

Immunoglobulin Replacement Therapy in Children

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KEYWORDS

- Intravenous immunoglobulin therapy
- Subcutaneous immunoglobulin therapy
- Primary immunodeficiency diseases

The benefit of immunoglobulin (IG) replacement in primary antibody deficiencies (AD) is unquestionable. Many of these congenital disorders present early in life and this therapy is often first implemented in the young. For many of these children, IG infusions will remain a requirement for the foreseeable future. No other therapy has demonstrated to be as efficacious as IG in reducing the number and severity of infectious complications in pediatric patients with AD. The consensus among pediatric immunologists is that, when combined with close clinical monitoring, timely and appropriate IG replacement could ultimately extend the life expectancy of these young patients to approach that of the general population.

The general concerns surrounding IG therapy affect adults and children equally. Issues regarding efficacy in the ever-expanding applications of IG, the predicted shortages of this drug, and the rising costs of therapy have been comprehensively addressed in a number of recent reviews.^{1–5} This article focuses on the indications of IG replacement in children, with an emphasis on the specific diagnostic problems encountered in this population. Also presented is an overview of the practical aspects of IG administration in the pediatric setting, including the recognition and management of adverse reactions. Finally, briefly discussed is the advent of subcutaneous IG, a therapeutic IG modality with the potential to have a great impact in the quality of life of children with AD and their families.

INTRAVENOUS IMMUNOGLOBULIN FOR ANTIBODY REPLACEMENT THERAPY

Intravenous immunoglobulin (IVIG) is a fractionated blood product made from pooled human plasma. Available in the United States since the early 1980s, it rapidly

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substituted the use of intramuscular preparations as replacement therapy in AD states. Because it is manufactured from plasma from thousands of individuals, IVIG contains a mixture of antibodies against a wide spectrum of infectious pathogens. The concentration of antibodies against hepatitis B, diphtheria, measles, tetanus, and polio in the final product must comply with Food and Drug Administration requirements. Titers against other pathogens, including those that more frequently affect patients with AD, such as *Streptococcus pneumonia* and *Haemophilus influenzae* subtype B, are presently not regulated by the FDA. These titers can vary significantly among different products and even from batch to batch.^{6,7}

To comply with World Health Organization and FDA guidelines, more than 90% protein content in commercial IVIG should be monomeric IgG with a distribution of IgG subclasses close to that in normal plasma.^{8,9} Traces of IgM and IgA are present in all products, but the content of the latter can vary significantly between manufacturers depending on the method of IgG purification followed. Other immunomodulatory proteins, such as cytokines, soluble CD4 and CD8 and CD40, and HLA molecules are also present in varying amounts.^{1,10} The risk of transmission of infectious pathogens by this blood-derived product is minimized by the careful selection of donors, plasma antibody screening, and various procedures of viral inactivation.

Since the early 1990s the distinction between IVIG products has increased because of refinements in manufacturing.¹¹ Most of these products have proved to be efficacious in the treatment of AD when compared with historical untreated controls or patients treated with intramuscular IG. The methods of purification, viral inactivation, and the addition of stabilizers vary between different manufacturers and can affect the clinical performance of the different products. Physicians need to be aware of these differences because that could influence their decision in selecting the appropriate product for each individual patient. Further, no one IVIG product currently on the market has approval for all of the FDA-sanctioned indications.

There are notably few studies comparing side by side the efficacy of different IVIG products.¹² In one such study, patients treated with an IVIG product prepared with a less harsh method of viral inactivation had fewer infections than those who received a solvent-detergent treated IVIG.¹³ Differences in efficacy between IVIG preparations have also been reported in children with Kawasaki disease.¹⁴

Production methods not only can affect efficacy but also tolerability. High sodium and sucrose-containing products, for instance, may be contraindicated in patients with marginal cardiac or renal function. This is also an important consideration in neonates and infants. Reduced blood volumes and immature renal function puts this population particularly at risk of developing electrolytic imbalances or volume overload. For these patients, IVIG products with a higher protein concentration, low osmolality, and neutral pH constitute the best option. IVIG with products with reduced IgA content may be preferred in patients with IgA deficiency who are still able to produce antibodies of IgE or IgG isotype, because these patients are at risk of developing anaphylactic-type reactions when they receive IgA containing blood products.¹⁵

IMMUNOGLOBULIN REPLACEMENT IN CHILDREN

In general, IG replacement therapy is indicated for patients with primary or secondary AD only if they have recurrent or severe infections and defective antibody production. The efficacy of IVIG in this setting is primarily related to the well-known attributes of IgG antibodies to neutralize bacterial toxins, superantigens, and viruses; activate complement; and promote phagocytosis and antibody-mediated cytotoxicity.

Additional benefits are probably drawn from the less well-characterized anti-inflammatory and immunomodulatory properties of IVIG.^{1,10}

In AD disorders, the host's ability to mount a protective antibody response against microbial pathogens is markedly impaired. Conceptually, AD can be divided into two groups: the hypogammaglobulinemias, in which deficits in antibody synthesis result in decreased levels of IGs, and the functional antibody defects in which the serum IGs are within the normal range but where the production of antigen-specific responses is defective.

HYPOGAMMAGLOBULINEMIA

Because of the substantial physiologic variation in the concentration of serum IGs in first few years of life, the correct interpretation of IG levels in pediatric patients relies on reference to age-matched controls rather than on absolute values. Evaluation of premature babies requires further adjustment according to their gestational age.¹⁶ In general terms, a child with serum IgG levels of less than 2 SD below the mean for age is considered to be hypogammaglobulinemic.¹⁷ The levels of the other isotypes (IgA and IgM) usually, but not always, correlate with those of IgG, which is the most abundant serum IG. Although decreased IgG values do not necessarily herald a primary immunodeficiency, the finding of hypogammaglobulinemia in a young patient warrants further investigation.

Low IGs in children can result from multiple causes, many of which are unrelated to a primary immunodeficiency (**Box 1**). In a recent retrospective study from the Children's Hospital of Philadelphia, about half of the cases of hypogammaglobulinemia were caused by a pre-existing condition known to be accompanied by decreased IG.¹⁸ In those in which the IG levels were obtained as part of a diagnostic work-up, only 50% were found to have an immunodeficiency.

PRIMARY IMMUNODEFICIENCIES

The first and foremost indication of IG replacement is to decrease the infections in patients with hypogammaglobulinemia and impaired antibody responses. The prototypical diseases in this group are the agammaglobulinemias: X-linked or autosomal recessive.¹⁹ The diagnosis of this condition is usually made in the second or third year of life in a child with a history of recurrent infection, profoundly decreased IGs, and extremely low or absent B cells. In these young patients, early institution of IG therapy can be life-saving.

Marked hypogammaglobulinemia across the three isotypes with conserved B cells numbers suggests the diagnosis of common variable immunodeficiency (CVI), whereas decrease in IgG and IgA with normal to elevated IgM is the hallmark of the hyper-IgM syndrome.²⁰⁻²² Children with CVI or hyper-IgM syndrome have a severe impairment in antibody responses and, like agammaglobulinemic patients, usually suffer from recurrent sinopulmonary infections that can be ameliorated by the regular IG infusions. IG replacement is also indicated in infants with severe combined immunodeficiency awaiting transplant and in those in which B-cell function is not restored following transplantation.

IgG subclass deficiency rarely results in marked hypogammaglobulinemia. Immunologists commonly request this determination in a child with recurrent infections and normal levels of total IgG.²³ In the absence of impaired antibody responses, the significance of a depressed level of any of the IG subclasses is unclear and IG replacement is not indicated.

Box 1
Causes of hypogammaglobulinemia in children
<i>Decreased production</i>
Primary antibody defects
Transient hypogammaglobulinemia of infancy ^c
X-linked agammaglobulinemia ^a
Autosomal-recessive agammaglobulinemia ^a
Hyper-IgM syndrome ^a
Common variable immunodeficiency ^a
Ataxia-telangiectasia ^a
Severe combined immunodeficiency ^a
Prematurity ^b
Malignancy ^c
Posttransplant (solid organ, bone marrow transplant) ^b
Chemotherapy ^c
Drugs
<i>Increased loss</i>
Congenital heart disease
Nephrotic syndrome ^c
Intestinal lymphangiectasia
Burns
Severe atopic dermatitis ^c
<i>Increased catabolism</i>
FcRN mutations
Myotonic dystrophy
Sepsis
^a IVIG customarily recommended.
^b Recommended in selected cases.
^c IVIG rarely indicated.

Transient hypogammaglobulinemia of infancy is the most common cause of symptomatic hypogammaglobulinemia in children under the age of 2.²⁴ This diagnosis can only be made in retrospect when the child's IG level reaches age-appropriate levels. Transient hypogammaglobulinemia of infancy follows a benign course, although a few of the young children originally diagnosed with transient hypogammaglobulinemia of infancy develop a more permanent defect.^{25,26} Most patients with transient hypogammaglobulinemia of infancy do well with appropriate antibiotic management but a few may require short-term IVIG support. The benefits of IVIG in these young patients should be balanced against the possibility of interfering with the normal maturation of the immune system, because at least in vitro, IVIG suppresses both T- and B-cell responses.^{3,27} For those who go on IVIG, periodic re-evaluation of their immune function is imperative.

SECONDARY HYPOGAMMAGLOBULINEMIAS

Protein-Losing Enteropathy

Protein-losing enteropathy is a condition characterized by severe loss of serum protein into the intestine. Hypogammaglobulinemia can occur in this setting, often associated with severe hypoalbuminemia and edema. A number of conditions have been associated with protein-losing enteropathy. In children, gastrointestinal disorders and congenital heart disease are the leading causes.^{28,29} Protein-losing enteropathy is a known complication of the Fontan circulation and in other cardiac disorders where an impaired mesenteric circulation results in an ischemic insult of the gastrointestinal mucosa and enteral protein loss.²⁸ Impairment of the lymphatic drainage of the gastrointestinal tract can also lead to protein-losing enteropathy.³⁰ In addition to hypogammaglobulinemia, patients with intestinal lymphangiectasia, also can present with T-cell lymphopenia of varying degrees, rising the suspicion of a combined primary immunodeficiency diseases (PID). IgG levels in protein-losing enteropathy are usually moderately decreased, but they can be very low. Even under these circumstances, IG replacement is not indicated because there is no evidence that infections in patients with protein-losing enteropathy occur at a higher rate or are more severe than in comparable patients with similar comorbidities. It can be argued that, in the face of ongoing protein losses, IG administration is futile. Correction of the underlying disorder usually results in normalization of the IG levels.

Nephrotic Syndrome

A low level of serum IgG with normal or increased IgM is a common finding in children with steroid-sensitive nephrotic syndrome in relapse and in remission.³¹ Originally presumed to be secondary to urinary protein loss, the hypogammaglobulinemia of steroid-sensitive nephrotic syndrome is now thought to result from complex immune mechanisms intrinsic to the pathogenesis of this disease. A recent study of 44 children with steroid-sensitive nephrotic syndrome showed that the IgG subclass distribution varies depending on the stage of the disease, leading to the suggestion that the preferential loss of certain IgG subclasses may underlie the unusual susceptibility of patients to pneumococcal infections.³² Although functional antibody defects may be a feature of steroid-sensitive nephrotic syndrome, there is no evidence that IG replacement is useful in this condition and it should not be recommended.

Medications

Several classes of medications can lead to secondary hypogammaglobulinemia.³³ These include glucocorticoids and other immunosuppressants, chemotherapeutic agents, and anticonvulsants. In most of these cases, the hypogammaglobulinemia is mild and of no clinical significance. IG replacement is not indicated. Discontinuation or substitution by an alternative drug should be considered in the rare instances where IG levels are substantially reduced or if the patient develops unusual or recurrent infections.

Hypogammaglobulinemia Caused by Increased IgG Catabolism

Although generalized hypercatabolic states (eg, infection) are often accompanied by quantitative or qualitative defects in IG production, decreased levels of serum IgG can also result from primary disorders of IG degradation or turnover. Hypogammaglobulinemia is a feature of familial hypercatabolic hypoproteinemia, which is caused by mutations in the β_2 -microglobulin gene,³⁴ a component of the neonatal Fc receptor (FcRN), which is critically involved in serum IgG homeostasis.³⁵

Although the mechanism is still unclear, accelerated IgG catabolism is also thought to be behind the hypogammaglobulinemia observed in some patients affected with myotonic dystrophy.³⁶ Interestingly, the gene associated with muscular dystrophy is upstream of the gene encoding the alpha chain of FcRn on chromosome 19, and it has been suggested that there might be a direct or indirect influence on the expression of FcRn and consequently in the catabolic rate of IGs.³⁷ Although the levels of IgG in patients with myotonic dystrophy occasionally are in the range observed in primary immunodeficiency, for the most part they do not suffer from recurrent infections and rarely warrant IG support.

FUNCTIONAL ANTIBODY DEFECTS

Primary Specific Antibody Defects

Children who have recurrent sinopulmonary infections with encapsulated bacteria, normal or near normal IgG levels, and impaired antibody responses may pose a diagnostic challenge. Some of these children have additional features that suggest a CVI phenotype and the presumption is that eventually the total IG levels will fall. Others never meet criteria for CVI and their antibody defects remain discrete, leading to the diagnosis of specific antibody deficiency (SAD). The impaired response against polysaccharide antigens is the best characterized feature of SAD.³⁸ More recently, Alachkar and colleagues^{39,40} showed that children and adults with SAD have decreased numbers of switched memory B cells, which have been argued to play a cardinal role in the protection against encapsulated bacteria.

The current view is that IG replacement in SAD should only be considered in the face of recurrent pyogenic infections poorly controlled with antibiotic therapy. In children with SAD who are started on IVIG, the recommendation is to re-evaluate them after a year. If antibody responses improve and infections do not recur, therapy should be discontinued.

Impaired polysaccharide responses are found in about one third of patients with DiGeorge syndrome, which is primarily considered a T-cell defect. These patients seldom warrant IVIG administration. Variable defects in antibody production have been reported in a number of complex immunodeficiencies, such as the hyperimmunoglobulinemia E syndrome, Wiskott-Aldrich syndrome, and X-linked proliferative disease.^{41–43} The efficacy of IVIG therapy in these rare disorders is mostly anecdotal but IG supportive therapy is routinely offered to these children in some centers.¹⁶

HIV Infection

Profound abnormalities in cellular and humoral immunity are the hallmark of HIV infection. Despite normal or even elevated levels of total serum IGG, children infected with HIV often have impaired antibody responses and suffer from recurrent infections with common pyogenic bacteria, such as *S pneumonia* and *H influenzae*. This is in contrast to adults, where opportunistic infections are the major concern. IVIG therapy is now part of the standard of care of pediatric HIV patients, this being one of the six FDA-approved indications for the drug.⁴ This indication followed the findings from two large randomized, placebo-controlled trials conducted in the early 1990s that demonstrated the benefits of IVIG infusions (400 mg/kg/4weeks) in reducing the number of serious bacterial infections in HIV-infected children.^{44,45} The advent of more effective antiretroviral therapies, such as highly active retroviral therapy may, however, change this prospect. In a recent study of 15 HIV-infected children by Grisaru-Soen and colleagues⁴⁶ short-term (<3 months) withdrawal of IVIG was not associated with a significant increase in incidence of infections or a decline in immunologic function.

Neonatal Sepsis

Neonates are a population at high risk for disseminated infection because of the relative immaturity of their host defense mechanisms.¹⁶ In terms of humoral immunity, maternal IgG can offer considerable protection but the infant's antibody responses to newly encountered antigens are either delayed (proteins) or absent (polysaccharides). The poor opsonic capacity of neonatal serum leads to inefficient phagocytosis and bacterial killing. These latter abnormalities are even more pronounced in premature babies whose IG levels are markedly lower than those in infants born at term. These observations have provided the rationale for the use of IVIG to improve the outcome of neonatal sepsis.

A number of studies have addressed the efficacy of IVIG in the management of neonatal infections. An earlier meta-analysis of trials found significant reduction in the mortality of neonatal sepsis when IVIG was added to conventional therapies.⁴⁷ In contrast, administration of IVIG seems to be only marginally beneficial for preventing neonatal sepsis and is probably not justified.⁴⁸

Sepsis in Pediatric Patients

In septic syndromes, the increased demands and the hypercatabolic state often lead to functional antibody deficits that could be partially corrected with IVIG infusions. Indeed, adjuvant therapy with IVIG decreases mortality by more than 30% in adult and in pediatric patients with bacterial sepsis or septic shock as demonstrated by meta-analysis of eight trials involving 492 patients.⁴⁹ Using slightly different selection parameters, another group reported similar conclusions.⁵⁰ Of note, IVIG products with high IgM content (not available in the United States) seemed to be superior in this setting, likely because of the increased capacity of pentameric IgM to activate complement and to opsonize gram-negative bacteria.⁵¹ Despite this promising evidence, at the present time IG replacement is by no means customary in the treatment of microbial sepsis. Further studies are required to delineate the precise indications, timing, dosage, and IVIG in the management of this disorder.

DOSAGE AND ADMINISTRATION

The primary goal of IG replacement is to reduce the incidence and the severity of infections in patients with AD. Although the efficacy of IG therapy was apparent from the very first clinical trials, the optimal dose to achieve this goal is still a matter of investigation.⁵²⁻⁵⁴ A number of studies established the superiority of higher IVIG doses (ie, 400–600 mg/kg versus 100–200 mg/kg every 3–4 weeks) in reducing the rate of infections, decreasing hospitalization and antibiotic usage, and improving pulmonary outcomes in patients with primary hypogammaglobulinemia.⁵⁵⁻⁵⁸

On the basis of these observations, the standard recommended IG replacement dose for children with AD is 100 mg/kg/wk. Doubling this standard dose may further decrease the number of bacterial and viral infections and should be considered in selected patients as recently proposed by Eijkhout and colleagues.⁵⁹ In this double-blind, randomized, crossover study of 43 patients with AD, 18 of whom were children, doubling the standard dose of IVIG significantly reduced the number and duration of infections. These findings suggest that, in selected patients, higher doses of IVIG associated with increased trough levels decrease long-term complications, especially pulmonary ones. For ease and convenience, when the intravenous route is chosen, the infusions are administered every 3 to 4 weeks. Patients with severe hypogammaglobulinemia (<100 mg/dL) may benefit from a total "loading" dose of 800 mg/kg given

in two separate doses a few days apart, followed by monthly injections of 400 to 500 mg/kg.^{4,16}

The average half-life of IgG is 21 days, but IgG metabolism shows significant variations among individuals.⁶⁰ Active infection, endocrine disorders, and autoimmunity have all been associated with increased IgG catabolism.⁶¹ These comorbidities, which could potentially reduce the effective dose of replacement IG, are not unusual in patients with PID. Genetic factors can also play a significant role, as illustrated by the higher catabolism of IgG in patients with mutations in the β_2 -microglobulin chain of the FcRn.³⁴ It is preferable to assess the adequacy of IG replacement in terms of the residual or trough levels of serum IgG rather than on the absolute dose infused. In general, serum IgG troughs of 500 to 600 mg/dL are effective in preventing acute bacterial infections in hypogammaglobulinemic patients. At replacement doses of 500 mg/kg/mo, these levels are usually attained after the sixth infusion (or about six half-lives), once redistribution to the tissues is complete and a steady state is reached.⁶⁰

Residual serum IgG should be monitored every 2 months until steady state is reached and every 6 months thereafter. In children, periodic dose adjustments are required during periods of accelerated growth but excessive monitoring of IG levels should be avoided. Higher residual IG levels (>800 mg/dL) may be indicated in selected patients with protracted sinus infections or progressive lung damage.^{4,57}

In children with mild to moderate decreases in serum IG (CVI) or in those with functional antibody deficits and normal levels of IGs (SAD), trough levels are more difficult to interpret given that these patients retain some antibody synthetic capabilities.^{17,62} Some immunologists aim for trough levels of 300 mg/dL higher than the preinfusion levels, whereas others favor troughs in the midrange of the normal for age. Dosing can be more complex, but a starting dose of 400 mg/kg/mo is generally acceptable. In some patients, increasing IG doses may be offset by concomitant enhancement IgG catabolism.⁶⁰ Increasing the dose does not necessarily raise residual levels of IgG.

ADVERSE REACTIONS

Although IG therapy is generally considered safe, adverse reactions associated with IVIG administration are not uncommon (**Box 2**). Because most adverse reactions occur in the first few infusions, it is advisable to initiate IG therapy in a hospital setting and under the supervision of a physician experienced in this type of treatment. In that way, adjustments in dosage, type of product, and rate of infusion can be made to ensure optimal tolerability.

The reported frequency of IVIG-associated adverse reactions ranges between 2% and 25% of all infusions, depending in the particular disease or patient population studied.^{63,64} At replacement doses in patients with AD, this frequency is in the order of 10% or less. IVIG-associated reactions tend to be mild to moderate in nature and, as a rule, occur during the first few infusions of the product. In this setting, children are not more likely to experience IVIG-associated adverse reactions than adults. Common symptoms, such as flushing, headaches, and malaise, tend to subside in subsequent administrations. A common practice in many centers is to premedicate patients with acetaminophen and antihistamines with the aim of minimizing these type of reactions. Often, slowing the rate of infusion suffices to abate the symptoms. Because each IVIG product potentially has unique safety and tolerability profiles, it is not uncommon to find that patients who react to one IVIG product tolerate the infusion with no problems when switched to another brand.

Box 2**Adverse reactions associated with IVIG therapy***Mild to moderate*Flushing^aChills^aFever^aHeadache^a

Back pain

Chest pain

Bronchospasm

Nausea

Myalgia^a

Aseptic meningitis

Transaminitis

Increase creatinine

Severe

Renal failure

Convulsions

Thrombosis and stroke

Pulmonary edema

Hemolysis

Anaphylaxis

^a IVIG customarily recommended.

The pathogenesis of IG-associated adverse reactions is variable and depends on the type of product, the amount and the rate of infusion, and the clinical characteristics of the patients. High-dose infusions, for instance, may induce to the formation of IG aggregates or immune complexes that potentially can prompt a generalized inflammatory response. A similar mechanism may be in patients with active infection, which is considered a relative contraindication for IVIG infusion. Severe adverse reactions, such as strokes, acute lung injury, kidney failure, anaphylaxis, and even death, have all been reported in association with IVIG therapy.^{65–68} Fortunately these are very rare events and tend to occur in patients receiving high-dose, repeated infusions for disorders other than AD.^{63,64}

IVIG is a human blood-derived product and, as such, its administration carries the potential risk of transmission of infectious pathogens. Manufacturing techniques now include a multipronged strategy to reduce the risk of potential infections, but in the past there have been a few instances in which this complication has been documented.⁶⁹ Notably, in the mid-1990s there were several reports of transmission of hepatitis C through IVIG infusions. Most of these cases were patients with PID, some were children.⁷⁰ Infectious lots were traced to a single manufacturer whose strategy had been to exclude donors positive for hepatitis C antibodies. No episodes of viral transmission caused by IVIG products have been reported after the institution of dedicated viral inactivation methods.

SUBCUTANEOUS IMMUNOGLOBULIN

Although IVIG clearly improves the quality of life for children with AD, there remain drawbacks to its use. Venous access, in particular, is a serious and potentially life-threatening concern for chronically ill children, including those with immune deficiencies. IVIG infusion requires newly obtaining venous access on a monthly basis in children. This causes some psychological distress and pain, and establishment of venous access tends to become more difficult over time, placing the patient and risk should resuscitation be required, and potentially compromising the ability to deliver immune globulin. On occasions, indwelling permanent central catheters are recommended to facilitate the infusion. Such an intervention places an already immune-deficient child at even higher risk for sepsis, thrombosis, arrhythmias, and emboli. The impact of this on the antibody-deficient child should not be underestimated.

An alternative exists using clysis, an older method of fluid delivery by subcutaneous infusion. Although clysis is clearly inferior to intravenous infusion for saline resuscitation, it is adequate for IG infusion and evades many of the issues that plague intravenous administration of IG. In a typical subcutaneous infusion of IG, a more concentrated preparation of IVIG is delivered by a catheter and small volume infusion pump into the subcutaneous tissue of the abdomen, thigh, or arm. The antibody solution is gradually absorbed from the subcutaneous tissue by lymphatics and is returned to the circulation by normal lymphatic pathways. This results in more stable levels of IgG over time, limits the fluid load imposed on the patient, and avoids the requirement for obtaining venous access.

Although the FDA only recently approved the first formulation for subcutaneous infusion in the United States (Vivaglobin), subcutaneous infusion of immune globulin (SCIG) has been in use since the 1970s and was in widespread use in Europe for many years before United States approval.^{71–82} In general, SCIG is at least equivalent to IVIG in reduction of infections and outcomes, with improved quality of life for patients and substantially reduced cost.^{76,83,84} SCIG may result in slightly higher trough levels of IgG, probably because of the increased frequency of infusion.⁷⁹ Although the number of infections is generally the same between SCIG and IVIG, some studies have shown improved outcomes over time and in bone marrow transplant patients that correlated with higher trough levels, suggesting some benefit to higher steady-state IgG levels.^{59,85–87} Other advantages to SCIG is the more limited fluid load and no association with renal failure, a concern for sucrose-containing intravenous preparations.

There are limitations to this procedure. Principally, the volume of fluid that can be delivered subcutaneously is limited, requiring the concentration of the IG preparation and potentially requiring infusion in multiple sites. In addition, because of the volume limitation, the infusion must be given weekly, rather than on a monthly basis. Despite the volume limitations, subcutaneous infusion has even been used successfully for a dermatomyositis patient who did not tolerate intravenous administration.⁸⁸ The primary adverse events are local site reactions, including redness, swelling, and pain. Although these are almost universal at the start (91%), as infusions continue these become less problematic and seldom require return to intravenous infusion.⁷⁷

Because subcutaneous access requires limited technical skill, parents and even the children themselves can deliver the infusion without the need for nursing services or being logistically dependent on an infusion center. Loss of work or school time is also not an issue for patients receiving SCIG.

Although SCIG has clear advantages over IVIG, for pediatric use the increased number of needle sticks is a concern. Although it is easier to obtain access, the number of needle exposures is increased fourfold because of the weekly infusion. This has been

a problem for some children with severe needle fears. A properly done subcutaneous puncture causes trivial pain and the principal problem that must be addressed in children is avoiding the negative stigma associated with the needle. Ideally, this problem should be managed from the beginning with careful and graded exposure to the infusion apparatus. Anesthetic creams should be used for the first few infusions to eliminate any possible pain associated with puncture.

Other strategies are also being investigated to reduce the number of infusions necessary for subcutaneous use of immune globulin. For example, it has already been demonstrated that similar results can be obtained by infusing once every 2 weeks using twice the dose. This can usually be tolerated, although a greater number of sites are needed to accommodate the increased volume.⁸⁹ Furthermore, a version of 10% IVIG solution (Gammagard or Kiovig) modified for subcutaneous infusion is currently in phase III trials. This preparation has a version of hyaluronidase included to improve diffusion through subcutaneous tissue, allowing a greater volume to be delivered. This permits the infusion to be delivered subcutaneously once per month with similar trough levels and infectious outcomes.^{90,91} It is not clear whether the same advantage of higher trough levels and more stable steady-state levels can be expected from these alternative preparations.

Despite the concern by providers and parents about increased exposure to needle sticks, children tolerate the procedure well and most children and families prefer subcutaneous infusion to intravenous infusion.⁹² The savings to the family and society are considerable, with SCIG infusions saving \$10,100 per patient-year over intravenous infusion in 1997 in a study in Sweden.⁷⁶ Similar impacts on quality of life were also found in a North American study.⁹³ SCIG also seems to be safe in pregnancy. Although it carries a pregnancy class C rating from the FDA, at least 12 pregnant women have received SCIG without any evident harm to the pregnancy.^{94,95} Patients with mild bleeding disorders also can tolerate therapy.⁹⁶ IgA-deficient patients, who are at risk for anaphylaxis caused by contaminating IgA in IVIG, can be tolerized to IgA using subcutaneous infusion.^{97,98} Although patients who have had severe reactions to IVIG can still have severe reactions to SCIG, these reactions are less common and many patients who do not tolerate IVIG may tolerate SCIG.^{99,100}

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