



# The Treatment of Primary Immune Deficiencies: Lessons Learned and Future Opportunities

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## Abstract

Primary immunodeficiency is a group of disorders associated with susceptibility to infectious agents and the development of various comorbidities. Many primary immunodeficiencies are complicated by immune dysregulation, autoinflammation, or autoimmunity which impacts multiple organ systems. Major advances in the treatment of these disorders have occurred over the last half-century, and deeper molecular understanding of many disorders combined with clinically available genetic testing is allowing for use of precision therapy for several primary immunodeficiencies. Patients with antibody deficiencies who rely on immunoglobulin replacement therapy now have many treatment options with products that are much safer and better tolerated compared to the past. Newborn screening for severe combined immunodeficiency, now implemented throughout the USA and in many countries worldwide, has lowered the age at which many patients are diagnosed with these diseases. Early diagnosis of severe combined immunodeficiency allows infants to proceed to definitive therapy such as stem cell transplantation or gene therapy prior to facing potentially life-threatening infections. While stem cell transplantation continues to carry significant risks, knowledge gained over recent decades is allowing for improved survival with less toxicity and less graft versus host disease.

**Keywords** Primary immunodeficiency · Immunoglobulin · Stem cell transplant · Gene therapy · Newborn screening

## Introduction

The recognition and treatment of infectious diseases have undergone incredible changes since the first recognition of microbes as being the cause of human disease and the subsequent development of antimicrobial medications. Newly emerging infections can impact all of us to varying degrees, as we experienced during the global pandemic in 2020 caused by the novel coronavirus SARS-CoV-2. However, it has been clear for a very long time that individuals might respond differently to the same pathogen. Even in biblical times, it was noted that individuals had unique susceptibilities to microbes and had outward signs of a

possible underlying disorder. While there is no evidence that he suffered from a primary immunodeficiency, the biblical character Job with his cutaneous boils and disfigurement has long been used among immunologists to describe one of these illnesses. Limited treatments would have existed during those times. Now, these fascinating disorders which impact our ability to ward off illness are now recognized as primary immunodeficiency diseases or PID/PI. Great strides in understanding these diseases have been gained over time, allowing us to recognize and classify these disorders, diagnose patients earlier in life, and tailor the treatment to the specific risks associated with the underlying immunologic defect. While immunologists have always recognized that primary immunodeficiencies affect all ages, this concept has never been more important than in the current era as genetic testing is now uncovering primary immunodeficiencies in patients who fall well beyond the prototypical young child with recurrent or opportunistic infections. Genetic testing may uncover primary immunodeficiencies in patients of any age who present with non-infectious symptomatology such as refractory cytopenias, inflammatory bowel disease, susceptibility to malignancies, and granulomatous

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(sarcoid-like) inflammation among other autoimmune conditions. Identification of the molecular defect in such patients may allow for targeted treatments which are effective in controlling the dysregulated immune response without the wide-sweeping side effects which would otherwise occur with use of prolonged systemic steroids and other traditional antiinflammatory drugs. For example, patients with CTLA-4 deficiency may have a common variable immunodeficiency (CVID)-like presentation along with severe symptoms of autoimmunity and immune dysregulation and may experience significant improvement when treated with CTLA-4 IgG fusion protein. Patients with STAT1-gain of function (GOF) or STAT3-GOF present with varying degrees of autoimmunity and may be treated with JAK inhibitors. The lymphoproliferation associated with the combined immunodeficiency activated PI3K delta syndrome (APDS) has been successfully treated with PI3K $\delta$  inhibitors [1]. All of these conditions encompass both susceptibility to infections and immune dysregulation and may be classified as primary immunodysregulatory disorders (PIRDs). Through increased understanding of the molecular pathways of these disorders and increased availability of clinical genetic testing, patients with these disorders may now benefit from precision therapy.

## Classification of Primary Immunodeficiency

Various classification schemata have been used over the years to describe the different forms of immunodeficiency, usually in the context of the type of immune cell affected by the disease. Currently, the International Union of Immunological Societies stratifies over 400 primary immunodeficiencies into ten categories: (1) immunodeficiencies affecting cellular and humoral immunity; (2) combined immunodeficiencies with associated or syndromic features; (3) predominantly antibody deficiencies; (4) diseases of immune dysregulation; (5) congenital defects of phagocyte number, function, or both; (6) defects in intrinsic and innate immunity; (7) autoinflammatory disorders; (8) complement deficiencies; (9) bone marrow failure disorders; (10) phenocopies of PID [2]. While a comprehensive list of primary immunodeficiencies is beyond the scope of this article, for illustrative purposes, Table 1 lists a few representative disorders from each category. Worldwide, the distribution of the forms of primary immunodeficiency within treatment centers is very similar. Antibody deficiencies make up most patients identified with an underlying immunodeficiency. Other forms frequently seen include phagocytic defects and combined T and B cell disorders. Complement deficiencies are seen less commonly.

While it was typical to group patients together by immunologic phenotype, identifying the underlying genetic cause of the deficiency has become more commonplace over the

last 10 years or so. Costs associated with these tests have decreased significantly while the number of disorders tested with a single sample has increased. At the time of this publication, one commercial lab offers a genetic panel test for 474 known causes of immunodeficiency using a single sample [3]. With so many newly recognized disorders, the treatment of primary immunodeficiency is more complex than in the past. Many of these forms of primary immunodeficiency have unique susceptibilities and require individualized treatment regimens; thus, it is impossible to discuss all in this review. However, we can focus on a few of the treatments for the more frequently seen forms of immunodeficiency.

## Use of Antimicrobial Therapy in Primary Immunodeficiency

Antimicrobial therapy is important for the treatment of all forms of immunodeficiency. Severe forms of immunodeficiency usually require antimicrobial prophylaxis regimens based on the known risk for infection, and a detailed description of these regimens is beyond the scope of this brief review. Infants with severe combined immunodeficiency (SCID) are typically managed with multiple forms of antimicrobial prophylaxis while moving toward definitive treatment such as stem cell transplant or gene therapy. Infants with SCID should receive prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) with trimethoprim/sulfamethoxazole using a dosage of 5 mg/kg/day of trimethoprim by mouth 3 times weekly, although alternative regimens exist [4]. Because infants with SCID are so profoundly immunocompromised, many centers also give prophylaxis against viral and fungal infections, using acyclovir and fluconazole, respectively. The RSV monoclonal antibody Palivizumab is also recommended [5]. If an infant with SCID develops signs or symptoms of infection, both common and opportunistic pathogens must be considered and aggressive broad-spectrum antimicrobials are needed until the source of the infection can be identified.

More commonly, the treatment of primary immunodeficiencies that cause various levels of hypogammaglobulinemia also consists of the provision of antimicrobials to clear intercurrent infections. For antibody deficiencies, these infections are typically caused by encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or other typical bacteria; therefore, it is important to select an antibiotic that will overcome known mechanisms of resistance to these drugs. Most immunologists treat patients with antibody deficiencies more aggressively than normal individuals, often prescribing antimicrobials at higher doses or for longer durations than is typically recommended for routine use. While data supporting this practice is lacking, the most recent Practice Parameter for the Diagnosis

**Table 1** The International Union of Immunological Societies classification of primary immunodeficiencies. A few representative immunodeficiencies are listed in each category for illustrative purposes only. A comprehensive list of disorders is available in the 2019 IUIS publication [2]

Category	Subcategory	Example
1. Immunodeficiencies affecting cellular and humoral immunity	1.a. SCID, defined by CD3 T cell lymphopenia	IL2RG JAK-3 def ADA def RAG 1&2 def
	1.b. Combined immunodeficiencies generally less profound than SCID	DOCK8 def MHC I&II def* CARD11 def CD40 ligand def (X-linked hyper IgM) Wiskott-Aldrich Ataxia-telangiectasia Chr22q11.2 deletion syndrome
2. Combined immunodeficiencies with associated or syndromic features		
3. Predominantly antibody deficiencies	3.a. Hypogammaglobulinemia	X-linked agammaglobulinemia CVID
	3.b. Other antibody deficiencies	Selective IgA def Specific antibody def
4. Diseases of immune dysregulation	4.a. HLH & EBV susceptibility	XLP 1&2 Chediak Higashi
	4.b. Syndromes with autoimmunity and others	ALPS* APECED IPEX CTLA-4 deficiency STAT3 GOF
5. Congenital phagocyte defects	5.a. Neutropenia (without anti-PMN)	Elastase def Shwachman-Diamond
	5.b. Functional defects	LAD* CGD*
6. Defects in intrinsic and innate immunity	6.a. Bacterial and parasitic infections	STAT1 GOF CARD9
	6.b. Mycobacterial and viral	IFNGR1&2 WHIM
7. Autoinflammatory disorders		Familial Mediterranean fever Mevalonate kinase def Familial cold autoinflammatory syn
8. Complement deficiencies		C5–C9 def (disseminated Neisserial infection) C1q,r,s (SLE-like syn) Factor H&I def (atypical hemolytic uremic syn)
9. Bone marrow failure		Fanconi anemia* Dyskeratosis congenita*
10. Phenocopies of PID		Autoantibody to IL-17 or IL-22 (chronic mucocutaneous candidiasis)

*SCID* severe combined immunodeficiency, *CVID* common variable immunodeficiency, *HLH* hemophagocytic lymphohistiocytosis, *EBV* Epstein-Barr virus, *XLP* X-linked lymphoproliferative disease, *ALPS* autoimmune lymphoproliferative syndrome, *APECED* autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy, *IPEX* immune dysregulation polyendocrinopathy enteropathy X-linked, *LAD* leukocyte adhesion deficiency, *CGD* chronic granulomatous disease, *GOF* gain of function, *WHIM* warts, hypogammaglobulinemia, infections, and myelokathexis, *SLE* systemic lupus erythematosus

\*Multiple molecular causes exist for the condition

and Management of Primary Immunodeficiency states: “The standard dose and duration of antimicrobial regimens might not be adequate to eradicate infections in immunocompromised hosts. Early combined antimicrobial therapy and prolonged courses should be considered.” [4]. Empiric therapy based on suspected organisms is the norm. However, the selection of an antimicrobial based on the culture of an adequate sample (i.e., sputum or tissue sample) is considered the gold standard and the preferred approach when possible.

Antimicrobial prophylaxis is also sometimes used to prevent infections with organisms that typically affect patients with antibody deficiency. Again, no published studies with large numbers of patients exist but experience in other disease states with similar risks of infection has given immunologists some evidence by which to choose a treatment regimen. For children, daily amoxicillin at doses of 20 mg/kg once or twice daily, trimethoprim/sulfamethoxazole given either daily or three times weekly at 5 mg/kg, or azithromycin 5 mg/kg thrice weekly has been reported to be beneficial to patients [4, 6]. For adults, often used regimens include either amoxicillin 500–1000 mg daily or twice daily, trimethoprim/sulfamethoxazole 160 mg daily or twice daily, or azithromycin 500 mg once weekly or 250 mg every other day [4]. In some cases of mild hypogammaglobulinemia or other disorders with less risk of invasive infection, a clinical response to antimicrobial prophylaxis can be employed to avoid the need for IgG replacement. Conversely, failure to respond to prophylactic regimens may prove the need for IgG replacement and better define a patient’s individual risk for infection.

## Immunoglobulin Replacement

The Nobel Prize in Medicine was presented to Emile von Behring in 1901 in recognition of his work to show that the serum of rabbits immunized against tetanus had protective qualities for animals who received a passive transfer of this serum. His work is felt to be one of the first in the field of antibody replacement. The concept was applied to the treatment of tetanus in humans during the first World War [7]. As researchers began to understand that these protective antibodies were a distinct subset of proteins within the serum, efforts were initiated to separate them for widespread human use. The fractionation method of serum which allows for the use of purified IgG was developed by Cohn in the 1930s and 1940s, and this technique is still employed today [8, 9].

The first immunoglobulin products obtained for clinical use were not as purified or stable as those available today. Intramuscular or subcutaneous use of these products was the norm. The products were relatively impure compared to today’s standards, and this was likely the cause of significant discomfort during administration. Intravenous (IV) use was

not possible due to aggregates and other impurities. Reactions to IV use of these preparations led to hypotension and shock [10].

Prior to the first highly purified licensed IgG product designed for IV use, management of antibody deficiencies consisted of treatment of infections with antimicrobials and provision of immunoglobulin via intramuscular (IM) or subcutaneous (SC) routes. The first use of immunoglobulin to treat a patient with antibody deficiency occurred in 1952 by Col Ogden Bruton, when he used subcutaneous immunoglobulin to successfully treat a boy with X-linked agammaglobulinemia [11]. Over the next 30 years or so, replacement of IgG intramuscularly was standard practice for patients with varying degrees of hypogammaglobulinemia. The dosing was limited due to side effects associated with IM administration. At the time, typical monthly doses ranged from 100 to 200 mg/kg [12]. Compared to today’s practices, these doses are significantly lower and not adequate for protection from all infections.

As the manufacturing processes and distribution of these lifesaving products improved over the next 25–50 years, the methods for infusion of IgG changed. The first product licensed for use intravenously was made available in 1981 [13]. This allowed for infusions of larger doses of gamma-globulin to be given to patients at relatively fast rates. Tolerability of the infusions was a limiting factor when selecting a dosing regimen. One issue with these early IVIG preparations was the development of renal complications. Higher doses, the presence of comorbidities, and the use of products stabilized with sucrose or maltose were associated with these rare complications [14].

As suggested earlier, the intravenous route has been associated with an increased risk of intolerance and systemic reactions. These adverse reactions are most often related to the rate of infusion. However, it is unclear what exactly causes these adverse events. Examples of adverse events commonly seen include headache, malaise, and fatigue. Fever, rash, and other complaints occur less often. Various interventions have been employed to mitigate these symptoms from adjustment of infusion rate, changes to the prescribed product, and premedication with antipyretics or antihistamines. While these are often successful, none have consistently changed outcomes across all patients, and it is sometimes difficult to predict who might be at higher risk for these adverse events. Currently, most immunologists would consider alternative infusion methods such as the subcutaneous route in cases where simple interventions failed to ameliorate symptoms [15].

One current strategy regarding the management of intolerance or adverse events involves understanding the profiles of patients who might be at higher risk for these complications and choosing a dose or mode of administration that might reduce the risk. For example, patients with a history

**Fig. 1** Characteristics of patients and/or IgG products that may impact tolerability of immunoglobulin infusion. With permission from Ig Clinicians Quick Reference published by Ig-NS (Immunoglobulin National Society)



## Patient and Product Risk Factors<sup>1-5</sup>

Patient Risk Factor	Concern	Ig Product Parameter Affecting Use	Appropriate Intervention	Risk Mitigation Strategies
Risk of thrombosis (See full prescribing information for complete Boxed Warning)	Thrombosis may occur with any immune globulin product.	Risk factors include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous catheters, hyperviscosity, and cardiovascular risk factors.	Monitor for signs and symptoms of thrombosis.  Assess blood viscosity in patients at risk of hyperviscosity.	Administer at the lowest infusion rate practicable Administer large doses over several days or non-consecutive days Consider concomitant anti-thrombotic therapy in high-risk patients Ensure hydration prior to and during infusion Consider SCIG
Renal impairment/renal failure (See full prescribing information for complete Boxed Warning)	Fluid overload	Volume	Consider IVIG 10% vs IVIG 5% Consider SCIG	Administer at the lowest infusion rate practicable.
	Increased plasma viscosity	Osmolality/osmolality	Choose products with physiologic osmolality (~300 mOsmol/L)	Administer large doses over several days or on non-consecutive days. Monitor fluid status.
	Sodium	Sodium content	Avoid products with high sodium content.	Ensure adequate hydration while considering fluid restriction.
Cardiac/pulmonary insufficiency	Potential for fluid overload	Volume	Consider IVIG 10% vs IVIG 5% Consider SCIG	Administer at the lowest infusion rate practicable
	Sodium	Sodium content	Avoid products with high sodium content	Administer large doses over several days or on alternate days
	Altered hemodynamics	Osmolality/osmolality	Select products with physiologic osmolality (~300 mOsmol/L)	Monitor fluid status
IgA deficiency	Potential for anaphylaxis in IgA deficient patients with antibodies to IgA.	IgA content	In patients with IgA deficiency and IgG antibodies to IgA, consider IVIG or SCIG products with the lowest IgA content In patients with a history of anaphylaxis to Ig or blood products, or with IgE antibodies to IgA, it is strongly advised to use an IgA-depleted IVIG or a low IgA containing SCIG.	Correlation of product IgA content and risk for anaphylaxis is not well established but caution is recommended. Monitor all patients closely for signs and symptoms of anaphylaxis and ensure an anaphylaxis kit is readily available.
Obesity	Adipose tissue is poorly perfused, and higher doses of IVIG increase the risk of serious adverse events.	Potential for higher Ig dose-related adverse events	Consider adjusted body weight dosing initially.	Optimal dosing must be adjusted based on clinical response
Diabetes	Potential for elevated blood glucose levels with glucose-stabilized products.	Glucose used as stabilizer	Avoid glucose-containing products if possible.	Administer at the lowest infusion rate practicable
	Potential for glucometer interference with maltose-stabilized products.	Maltose used as stabilizer	If using maltose-stabilized product, ensure glucometer and test strip accuracy are not affected.	Administer large doses over several days or on non-consecutive days Monitor fluid status
	Greater risk for renal complications.	Volume, sodium content, osmolality	Select Ig products with best parameters; Consider IVIG 10% vs IVIG 5% Consider SCIG	
Non-O blood type	Potential for hemolysis/hemolytic anemia with high doses of IVIG (≥2gm/kg).	anti-A, anti-B antibody levels	Consider products containing the lowest anti-A, anti-B antibody titers.	Be knowledgeable of patient blood type to identify patients at risk Administer at the lowest infusion rate practicable Closely monitor for signs of hemolysis/hemolytic anemia with large doses
Hereditary fructose intolerance	Sorbitol presents a risk to patients with hereditary fructose intolerance (HFI). In patients <2 years old, HFI may not yet be diagnosed and may be fatal.	D-sorbitol used as stabilizer	Products stabilized with d-sorbitol are contraindicated in patients with hereditary intolerance to fructose, and in infants and neonates for whom sucrose or fructose tolerance has not been established.	Products stabilized with d-sorbitol are contraindicated in patients with hereditary intolerance to fructose, and in infants and neonates for whom sucrose or fructose tolerance has not been established.
Hyperprolinemia	A dysfunction of proline metabolism may lead to seizures or other neurological abnormalities. Additional exposure of these patients to proline should be limited.	L-proline used as a stabilizer	In patients suffering from hyperprolinemia, a dysfunction of proline metabolism may lead to seizures or other neurological abnormalities. Additional exposure of these patients to proline should be limited. Avoid products with l-proline.	In patients suffering from hyperprolinemia, a dysfunction of proline metabolism may lead to seizures or other neurological abnormalities. Additional exposure of these patients to proline should be limited. Avoid products with l-proline.
Neonatal and geriatric patients	Potential for volume overload.	Volume	Consider IVIG 10% vs IVIG 5% Consider SCIG	Administer at the lowest infusion rate practicable.
	Potential for vein irritation and/or fluid shift.	Osmolality	Choose products with physiologic osmolality. (~300 mOsmol/L)	Administer large doses over several days or on non-consecutive days Monitor access site for irritation. Monitor appropriate blood chemistry.
Compromised acid-base compensatory mechanisms in neonates.		pH	Caution with products having low pH.	
	Development of non-neutralizing antibodies to recombinant human hyaluronidase (PH20) present in HyQvia, and potential cross-reactivity with endogenous PH20 expressed in adult testes, epididymis, and sperm.	Recombinant human hyaluronidase (PH20) used in HyQvia	Assess risk/benefit in male patients of child-bearing age and consider alternative products without PH20.	Clinical significance of anti-PH20 antibodies is unknown. Consider using products that do not contain PH20 in male patients of reproductive age.
Fluid restriction	Fluid overload	Volume of IV fluids infused	Consider IVIG 10% vs IVIG 5% Consider SCIG	Administer at the lowest infusion rate practicable. Administer large doses over several days or on non-consecutive days. Monitor fluid status.

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of migraine headache are felt to be at higher risk of developing headache during or after infusion with IVIG. Therefore, lower dosing or slower infusions would be a first-line intervention. Infusion of IVIG imparts a known risk for thromboembolism. Studies have revealed that Factor XIa activity in the product is a significant contributor to thrombosis, and measures have been implemented to reduce Factor XIa activity in immunoglobulin products [16]. Patient characteristics including older age, prior history of thromboembolism, hypercoagulable state, and alcohol abuse also increase the risk of experiencing thromboembolic events with IVIG infusion [16]. Therefore, patients with an increased risk for these events should receive IgG at slower rates or via the subcutaneous route to allow for slow absorption into the bloodstream via the lymphatics [4]. Multiple products are currently available for use intravenously and no one product has been shown to be better tolerated or more efficacious than others. Figure 1 describes patient and product risk factors that may impact the tolerability of immunoglobulin infusions.

Subcutaneous immunoglobulin (SCIG) has advantages over IVIG in regard to systemic tolerability although clinical efficacy is similar. The frequency of local injection site reactions is high when initiating therapy, although these decrease over time [17]. Limitations of SCIG include the need for multiple needle sticks with some products, frequent therapy sessions, and self-administration of the drug. The first licensed product for subcutaneous use in the USA was approved in 2006 [17]. Prior to 2006, the subcutaneous route was infrequently used by immunologists in the USA although immunologists in other countries did so. Now, multiple products are available in varying concentrations of 10–20% and this route is commonly prescribed to patients who need immunoglobulin replacement.

More recently, recombinant human hyaluronidase has been used to facilitate infusions of 10% immunoglobulin. The trials leading to US Food and Drug Administration (FDA) approval in 2014 showed tolerability of up to 600 ml of 10% IgG solution in a single subcutaneous site with low rates of systemic adverse events. While this infusion method is generally well tolerated, it has a higher rate of systemic adverse events compared with the subcutaneous infusion. The systemic reaction rate was significantly less than IVIG, however [18]. Figures 2 and 3 show the common adverse events associated with IVIG and SCIG as well as suggested mitigation techniques for each.

Currently, there are multiple products available for use in the USA and worldwide, some being specific to one of the three modes of administration routinely used. Other products can be used interchangeably between administration routes. Consideration of a patient's diagnosis, comorbidities,

**Fig. 2** Adverse events associated with IVIG and mitigation techniques recommended by Ig-NS (Immunoglobulin National Society). With permission Ig Clinicians Quick Reference 2020 Edition 1.0 [www.Ig-NS.org](http://www.Ig-NS.org)

and preferences are all important when determining product selection, dosing, infusion method, and site of care. It is important to understand the differences in the available products in terms of their chemical properties, stabilizers used, and dosing/administration limitations. When choosing therapy, it is often helpful to reference the currently available IgG products that are FDA-approved for use in the USA. For example, the Immunoglobulin National Society (Ig-NS), an organization that works with healthcare providers involved in the care of patients receiving immunoglobulin replacement, has compiled a detailed chart of these products and this is available online [19].

Various dosing regimens have been suggested over the years with the intention of preventing infection. Previously, targeting a particular trough level measured just before an IV infusion was used to adjust therapy. Patients with underlying pulmonary disease and recurrent cases of pneumonia may need higher dosing regimens as these have been shown to reduce the incidence of pneumonia [20]. As physicians, however, we are often reminded to treat the patient and not necessarily a number or lab value. The concept of a biologic trough was introduced by Bonagura et al. [21], in which it was recognized that each patient seemed to require different serum IgG concentrations to remain infection-free. It is now more commonplace for physicians to adjust dosing based on clinical response to prevent breakthrough infections during therapy.

Other parameters of therapy such as the mode of administration or site of care are more subjective in nature. A careful selection can reduce the burden of care by matching the properties of the infusion to the needs of the patient. It is important that prescribers of immunoglobulin understand the differences between the various modes of administration. IVIG is typically given in a healthcare setting every 3–4 weeks. Home treatment is standard for both subcutaneous immunoglobulin (SCIG) and facilitated subcutaneous immunoglobulin (fSCIG) administration, although the latter may also be routinely given in physician offices or infusion centers. The length of each infusion session for each mode of administration also differs, with IVIG typically taking several hours to infuse compared to SCIG infusions that might last 1 h or less depending on the product selected. SCIG can be given as frequently as daily, or every 2 weeks.

Deciding upon a mode of administration, the product used, and the site of care requires that both the patient and

## INTRAVENOUS IMMUNE GLOBULIN (IVIG): ADVERSE EVENTS AND RISK MITIGATION<sup>1-20</sup>

Adverse Event	Appropriate Intervention	Risk Mitigation Strategies
Anaphylactoid Reaction	Slow or stop the infusion Administer antihistamine Administer corticosteroid Administer fluids	Consider pretreatment with corticosteroids, as they are the most effective treatment Consider pretreatment with antihistamine Consider brand change or SCIG when appropriate
Anaphylaxis	Stop the infusion Emergency medical services activation Administer epinephrine Administer supplemental therapies as ordered	Ensure anaphylaxis kit dispensed and available at every infusion In IgA deficient patients (known/suspected IgE anti-A antibodies), use IgA-depleted IVIG products or SCIG
Aseptic Meningitis	Stop the infusion Administer antimigraine medication for patients with a history of migraines Administer corticosteroid Administer opioid /non-opioid analgesic	Ensure hydration prior to, during, and after infusion Consider pretreatment with antimigraine product, corticosteroid, and/or analgesic Administer at the lowest infusion rate practicable Administer large doses over several days or alternate days Consider brand change, a 5% IVIG, or SCIG when appropriate
Back or Leg Pain (severe)	Slow or stop the infusion Administer opioid/non-opioid analgesic Administer antihistamine Administer corticosteroid	Consider pretreatment with antihistamine, corticosteroid, and/or opioid/non-opioid analgesic Consider brand change or SCIG
Dermatological Reactions (rash)	Stop the infusion Administer antihistamine Administer corticosteroid	Consider pretreatment with antihistamine and/or corticosteroid Consider brand change or SCIG
Flu-like Symptoms	Slow or stop the infusion Administer analgesic	Ensure adequate hydration Consider pretreatment with antihistamine and/or analgesic Consider brand change or SCIG

Adverse Event	Appropriate Intervention	Risk Mitigation Strategies
Headache	Slow or stop the infusion Administer an analgesic	Ensure adequate hydration Administer subsequent infusions at lower infusion rate, as common headache is usually rate-related Consider pretreatment with analgesic Consider antimigraine medication for patients with a history of migraine (See Aseptic Meningitis above) Consider pretreatment with corticosteroid if severe Consider brand change, a 5% IVIG, or SCIG when appropriate
Hypotension/hypertension	Stop the infusion Medical management	Administer subsequent infusions at a lower rate Consider brand change, a 5% IVIG, or SCIG in extreme cases
Hemolysis/hemolytic anemia	Stop the infusion Refer to emergency department based on severity Refer to prescriber for medical management	Identify patient blood type and consider products with low levels of anti-A, anti-B antibody titers in patients with non-O blood type Administer at the lowest infusion rate practicable Administer large doses over several days or alternate days
Rigors	Stop the infusion Administer meperidine or another suitable opioid if available Supportive treatment with analgesics, antihistamine, and/or corticosteroids may be warranted Medical management	Consider pretreatment with acetaminophen and/or meperidine or another suitable opioid Consider brand change or SCIG
Thrombosis	Stop the infusion Refer to emergency department based on severity Refer to prescriber for medical management	Ensure adequate hydration Choose products with the lowest level of Factor XIa, such as Ig products with pasteurization steps in manufacturing Consider antithrombotic therapy in high-risk patients Administer at the lowest infusion rate practicable Administer large doses over several days or alternate days

## SUBCUTANEOUS IMMUNE GLOBULIN (SCIG): ADVERSE EVENTS AND RISK MITIGATION<sup>1-20</sup>



Adverse Event	Appropriate Intervention	Risk Mitigation Strategies
Infusion site leaking	Check needle and catheter to ensure proper insertion and securement Check needle placement to ensure no movement Check needle size is not too short Ensure sufficiency of tissue at infusion site	Assess and/or lower infusion rate and/or volume based on tolerability Consider changing needle length or brand
Infusion site/local site reactions	Check needle length to ensure SC administration; a needle that is too short may cause intradermal delivery Check needle gauge to accommodate volume infused Ensure sufficiency of tissue at infusion site Assess sensitivity to tape Employ a dry priming technique to decrease redness and itching Gentle massage or warm/cold compress	Rotate infusion sites Decrease volume per site, administer lower doses more frequently, or increase infusion time If generalized urticaria occurs, stop infusion and contact prescriber immediately per organizational policies
Needle discomfort	Check needle length; a needle that is too long may irritate the infusion site Assess ease of insertion and consider changing needle brand	Consider cold pack and/or topical anesthetic cream prior to insertion
Long infusion times	Check tubing patency, size and length to ensure support of infusion rate Check needle size and length to ensure support of infusion rate Assess number of sites and volume per site Check pump function, battery, and other mechanics Assess patient self-administration technique	Adjust infusion parameters based on tolerability Consider changing the infusion site Assess tissue and ensure that needles are not placed near/in scar tissue or nodules

**Fig. 3** Adverse events associated with SCIG and mitigation techniques recommended by Ig-NS (Immunoglobulin National Society). With permission Ig Clinicians Quick Reference 2020 Edition 1.0 [www.Ig-NS.org](http://www.Ig-NS.org)

the physician understand the choices available. The inclusion of shared decision-making (SDM) has become widely used for several disease states including the treatment of primary immunodeficiency. SDM is especially important at the onset of therapy because it can lead to better engagement of the patient in his or her healthcare decisions and improve adherence to therapy. Patients should understand however that treatment plans can change as needed to meet their needs. For example, it is not uncommon for pediatric patients to receive IVIG during early childhood when their parents might feel uncomfortable placing subcutaneous needles each week for therapy sessions. As the child becomes older, a change to subcutaneous therapy at home might fit the family's lifestyle better. Subcutaneous administration also allows flexibility for college students and working adults. It is important to revisit treatment decisions every so often to ensure that the mode of administration and site of care is appropriate for the patient.

### Newborn Screening for Severe Combined Immunodeficiencies

While not a definitive treatment for primary immunodeficiency per se, it would be remiss to not discuss newborn screening (NBS) for T cell lymphopenia, as it has been a major advancement impacting the success of SCID treatment.

Prior to the implementation of NBS, the diagnosis of patients with immunodeficiency relied on physicians and other health-care providers having a suspicion that an individual might be affected due to recurrent or unusual infections or failure to thrive or by having a family history of the disease. Unfortunately, patients affected by SCID almost always appear normal in the first few weeks or months after birth. Only after infections occur or if the infant fails to gain weight or develop appropriately would someone suspect an underlying disease. SCID is a disease amenable to screening for several reasons. Patients otherwise appear normal, fatality is almost certain without treatment, a low-cost validated test is available, and treatment of the disease is highly successful [22, 23]. Before the implementation of NBS with the method developed in 2005, a CBC was often recommended as a screening method to identify infants with SCID but some individuals were missed due to relatively high numbers of B or NK cells or the presence of maternally engrafted T cells [23].

The assay employs the use of the dried blood spot obtained on every newborn for screening of other diseases. This RT-PCR-based assay measures the presence of T cell receptor excision circles (TRECs) which are representative of the presence of naïve T cells that have recently emigrated from thymus. Low or absent TRECs suggest significant T cell lymphopenia and must be confirmed by flow cytometry. It is now routinely performed in all 50 states, in Puerto Rico, and in other nations worldwide.



NBS was intended to identify infants with SCID who are known to be at high risk for early death due to opportunistic infection. After it was implemented in larger pilot studies and then as routine screening for the general population, it was shown to also identify other causes of non-SCID T cell lymphopenia (both mild and severe). Immunodeficiencies such as DiGeorge syndrome and ataxia-telangiectasia are sometimes identified, and novel mutations in other genes have been discovered in patients with low or absent TRECS. Syndromes such as trisomy 21 and Noonan syndrome can also cause low TRECs. Secondary causes of lymphopenia also cause abnormal results on the TREC assay [24].

Once a newborn with SCID has been identified by NBS, treatment must begin immediately. Whereas previous management for SCID differed between centers, there is now some consensus regarding initial management. Isolation of the patient and family should occur as soon as possible to prevent infection. Infants must also undergo confirmatory testing. This is best done at a center where experts skilled at interpretation of the results are available. Antibiotic and antifungal prophylaxis should begin with medications tailored to the age and clinical status of the patient. Other supportive treatments may be indicated such as the provision of immunoglobulin replacement and transfusion of leukoreduced, irradiated, cytomegalovirus (CMV)-negative red blood cells (RBCs) if significant anemia is present [5].

As previously mentioned, NBS allows for the identification of patients with SCID prior to the onset of infections in many cases. NBS has lowered the age of diagnosis of SCID, and we have a better understanding of the true prevalence of the various forms of SCID. In one series, 19% of patients identified with SCID had mutations in IL2RG whereas 10% were ADA-SCID. The overall prevalence of these diseases is more common than previously thought, affecting approximately 1/50,000–1/60,000 live births [25].

## Hematopoietic Stem Cell Transplant

As mentioned earlier, for a disease to qualify for implementation of newborn screening, there must be a proven successful treatment for the underlying disease. Hematopoietic stem cell transplant (HSCT or SCT) was first used as a curative therapy for a patient with SCID in 1968 by Dr. Robert A. Good. The unique situation in which the recipient was unable to reject the bone marrow of his HLA-compatible sibling was a first in regard to the treatment of non-malignant diseases with HSCT [26]. Since that time, the use of SCT for the treatment of SCID and other forms of primary immunodeficiency has become the standard of care when a compatible match is available.

When a fully HLA-matched sibling donor is used for SCT, no conditioning with chemotherapy is required for

most forms of SCID. The use of a matched sibling donor is also associated with higher survival rates, fewer complications such as graft versus host disease (GVHD), and more complete B cell engraftment [27]. Unfortunately, most patients do not have an available HLA identical sibling, and so other donor sources must be used despite their potential for increased risk of graft rejection and complications.

Mismatched related donors (MMRD) can be used and are the most common donor source in some series. Success with these transplants is higher at centers with experience and has continued to improve with time [28]. Matched unrelated donors (MUD) and umbilical cord blood (UCB) are also used. Transplantation with UCB is limited by the fixed number of donor cells in the umbilical cord and is not usually adequate for larger patients. For infant recipients, this limitation of UCB is less problematic due to their low body weight. In one study, the overall survival after UCB transplant for SCID was similar to other donor sources. The degree of HLA match impact survival [29]. It is difficult to compare outcomes based on a donor source alone, since many factors impact success. Most importantly, there is increased survival when infants are treated with SCT at <3.5 months of age. If an infant with SCID is transplanted at an older age, they can also do well if there is no evidence of active infection [27]. Age at transplant is, nonetheless, an important factor since younger patients with infection do better than older patients with infections [30]. This lends further importance to early diagnosis via NBS as a way to improve the outcomes of patients with SCID.

Conditioning with chemotherapy before transplant has been a topic of great debate when treating patients with SCID using donor sources other than an HLA-matched sibling. Two studies have shown that the use of a conditioning regimen led to better T cell reconstitution [27, 30]. In another study, the use of reduced-intensity conditioning was associated with better overall survival when compared to myeloablative conditioning (94% vs 53%) [31].

HSCT is also curative for the treatment of chronic granulomatous disease (CGD), a primary immunodeficiency causing recurrent deep-seated infections and inflammatory complications in multiple organs. Significant conditioning before transplantation is required and often comorbidities exist in the recipient that can impact the development of post-transplant complications [32]. In recent years, HSCT for CGD has been increasingly successful as shown by a multicenter study describing transplantation using reduced-intensity conditioning and matched unrelated or sibling donors [33]. Other forms of immunodeficiency can also be definitively treated with SCT including Wiskott-Aldrich syndrome, X-linked hyper IgM syndrome, and X-linked lymphoproliferative disease [34].

New techniques in the approach to both host conditioning and graft preparation could allow for successful SCT

while essentially eliminating toxicity. Taking advantage of the fact that CD45 is present on the surface of all nucleated hematopoietic cells and their precursors [35], the use of an anti-CD45 antibody is a promising non-chemotherapy conditioning tool [36]. Graft manipulation, specifically ex vivo alpha/beta T cell depletion, is currently being used to decrease GVHD [36]. With this approach, the gamma/delta T cells are allowed to remain in the graft, with the benefit of antiviral activity. As they are MHC-independent, the gamma/delta T cells do not mediate GVHD [36, 37].

Approaches have also been developed to combat the often devastating post-transplant complication of severe viral infection. Viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus, among others, are potentially fatal in the post-transplant period and may be extremely challenging to control with conventional antiviral treatments alone. One immunologic method of treatment is donor lymphocyte infusion (DLI), although this approach is limited by lack of specificity against the virus and risk for GVHD [36]. A newer approach uses virus-specific T lymphocytes (VSTs) with the goal of isolating donor T cells with activity against certain virus(es) of interest without including alloreactive T cells [38]. This technology has also been used to isolate third-party VSTs for “off-the-shelf” availability for prophylaxis or treatment of viral infections [38]. The use of VSTs appears to be effective, but remains available in the USA only in clinical trials.

## Gene Therapy

Current approaches to gene therapy (GT) for primary immunodeficiencies use autologous stem cells harvested from an affected patient. These cells then undergo genetic transformation with the wildtype or normal gene, and are re-infused into the patient where they differentiate into immune cells that express the normal gene [39]. Gene therapy has been used to treat patients with T cell deficiencies such as IL2RG deficiency and ADA-SCID and can correct the immunologic defect [40]. A benefit of gene therapy is that a suitable donor is not necessary; therefore, it is a possible treatment for patients lacking either a sibling donor or a well-matched unrelated donor. Unfortunately, gene therapy is not yet available for most patients. Initial trials of GT for the treatment of ADA-SCID were not entirely successful, most likely due to the lack of pretreatment conditioning [41]. The addition of pretreatment conditioning with a gamma-retroviral vector was later shown to be successful. Currently, an approved product (Strimvelis) is available in the EU for the treatment of ADA-SCID [42]. In the USA, we are awaiting an approved GT treatment product for patients who lack an adequately matched stem cell donor.

Gene therapy for IL2RG SCID was also developed, and gamma-retroviral vectors were used in the initial clinical trials in 1999. GT was successful in the correction of the immunologic defect, but it was noted that T cell leukemia developed in 25% of study participants due to the integration of the vector close to protooncogenes. Alternative lentiviral vectors felt to have less risk of insertional mutagenesis are now being used in the context of clinical trials at several centers and these complications have not been observed [43].

Currently, there are multiple clinical trials ongoing for the use of gene therapy in various primary immunodeficiencies including SCID, Wiskott-Aldrich syndrome, and chronic granulomatous disease [34]. It is hoped that it will be a safe and viable therapy for widespread use in our patients without an acceptable stem cell donor.

## Summary

Significant advances in the treatment of primary immunodeficiency have occurred during the last century. Patients now have choices regarding immunoglobulin replacement and infusion modes of administration that are flexible and can be adjusted to their needs and comorbidities. Diagnosis of patients via NBS has led to the ability to treat the most fragile patients early with increasing success. When a stem cell donor is identified in a timely manner, many forms of primary immunodeficiency can be cured by hematopoietic stem cell transplantation although there is still a significant risk for complications. For those infants lacking an adequate stem cell donor, autologous gene therapy is becoming a viable alternative with approved products being currently available or on the horizon.

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## Declarations

**Ethical Approval** Not applicable/no human subjects.

**Informed Consent** Not applicable/no human subjects.

**Conflict of Interest** Kenneth Paris MD: Dr. Paris has been a member of advisory boards and a speaker for Takeda Pharmaceuticals regarding the treatment and diagnosis of primary immunodeficiency. He has participated in clinical trials with Takeda regarding immunoglobulin products and with Chiesi Pharmaceuticals regarding enzyme replacement for ADA-SCID. He is also on the Medical Advisory Committee for the Immunoglobulin National Society who provided figures for this manuscript. Luke Wall MD: Dr. Wall has participated in clinical trials with Takeda Pharmaceuticals regarding immunoglobulin products, and with Chiesi Pharmaceuticals regarding enzyme replacement for ADA-SCID.

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