donation will be discarded.

After donation, the individually donated plasma is tested for infectious agents before being pooled with plasma from other donors. Once the plasma is pooled, the entire pool is tested for the markers of HIV and hepatitis A, B, and C viruses. The pooled plasma is then divided up and different methods of fractionation and filtration help to separate out the actual IgG molecule. At multiple times throughout this process, the pool is tested for viral safety before additional safety measures are implemented.

In the mid-1990s, rare clusters of non-A, non-B hepatitis (now called hepatitis C) were documented after the use of some IVIG products. This prompted the addition of an extra viral inactivation step in the manufacturing process. Now multiple safety measures, including pasteurization, low pH, low pH with pepsin, and solvent detergent help dissolve the lipid enveloped viruses, including hepatitis C. An additional safety step is chromatography, a technique widely used to obtain pure compounds from mixtures. More recently, a final ultrafiltration step has been added to remove the possibility of transmission of prion related diseases. Transmission of HIV has never been documented with the use of any Ig replacement therapy[8].

Dosing

Ig replacement therapy is typically dosed based on the patient's weight. Many factors, however, are considered when the medication is prescribed. Typically, a starting dose is between 400-600mg/kg/month. Doses are adjusted to clinical effect, with the expectation of minimizing the frequency and severity of recurrent infections while minimizing side effects of the medication. IgG levels are usually monitored over time and correlated with the patient's response to therapy, specifically related to infection rates.

With SCIG, there is a steady level of IgG present in the bloodstream due to the more frequent dosing regimens (Figure 1.1). With IVIG, the dosing at longer intervals may cause peaks and valleys (Figure 1.2), but the goal is to keep the levels of Ig in the blood stream above a certain level even at the lowest points.

Figure 1.1: SCIG Weekly

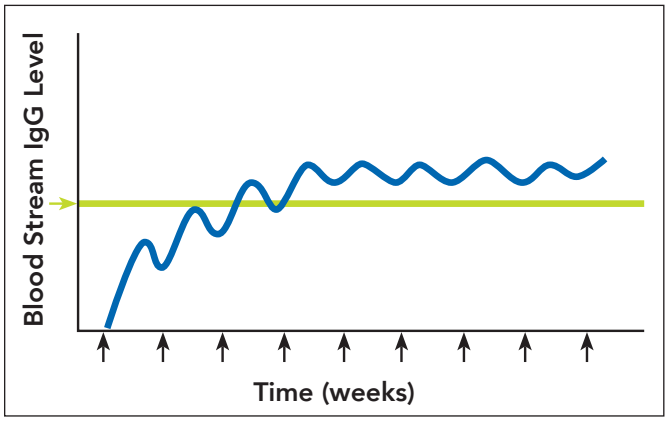
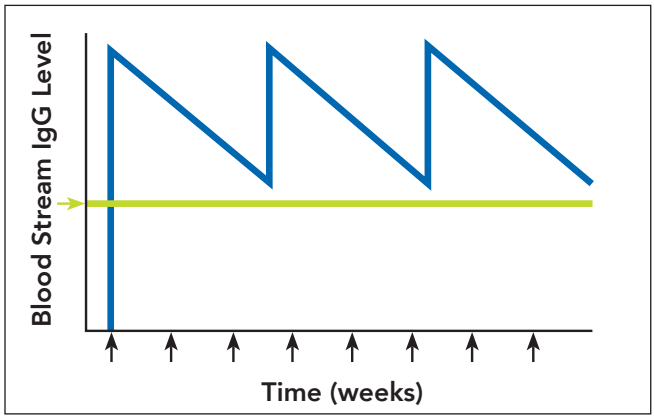


Figure 1.2: IVIG Every 3-4 Weeks



Chapter 2 Intravenous Immunoglobulin Replacement Therapy (IVIG)

Uses of Intravenous Immunoglobulin Replacement Therapy (IVIG)

Intravenous immunoglobulin replacement therapy (IVIG) has been used in primary immunodeficiency diseases (PI), other immune deficiency disorders, and in a variety of inflammatory and autoimmune diseases. This therapy has been approved by the Food & Drug Administration (FDA) for use in primary immunodeficiency diseases; idiopathic thrombocytopenic purpura (ITP); Kawasaki disease; chronic inflammatory demyelinating polyneuropathy; pediatric HIV; chronic B-cell lymphocytic leukemia; and bone marrow transplantation[3].

Infusions of immunoglobulin (Ig) are given through an IV in your arm (Figure 2.1). Most immunologists strongly discourage the use of central catheters to administer IVIG due to the increased risk of serious blood infections. Placing a central venous catheter (i.e., port) due to poor venous access increases the risk of infections and should not be done. Given the very serious risk involved with the use of implantable ports, patients should consider switching to the subcutaneous route of Ig administration.

Figure 2.1: Intravenous Access through Arm

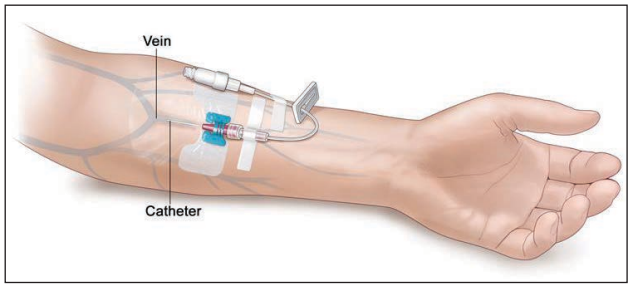


Photo Credit: National Cancer Institute, www.cancer.gov

IVIG is typically given every 3-4 weeks at a dose determined by the prescriber. Infusions can be given in various settings including an inpatient or outpatient infusion suite, physician office, or in the home. IVIG is administered by a medical professional, and the procedure is scheduled in advance. In special extenuating circumstances, patients can be instructed to self-infuse this therapy after they are stable on the treatment as long as IV access can be established. The medical professional should, however, stay with the patient for the length of the infusion.

The limitations of IVIG include:

- Some people may have poor venous access.
- There can be recurrent and limiting systemic reactions in some patients.
- IVIG requires treatment in an infusion center or through home infusion.

Currently, there are several products available that can be administered intravenously using a number of regimens. They differ based on concentration, stabilizers and infusion specifics. For a complete, updated list of Ig products and details, visit the IDF website: www.primaryimmune.org/ig-products.

Detailed information including training videos and patient resources is available on the manufacturer's websites for each product.

Side Effects

Although IVIG is frequently used for long periods of time and is generally considered safe, IVIG can have adverse effects, both localized and systemic. Systemic reactions to IVIG infusion occur in 3% to 15% of patients. They are usually self-limiting and can be avoided by decreasing the rate of the infusion[9].

Patients who have never received IVIG or who are switching manufacturers may be at increased risk for adverse reaction. If someone receives IVIG during an acute, severe infection, they may also be at increased risk for adverse reactions. Patients with a history of migraine headache may be at risk for a post-infusion headache reaction. The prescriber of the therapy can modify IVIG dosing by decreasing the rate of infusion or adding other medications to the prescription. Medications such as acetaminophen, diphenhydramine, non-steroidal anti-inflammatory drugs, or steroids can help prevent side effects during and after an infusion.

While IVIG brands differ by manufacturer, the listed side effects are almost identical on each package insert. Some common infusion reactions are headache, nausea, fever and chills, flushing, wheezing, vomiting, backache, muscle aches, joint aches or chest tightness. Side effects experienced during an infusion of Ig are almost always related to the rate of the infusion. Stopping or slowing the infusion is usually the only intervention needed to alleviate symptoms. Sometimes a switch in product is tried as some patients may tolerate a different brand better than another.

Some side effects can happen up to 72 hours after an infusion of Ig. These delayed symptoms are not usually associated with the rate of infusion. Some rare side effects include:

- Aseptic meningitis has been seen up to 72 hours after infusion of IVIG[10] and may be more prevalent in people with a history of migraine headaches. Hydrating prior to IVIG may protect from this side effect.
- Anaphylaxis is very rare and may be associated with anti-IgA antibodies in some patients who have the absence of IgA[11]. The role of anti-IgA antibodies in causing anaphylaxis in IgA-deficient patients receiving Ig replacement therapy is still controversial[12]. The newer liquid IVIG products have low concentrations of IgA. In addition, reactions due to anti-IgA antibodies do not occur with SCIG.
- Acute renal failure has been seen after infusion of IVIG; 90% of these cases, however, are associated with sucrose-based products and are not necessarily associated with the timing of the infusion. Individuals over age 65 or who have preexisting kidney failure may be at an increased risk of acute renal failure[13].
- Blood clots have been associated with IVIG infusion. The relationship between IVIG infusion and an increased risk of blood clots is thought to be due to a plasma contaminant (Factor XIa) that all manufacturers test for in the final product to reduce this risk. Risk factors for blood clots include heart disease, advanced age, previous thrombotic event, clotting disorder, hypertension, diabetes, high cholesterol, renal disease, obesity and immobility[14].
- Hemolytic anemia is a rare but reported side effect of IVIG. The risk of significant hemolysis (breakdown of blood cells) appears greater in patients who receive high dose IVIG[15].

What Side Effects to Report to the Prescriber

The patient is responsible for reporting any side effects or discomforts experienced during or after an infusion of IVIG to the prescriber of the therapy and to the nurse administering the therapy.

Side effects to report include but are not limited to:

- Headache
- Body aches
- Fever/chills
- Diarrhea
- Muscle cramps
- Nausea and vomiting
- Symptoms of infection

Optimized Infusion Experience

A nurse trained in the administration of this therapy should administer IVIG therapy. Many of the side effects that happen during an infusion are related to rate. The nurse should be experienced in infusing this medication and aware of when to slow the rate of infusion or stop the infusion if necessary. If the patient is aware of steps that they can take to prepare for each infusion, the infusion process will be much smoother. It is important to be well hydrated going into an infusion of IVIG. This will not only help the nurse get an IV started, but it will decrease the risk of headache after each infusion. Premedication prescribed by each prescriber is designed to prevent side effects. It is important to take the premedication as prescribed. Patients should record the infusion experience on a calendar or journal so that any adverse experience can be reported to the nurse and the prescriber prior to the next infusion so that adjustments can be made to the rate, premedication, dose, etc.

The IDF ePHR is an electronic personal health record designed for people with PI that allows users to record health information like their infusion experience. Learn more at: www.idfephr.org.

Monitoring

Routine lab tests may be ordered by the prescriber to make sure the patient is tolerating IVIG. This may include looking at IgG levels just before the next infusion is due. It is also necessary to monitor other blood levels such as total blood counts and measures of kidney and liver function. Most importantly, the prescriber will want to monitor the patient for infections to be sure IVIG is having the desired effect of decreasing serious infection. Usually these blood tests are only performed yearly unless there is a change in the patient's condition.

Chapter 3 Subcutaneous Immunoglobulin Replacement Therapy (SCIG)

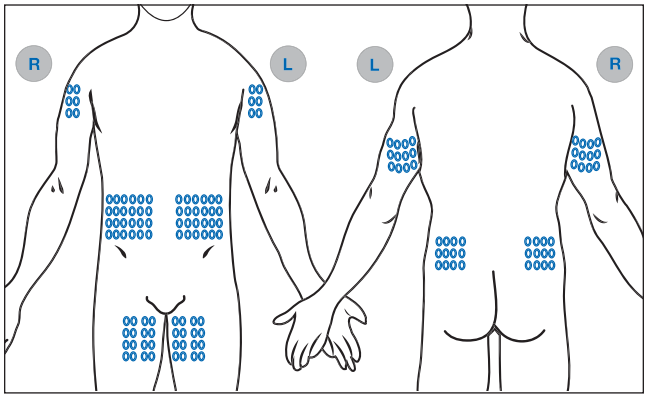
Use of Subcutaneous Immunoglobulin Therapy (SCIG)

The first use of immunoglobulin (Ig) replacement therapy for primary immunodeficiency diseases (PI) was delivered subcutaneously approximately 70 years ago. Later, the intramuscular then intravenous routes of administration replaced this. Given various practical factors, subcutaneous immunoglobulin replacement therapy (SCIG) has regained popularity in the U.S., since the 2000s. SCIG has increased the options available for patients needing Ig replacement therapy for PI and certain neuromuscular diseases. Currently, there are several products available that can be administered subcutaneously using a number of regimens. They differ based on concentration, stabilizers and infusion specifics. For a complete, updated list of Ig products and details, visit the IDF website: www.primaryimmune.org/ig-products. Detailed information including training videos and patient resources is available on the manufacturer's websites for each product.

SCIG Regimens

Greater flexibility in the dosing and an increase in the number of products available has contributed to the expanded use of SCIG. The following are currently available for subcutaneous use: 10% preparations, 20% preparations, and facilitated SCIG (a 10% SCIG preparation plus hyaluronidase). In general, SCIG regimens require the patient or caregiver to learn how to self-administer at home. Both forms of SCIG allow for self-administration at home, while facilitated SCIG allows for self-administration at home or in-office administration with a nurse, depending on the patient's insurance and preference.

Figure 3.1: SCIG Infusion Sites



SCIG is usually infused under the skin of the abdomen, thighs or outer buttocks at one or multiple sites, depending on the volume being infused (Figure 3.1). The total monthly dose is calculated by the prescriber, then divided according to the interval between infusions. The number of needle sticks (sites) is also calculated for the patient depending on the volume and the concentration of the SCIG to be infused. Larger intervals between infusions require larger volumes of product to achieve the same total dose. SCIG can be given daily, weekly, every 2 weeks, or multiple times per week, as long as the total monthly dose is divided appropriately. Dosing daily involves subcutaneous injection of small volumes without the need for a pump using only a syringe. Facilitated SCIG can be given every 3-4 weeks, to deliver the total monthly dose at once, into the subcutaneous space. This is "facilitated" by the use of human bioengineered hyaluronidase. Hyaluronidase is an enzyme which is injected into the subcutaneous space before the Ig to expand the subcutaneous space and allow more medication into each site. The effects of the hyaluronidase enzyme revert back to normal subcutaneous tissue in 24-48 hours.

The length of the infusion varies depending on the volume infused, but generally takes up to 1-2 hours (or less). For SCIG, some of the standard (less concentrated) 10% IVIG preparations can be used via the subcutaneous route. There are two 20% (more concentrated) preparations indicated for subcutaneous use only that allow for smaller volumes to deliver the same dose with fewer needle sticks. With the 20% preparations, site volumes can range from 30ml to 60ml per site depending on patient tolerance. In facilitated SCIG, about 300-600ml can be delivered in one site or divided into two sites as tolerated.

In general, SCIG is delivered using a small needle attached to tubing and a syringe that is placed in either an automatic mechanical pump or an electric programmable pump. Both pumps are portable. Alternatively, some patients may prefer or better tolerate SCIG delivered by subcutaneous push, meaning that a small amount of SCIG is injected daily under the skin without the use of a pump. The Ig products come in a variety of vial sizes depending on the manufacturer. Several needle and tubing sizes are available, and troubleshooting problems with SCIG often involves reviewing that the equipment being used, such as needle sets, tubing, pump, etc., are appropriate for the patient.

Dosing

As in IVIG, the typical starting dose is between 400-600mg/kg/month. The monthly dose is divided into infusions daily, weekly, or every 2 weeks. In contrast, facilitated SCIG enables the whole monthly dose to be infused every 3 to 4 weeks. Doses are adjusted to clinical effect, with the expectation of minimizing the frequency and severity of recurrent infections. IgG levels are monitored over time, correlated with clinical outcomes, and the dose is adjusted as necessary. With SCIG, there is a steady level of IgG present in the bloodstream due to the more frequent dosing. With facilitated SCIG, peak levels are not as high and trough levels are not as low, as with IVIG.

Optimized Infusion Experience

Several variables involved with SCIG allow optimization of the infusion experience for patients. Some of these variables include number of needle-sticks, infusion sites, volume infused/site, needle length and pump type. The number of needle-sticks may be reduced by increasing the volume infused per site. Less number of sites are needed with the more concentrated 20% products. Conversely, more sites may be needed if the less concentrated solutions are used. With facilitated SCIG, which delivers the whole month's dose at once, the dose can be divided between 1-2 sites, depending on how the patient tolerates. If the patient is experiencing discomfort using the abdomen, other sites such as the thighs can be used. If the patient prefers to dose every month rather than weekly or every 2 weeks, then facilitated SCIG using 1-2 sites may be the best choice. For patients who have issues with tolerating infusions, smaller volumes of SCIG daily may be needed. Several needle lengths are also available that can be tried depending on how lean the patient is. A variety of infusion pumps are available ranging from a simple and portable mechanical pump to more complicated programmable pumps. Additionally, SCIG provides freedom of scheduling for those who self-infuse at home, resulting in fewer school and workday losses.

Side Effects

In general, SCIG is associated with fewer severe adverse events than IVIG. SCIG is an option to consider when IVIG is not well tolerated, when there is poor venous access, or when the patient's lifestyle is more compatible with SCIG than IVIG. SCIG can be considered for children, adults, pregnant women and the elderly, and for patients with IgA deficiency. Systemic side effects are usually mild, although adverse reactions have been reported. Severe reactions rarely occur, and patients who have had severe reactions to IVIG might be at a higher risk. Premedication is usually not required for SCIG. The most common adverse reaction reported is a local redness and irritation at the injection site. Usually these mild localized reactions improve with repeated infusions. In rare cases, the injection site reactions can be severe. To improve or avoid the infusion site reactions, and decrease the chance of other problems, patients need thorough training to ensure that proper technique is used to access the subcutaneous tissue. Local skin reactions may be due to inadequate needle length not satisfactorily reaching the subcutaneous tissues. For those with fear of needles, a topical numbing medicine can be applied to the skin prior to the subcutaneous infusion. Also, it is important to note that the 20% formulations are intended only for subcutaneous use.

Monitoring

With SCIG, there is a steady state level of IgG in the circulation due to more frequent infusions of smaller doses. Peak and trough levels are not as extreme, and the level is more consistent on a daily basis. Routine lab work including blood counts and markers of liver and kidney functions should be performed at least once per year, and more often depending on clinical circumstances or insurance requirements. None of the currently available products for SCIG, however, are stabilized with sucrose, making renal complications less likely. Smaller doses given subcutaneously also minimize risks due to fluid overload.

Practical considerations

Many practical considerations should be taken into account when deciding if SCIG is the right choice. SCIG requires more frequent administrations (daily, weekly, every 2 weeks), unless the facilitated SCIG route is chosen (every 3-4 weeks). Medical supervision is not required for home infusion, so the ability of the patient to adhere to the treatment regimen is an important consideration. If there is a fear of needle-sticks, training strategies for self-infusion including numbing creams should be considered. Manual dexterity, or the ability to make coordinated hand and finger movements to manipulate objects, is also required to draw up SCIG and manage the pump. SCIG provides the freedom to administer Ig at home at any time of day. This has been shown to enhance the quality of life for many patients. SCIG is associated with a lower rate of systemic side effects[16], making this route of administration a good option for those experiencing unwanted adverse effects from IVIG. Administration of more frequent, smaller volumes provides a steady level of Ig, avoiding high peak levels that may be associated with side effects of IVIG, such as headaches and symptoms of wear-off. Furthermore, the optimal route of infusion (SCIG vs. IVIG) may change over time for any given patient. SCIG should be given serious consideration for college students and those patients whose jobs require frequent travel. Patients should remember that these options are available and to talk with their doctor regarding changes in route as appropriate.

Immunoglobulin Treatment Options

This chart is designed to facilitate a discussion between individuals and caregivers living with primary immunodeficiency diseases (PI) and their healthcare providers when immunoglobulin (Ig) replacement therapy is determined to be the treatment of choice and is deemed medically necessary. Decisions on which therapy is best should be made with some of these factors in mind.

	Intravenous Immunoglobulin (IVIG)	Subcutaneous Immunoglobulin (SCIG)	Hyaluronidase Facilitated Immunoglobulin (fSCIG)
Who?	Indicated for adult and pediatric patients with PI.	Indicated for adult and pediatric patients with PI.	Indicated for adult patients with PI.
How?	Usually administered by a nurse.	Self-administered.	Either self-administered or given by a nurse.
Where does it go?	Infused directly into the bloodstream through a vein.	Infused or injected under the skin into the subcutaneous tissues of the arms, belly, outer buttock or the thighs.	Infused under the skin into the subcutaneous tissues of the belly, outer buttock or the thighs.
When?	Usually given every 3-4 weeks.	Can be given on a flexible schedule from daily to every 2 weeks.	Can be given every 3-4 weeks.
How long?	Can take 2-6 hours to infuse.	Can take 5 minutes to 2 hours to infuse or inject.	Can take 1-2 hours to infuse.
Where is it given?	Can be infused at home, in a hospital or an outpatient infusion center depending on insurance and patient preference.	Usually administered in a home setting after the patient is trained to be independent.	Can be infused at home or in an outpatient infusion center depending on insurance and patient preference.
Side effects?	Patients can have side effects that are often related to the rate of infusion and can be treated and prevented with other medications, given before or after the treatment.	Skin can be red and irritated at the site of injections. This often improves with each injection.	Skin can be red and irritated at the site of injections. This often improves with each injection. The volume per injection is larger than standard subcutaneous (under the skin) injection, so the volume is more visible under the skin, and may take 48-72 hours to totally absorb.

Frequently Asked Questions

What if I choose one type of immunoglobulin replacement therapy and I am not satisfied?

People with primary immunodeficiency diseases (PI) often switch between methods of immunoglobulin (Ig) replacement therapy based on life circumstances. For instance, a teenager may be more compliant when a nurse is administering the medicine intravenously (IVIG), but when that teen grows up and goes away to college, they may choose to do subcutaneous immunoglobulin (SCIG). Also if one method causes undesirable side effects, you can switch to another method. With consultation from your provider, you can decide what treatment works best for you.

Which immunoglobulin product is more effective?

All immunoglobulin products are composed of the same active antibody components so they will all help replace missing antibodies in patients with antibody deficiency. Some patients have side effects to one or more products, but these reactions are more likely related to the stabilizers and other components used in the manufacturing of the different products. Insurance companies may restrict certain IVIG or SCIG brands depending on their formulary, but patients should have access to the treatment that is best for them. A patient or caregiver should work with healthcare providers and the insurer to confirm that the patient has access to the treatment he or she needs.

Can I travel if I am receiving immunoglobulin replacement therapy?

Yes, it is possible to travel with all the Ig replacement therapy methods. If someone is receiving treatment every 3-4 weeks, it is easy to schedule the therapy around one's travel schedule. If they are using SCIG, it is possible to carry one's medication and supplies during the trip. It is also possible to be flexible with dosing to make the itinerary work. Consider having a letter from your healthcare provider if you are flying with your product and supplies. For more information, go to: www.primaryimmune.org/travel.

Which method costs less?

After it is determined to be medically necessary for the type of PI, that patient's insurance company will pay for their Ig. The cost of the different products vary greatly, but the financial responsibility of the insured is usually based on the insurance plan. Nursing costs are sometimes an added expense to the therapy. Home care benefits can be different from major medical benefits and that can sometimes make one site of care more expensive than another. It is important to know the coverage of the patient's insurance plan. For more information about choosing insurance and other related issues, visit the IDF Patient Insurance Center: www.primaryimmune.org/patient-insurance-center.

What is the difference between the manufacturer and the specialty pharmacy? Why can't I get my Ig at the local pharmacy?

Human immunoglobulin is not available at the local pharmacy. Human immunoglobulin is considered a specialty drug due to its high cost, use for complex disease, and requirement for special handling and administration. The manufacturers produce the immunoglobulin products that are then distributed to specialty pharmacies. According to the Academy of Managed Care Pharmacy (AMPC), specialty pharmacies are different from traditional pharmacies because they coordinate many aspects of patient care and disease management. Specialty pharmacies are designed to deliver medications with specialized handling, storage and distribution requirements with standardized processes. Because of its status as a specialty drug, prior authorization for use of human immunoglobulin from the insurance company is required. The specialty pharmacy can sometimes assist the prescriber in obtaining prior authorizations and in accessing financial assistance for patients requiring treatment with specialty drugs such as immunoglobulin.

Does my infusion nurse have to be certified?

No, an infusion nurse does not have to be certified, but requiring documentation of competency or experience may include Certified Registered Nurse Infusion (CRNI) from the Infusion Nurses Society (INS), Immunoglobulin Certified Nurse (IgCN) from the Immunoglobulin National Society (IgNS), or evidence of training by the specialty pharmacy itself or by the individual as many specialty pharmacies mandate training before the nurse can administer or teach Ig replacement therapy.

Questions that could be asked of an infusion nurse:

- Have you been formally trained on Ig replacement therapy administration? Please provide evidence.
- How much experience do you have giving IVIG? Teaching SCIG self-administration?
- How confident are you that you will do a good job with my therapy? What resources do you have as nurse if you need help with any aspect of administration? (There is usually a plan that should be articulated to the patient about possible situation, including emergent situations).

Guide for Troubleshooting SCIG Administration

Leaking at Site

- Look at needle. Is it screwed on to the tubing securely?
- Check needle placement. It should not move or wiggle.
- Check the amount of subcutaneous tissue at injection site. Consider choosing a site with more tissue.
- Check the length of needle: may be too short—could ask nurse about needle brand change.
- Look at volume being infused. It may be too much volume into each site. Ask nurse about adjusting accordingly.

Local Irritation (Redness, Swelling, Itching)

- Know that skin reactions are common and expected, and most are mild in nature.
- Check size: mosquito bite, quarter-sized, plum, peach, grapefruit—size should be consistent with volume being infused and amount of subcutaneous tissue. Thinner patients may have more prominent raised areas; decrease amount of volume per site if necessary. Ask nurse about adjusting site location accordingly.
- Check length of needle: may be too short. Nurse can suggest longer needle length or brand change to avoid discomfort.
- If you have a tape allergy, change to paper/hypoallergenic tape.
- Ask your nurse about rotating sites appropriately: may decrease frequency of irritation.
- Check with nurse about decreasing volume per site and/or slowing infusion time
- When priming the subcutaneous needle sets, do not allow drops of Ig to cover needle.
    - Leave a small amount of air before needle. It has been suggested that the Ig can track up the needle and out of the skin, and can cause site reactions such as redness and itching.
- Use gentle massage, warm or cool compresses post infusion.
- Stop the infusion if you develop a rash or hives all over your body. Contact physician.

Extreme Discomfort with Needle Placement

- Check length: may be too long and causing irritation to abdominal muscle if going too deep.
- Ask nurse about topical anesthetic prior to insertion.

Blood Return Observed

- Do not infuse in site that has blood return. SCIG should be infused into subcutaneous tissue only.
- Do not administer if blood is seen in the tubing after the needle is placed.
- In single-site tubing, remove and discard the needle. Use new set. Notify supplier of need for replacement sets.
- If using multiple needle sets, clamp off the tubing that shows the blood return and then remove the needle from that site. It is ok to infuse into the other sites thus increasing the volume per site.

Infusion Times Too Long

- Check site location (do not inject into skin that has scar tissue).
- Ask nurse about infusion rate settings, correct selection of tubing size and length to match infusion rates, check pump function, battery function, etc.

Needle Contaminated by Touching, Dropping, etc.

- It is important that the needles that go into the skin not be contaminated. Discard questionable needles in appropriate waste container and start over.

Infusion Pump Stops during Infusion

- Check battery. Check for any line kinks or clamps. Do not override occlusion alarm unless instructed to do so by a nurse.
- Change size of needle. Perhaps a thin needle is causing too much pressure for the pump.
- Change type of infusion pump.
- Contact specialty pharmacy provider or supplier for further information.
- If there is suspected pump failure, the patient can try to manually push the medicine into the subcutaneous space. This will take a lot of force and will take some extra time.

Difficulty with Manipulating Syringes for Filling

- Loosen the syringe for easy manipulation by 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.

Resources

Immune Deficiency Foundation Resources

The Immune Deficiency Foundation (IDF), founded in 1980, is the national nonprofit patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases (PI) through advocacy, education and research.

Immune Deficiency Foundation

www.primaryimmune.org, 800-296-4433, idf@primaryimmune.org

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.

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

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

- **Education Meetings** – Local & National 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.

- **Young Adult Online Education Series** – Presentations and Discussions to Answer Your Questions

  The IDF Young Adult Online Education Series was developed specifically for young adults to meet the needs and interests of this group. Learn tips for tackling the unique issues faced by young adults with PI: www.primaryimmune.org/young-adults/webinars.

- **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. People living with PI 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.

- **IDF Peer Support Program** – Speak with Someone Who Understands

  The IDF Peer Support Program is a caring community that connects people who share similar relationships to PI. Participation in the program gives you the opportunity to interact with one of IDF's peer support volunteers, who is a trained volunteer with personal experience living with PI. This free resource is for anyone personally affected by PI – a patient, parent or other family member, friend or caregiver. In addition, you can take comfort in knowing your communications and correspondence will be held in the strictest confidence. Request peer support at: www.primaryimmune.org/ask-idf.

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

- **IDF Friends Community Page**

  IDF Friends, www.idffriends.org, is an exclusive social network for people living with PI.

- **IDF Get Connected Groups**

  Individuals and families can meet others living with PI in their local area. To find an upcoming group, visit www.primaryimmune.org/events.

- **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 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. For more information, visit www.walkforpi.org.

- **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.

- **Immunoglobulin 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 the IDF website: www.primaryimmune.org/ig-products.

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/idf-publications.

- **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.

- **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. 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.

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Information about Primary Immunodeficiencies

Immune Deficiency Foundation
www.primaryimmune.org
800-296-4433

The Immune Deficiency Foundation (IDF), founded in 1980, is the national nonprofit patient organization dedicated to improving the diagnosis and treatment of people with primary immunodeficiency diseases through advocacy, education and research.

International Patient Organization for Primary Immunodeficiencies
www.ipopi.org

International Patient Organization for Primary Immunodeficiencies (IPOPI) is an international organization whose members are national patient organizations for primary immunodeficiency diseases. The website provides general information on primary immunodeficiency diseases and resource contacts for patients and professionals worldwide.

The Jeffrey Modell Foundation
www.info4PI.org
The Jeffrey Modell Foundation is dedicated to early and precise diagnosis, meaningful treatments, and ultimately cures of primary immunodeficiency diseases.

Disease Specific Patient Groups and Organizations

A-T Children's Project
www.atcp.org

The A-T Children's Project is a nonprofit organization that raises funds to support and coordinate biomedical research projects, scientific conferences and a clinical center aimed at finding a cure for Ataxia-Telangiectasia (A-T), a lethal genetic disease that attacks children, causing progressive loss of muscle control, cancer and immune system problems.

Hereditary Angioedema Association, Inc.
www.haea.org

Founded and staffed by patients with HAE and caregivers, U.S. Hereditary Angioedema Association, Inc. (US HAEA) is a nonprofit patient advocacy organization dedicated to serving persons with angioedema. The Association provides patients and families affected by HAE with a support network and a wide range of services including physician referrals, and individualized patient support.

Severe Combined Immune Deficiency
www.scid.net

The SCID Group is designed to help families dealing with Severe Combined Immune Deficiency (SCID) find a support network of similar families. Go to www.scid.net, and select the "SCID Email Listserv Support Group" to sign up.

SCID, Angels for Life
www.scidangelsforlife.com

The SCID, Angels for Life Foundation offers emotional support to affected families while also providing limited financial assistance to families currently going through treatment for Severe Combined Immune Deficiency (SCID).

Understanding XLP
www.xlp.ca

This site provides families and patients with X-linked Lymphoproliferative Disorder (XLP) a means of communication.

Wiskott-Aldrich Foundation
www.wiskott.org

This site provides information about Wiskott-Aldrich Syndrome (WAS). The links on this site include information for patients and families, the latest research related to WAS and financial support.

XLP Research Trust
www.xlpresearchtrust.org

This organization promotes and funds research into the cause, management, symptoms and cure for X-linked Lymphoproliferative (XLP) disease, raises awareness of the disease, and is a point of contact and support for families affected by XLP.

Immunoglobulin Replacement Therapy Manufacturer Information

Companies who manufacture immunoglobulin (Ig) replacement therapy offer a wealth of valuable information for individuals and families living with primary immunodeficiency diseases (PI). Learn more about the companies, their products, general information about PI and/or reimbursement assistance programs on their websites.

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), a trade association that represents a unique sector of the biologics and biotechnology industry, to notify patients who receive plasma products, such as immunoglobulin replacement therapy, about product recalls.

BPL
www.bpl-us.com

BPL manufactures Gammaplex.

CSL Behring
www.cslbehring.com
IgIQ Resource Hotline: 877-355-IgIQ (877-355-4447)

CSL Behring manufactures Hizentra and Privigen.

Grifols
www.grifols.com
Grifols Customer Support Center: 888.GRIFOLS (888-474-3657)
Gamunex Connexions Program (comprehensive support program): 888-694-2686

Grifols manufactures Flebogamma DIF and Gamunex-C.

Kedrion
www.kedrionusa.com

Kedrion manufactures Gammaked.

Octapharma
www.octapharma.com
Octapharma Support Center: 800-554-4440

Octapharma manufactures Octagam.

Shire
www.MyIgSource.com
MyIgSource: 855-250-5111

Shire manufactures Cuvitru, Gammagard Liquid, Gammagard S/D and HyQvia.

Manufacturers and products are subject to change. Please check the IDF website for updated manufacturers and products: www.primaryimmune.org/ig-products.

Additional Resources

American Academy of Allergy, Asthma, and Immunology (AAAAI)
www.aaaai.org

Physician Referral Service: 800-822-2762

The American Academy of Allergy, Asthma, and Immunology (AAAAI) is a professional organization for physicians who treat patients with allergies, asthma and immunologic disorders. The organization provides a worldwide referral system for physicians in various geographical regions.

American Academy of Pediatrics
www.aap.org

The American Academy of Pediatrics (AAP) is a professional organization for pediatricians. It is committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.

Center for Biologics Evaluation and Research, FDA
www.fda.gov/BiologicsBloodVaccines

A division of the Food and Drug Administration (FDA) whose mission is to protect and enhance public health through regulation of biological products to ensure their safety, effectiveness and timely delivery to patients. This agency provides information on biological products, such as blood and plasma, including new product approvals, adverse events, product recalls and withdrawals.

Clinical Immunology Society
www.clinimmsoc.org

The mission of the Clinical Immunology Society (CIS) is to facilitate education, translational research and novel approaches to therapy in clinical immunology to promote excellence in the care of patients with immunologic/inflammatory disorders.

Immunoglobulin National Society
www.ig-ns.org

Immunoglobulin National Society (IgNS) is a professional organization dedicated to nursing professionals in education, management, practice and research in the field of immunoglobulin (Ig) therapy.

Infusion Nurses Society
www.ins1.org

The Infusion Nurses Society (INS) is dedicated to exceeding the public's expectations of excellence by setting the standard for infusion care.

Primary Immune Deficiency Treatment Consortium
www.rarediseasesnetwork.org/cms/pidtc/

The Primary Immune Deficiency Treatment Consortium (PIDTC) consists of 45 centers in North America whose shared goal is to improve the outcome of patients with rare, life threatening, inherited disorders of the immune system. Basic scientists, immunologists, and transplant physicians from the participating centers have contributed much of the current knowledge of the cause and treatments of PI. The immediate focus of the consortium is to concentrate on severe immune disorders that can be cured by hematopoietic stem cell transplantation, enzyme replacement, and/or gene therapy by bringing together physician/scientists who evaluate and care for the majority of children with PI in North America.

National Organization for Rare Disorders
www.rarediseases.org

The National Organization for Rare Disorders (NORD) is a nonprofit organization which provides information, programs and services for thousands of rare medical conditions, including primary immunodeficiencies.

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Notes

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Immune Deficiency Foundation

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