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Immunoglobulin Replacement Therapy in Children

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INTRODUCTION

The benefit of immunoglobulin (IG) replacement in primary antibody deficiencies (AD) is unquestionable. Many of these congenital disorders present early in life and, therefore, 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 a number of recent reviews¹⁻⁵. Here we will focus on the indications of IG replacement in children, with an emphasis on the specific diagnostic problems encountered in this population. We also present an overview of the practical aspects IG administration in the pediatric setting, including the recognition and management of adverse reactions. Finally, we will briefly discuss 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 US since the early 80's it, it rapidly substituted the use of intramuscular preparations as replacement therapy in antibody deficiency 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, polio in the final product must comply with FDA requirements. Titers against other pathogens, including those that more frequently affect patients with AD such *Streptococcus pneumoniae* 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}.

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To comply with WHO 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 90s the distinction between IVIG products has increased due to refinements in manufacturing¹¹. Most of these products have proven to be efficacious in the treatment of antibody deficiencies when compared with historical untreated controls or patients treated with intramuscular immunoglobulin. Yet, 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 in the market has approval for all the FDA sanctioned indications.

There are notably few studies comparing side by side the efficacy of different IVIG products¹². In one such study, patients treated with an IVIG product prepared with a less harsh method of viral inactivation had fewer infections than those that received a solvent-detergent treated IVIG¹³. Differences in efficacy between IVIG preparations have also been reported for example in children with Kawasaki disease¹⁴.

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 and/or volume overload. For these patients, IVIG products with a higher protein concentration, low osmolarity 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 since these patients are at risk of developing anaphylactic-type reactions when they receive IgA containing blood products¹⁵.

IG 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 there are deficits in antibody synthesis resulting in decreased levels of Igs and the functional antibody defects in which the serum immunoglobulins are within the normal range but where the production of antigen specific responses is defective.

HYPOGAMMAGLOBULINEMIA

Because of the substantial physiological 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 in premature babies requires further adjustment according to their gestational age¹⁶. In general terms, a child with serum IgG levels of less than 2 SD below the mean for age is considered to be hypogammaglobulinemic¹⁷. The levels of the other isotypes (IgA and IgM) usually, but not always, correlate with those of IgG, which is the most abundant serum immunoglobulin. While decreased IgG values do not necessarily herald a primary immunodeficiency, the finding of hypogammaglobulinemia in a young patient warrants further investigation.

Low immunoglobulins in children can result from multiple causes, many of which are unrelated to a primary immunodeficiency (Table 1). In a recent retrospective study from the Children's Hospital of Philadelphia, about half of the cases of hypogammaglobulinemia were due to a pre-existing condition known to be accompanied by decreased IG¹⁸. 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 (XLA) or autosomal recessive (ARA)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 (HIGM)²⁰⁻²². Children with CVI or HIGM 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 (SCID) awaiting transplant and in those in which B cells function is not restored following transplantation.

IgG subclass deficiency rarely results in marked hypogammaglobulinemia. In fact, immunologists commonly request this determination in a child with recurrent infections and normal levels of total IgG²³. 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.

Transient hypogammaglobulinemia of infancy (THI) is the most common cause of symptomatic hypogammaglobulinemia in children under the age of two²⁴. This diagnosis can only be made in retrospect when the child's immunoglobulin level reaches age-appropriate levels. THI follows a benign course, although a few of the young children originally diagnosed with THI will develop a more permanent defect^{25,26}. Most patients with THI 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, since, at least in vitro, IVIG suppresses both T and B cell responses^{3,27}. For those that go on IVIG, periodic re-evaluation of their immune function is imperative.

SECONDARY HYPOGAMMAGLOBULINEMIAS

PROTEIN LOSING ENTEROPATHY

Protein losing enteropathy (PLE) 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 PLE. In children, gastrointestinal disorders and congenital heart disease are the leading causes^{28, 29}. PLE 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 loss²⁸. Impairment of the lymphatic drainage of the gastrointestinal tract can also lead to PLE³⁰. In addition to hypogammaglobulinemia, patients with intestinal lymphangiectasia, also can present with T cell lymphopenia of varying degrees, arising the suspicion of a combined PID. IgG levels in PLE are usually moderately decreased, but they can be very low. Even under these circumstances, IG replacement is not indicated since there is no evidence that infections in patients with PLE occur at a higher rate or are more severe than in comparable patients with similar co-morbidities. It can be argued that, in the face of ongoing protein losses, IG administration would be 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 (SSNS) in relapse as well as in remission³¹. Originally presumed to be secondary due to urinary protein loss, the hypogammaglobulinemia of SSNS is now thought to result from complex immune mechanisms intrinsic to the pathogenesis of this disease. A recent study of 44 children with SSNS 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 which may underlie the unusual susceptibility of patients to pneumococcal infections³². While functional antibody defects may be a feature of SSNS, 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 hypogammaglobulinemia³³. These include glucocorticoids and other immunosuppressants, chemotherapeutic agents and anticonvulsants. In most of these cases, the hypogammaglobulinemia is mild and of no clinical significance. Therefore, 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 and/or if the patient develops unusual or recurrent infections.

HYPOGAMMAGLOBULINEMIA DUE TO INCREASED IGG CATABOLISM

While generalized hypercatabolic states (e.g. infection) are often accompanied by quantitative or qualitative defects in immunoglobulin production, decreased levels of serum IgG can also result from primary disorders of immunoglobulin degradation/turnover.

Hypogammaglobulinemia is a feature of familial hypercatabolic hypoproteinemia which is caused by mutations in the beta 2 microglobulin gene³⁴, a component of the neonatal Fc receptor (FcRn) which is critically involved in serum IgG homeostasis³⁵.

Although the mechanism is still unclear, Accelerated IgG catabolism is also thought to be behind the hypogammaglobulinemia observed in some patients affected with myotonic dystrophy³⁶. 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 either a direct or indirect influence on the expression of FcRN and consequently in the catabolic rate of immunoglobulins³⁷. 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 SAD³⁸. More recently Alachkar et al 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^{39,40}.

The current view is that IG replacement in SAD should only be considered if the face of recurrent pyogenic infections poorly controlled with antibiotic therapy. In children with SAD 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 1/3 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 Hyper IGE syndrome, Wiskott-Aldrich syndrome and X-linked proliferative disease⁴¹⁻⁴³. The efficacy of IVIG therapy in these rare disorders is mostly anecdotal but IG supportive therapy is routinely offered to these children in some centers¹⁶.

HIV infection

Profound abnormalities in cellular as well as humoral immunity are the hallmark of human immunodeficiency virus (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 *Streptococcus pneumoniae* and *Haemophilus 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 drug⁴. This indication followed the findings from two large randomized placebo-controlled trials conducted in the early 90's 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 HAART may, however, change this prospect. In a recent study of 15 HIV infected children by Grisaru-Soen et al short-term (<3months) withdrawal of IVIG was not associated with a significant increase in incidence of infections or a decline in immunologic function⁴⁶.

Neonatal sepsis

Neonates are a population at high risk for disseminated infection due to the relative immaturity of their host defense mechanisms¹⁶. 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 immunoglobulin 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 therapies⁴⁷. In contrast, administration of IVIG appears to be only marginally beneficial for preventing neonatal sepsis and is probably not justified⁴⁸.

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 as well as in pediatric patients with bacterial sepsis or septic shock as demonstrated by meta-analysis of 8 trials involving 492 patients⁴⁹. Using slightly different selection parameters, another group reported similar conclusions⁵⁰. Of note, IVIG products with high IgM content (not available in the US) appeared to be superior in this setting, likely due to the increased capacity of pentameric IgM to activate complement and to opsonize Gram-negative bacteria⁵¹. Despite this promising evidence, 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 as well as 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. While 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 investigation⁵²⁻⁵⁴. A number of studies established the superiority of higher IVIG doses (i.e. 400-600 mg/kg vs 100-200 mg/kg q 3-4 weeks) in reducing the rate of infections, decreasing hospitalization and antibiotic usage as well as improving pulmonary outcomes in patients with primary hypogammaglobulinemia⁵⁵⁻⁵⁸.

On the basis of these observations, the standard recommended IG replacement dose for children with AD is 100mg/kg/week. 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 et al⁵⁹. In this double blind randomized crossover study, 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 IV route is chosen, the infusions are administered every three to four 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 400-500 mg/kg^{4,16}.

The average half-life of IgG is 21 days but IgG metabolism shows significant variations among individuals⁶⁰. Active infection, endocrine disorders and autoimmunity have all been associated with increased IgG catabolism⁶¹. These co-morbidities, 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 $\beta 2$ microglobulin chain of the FcRn³⁴. Therefore, 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/month, these levels are usually attained after the sixth infusion (or about 6 half-lives), once redistribution to the tissues is complete and a steady state is reached⁶⁰.

Residual serum IgG should be monitored every two months until steady state is reached and every six 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 and/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 immunoglobulins (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 pre-infusion levels while others favor troughs in the midrange of the normal for age. Dosing can be more complex, but a starting dose of 400 mg/kg/month is generally acceptable. In some patients, increasing IG doses may be offset by concomitant enhancement IgG catabolism⁶⁰. Therefore, increasing the dose will not necessarily rise residual levels of IgG.

ADVERSE REACTIONS

Although Immunoglobulin therapy is generally considered safe, adverse reactions (AR) associated with IVIG administration are not uncommon (Table 2). Because most AR 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 AR ranges between 2% to 25% of all infusions, depending in the particular disease and/or patient population studied^{63,64}. At replacement doses in patients with antibody deficiencies, 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 AR than adults. Common symptoms such as flushing, headaches and malaise tend to subside in subsequent administrations. A common practice in many centers is to pre-medicate patients with acetaminophen and antihistamines with the aim of minimizing this type reactions. Often, slowing the rate of infusion suffices to abate the symptoms. Since 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.

The pathogenesis of IG associated AR is variable and depends on the type of product, the amount and the rate of infusion as well 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 at in patients with active infection, which is considered a relative contraindication for IVIG infusion. Severe AR, such as strokes, acute lung injury, kidney failure, anaphylaxis and even death have all been reported in association with IVIG therapy⁶⁵⁻⁶⁸. Fortunately these are very rare events and tend to occur in patients receiving high dose, repeated infusions for disorders other than antibody deficiencies^{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 documented⁶⁹. Notably, in the mid-90s there were several reports of transmission of Hepatitis C through IVIG infusions. Most these cases were patients with PID, some were children⁷⁰. 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 due to IVIG products have been reported after the institution of dedicated viral inactivation methods.

SUBCUTANEOUS IG

Though IVIG clearly improves the quality of life for children with antibody deficiencies, 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, of course, 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. While clysis is clearly inferior to intravenous infusion for saline resuscitation, it is adequate for IG infusion and evades many of issues that plague intravenous administration of IG. In a typical subcutaneous infusion of IG, a more concentrated preparation of IVIG is delivered via 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 via lymphatics and is returned to the circulation via 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.

Though the FDA only recently approved the first formulation for subcutaneous infusion in the US (Vivaglobin, CSL Behring), subcutaneous infusion of immune globulin (SCIG) has been in use since the 1970s and was in widespread use in Europe for many years before US approval⁷¹⁻⁸². 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 due to the increased frequency of infusion⁷⁹. While the number of infections is generally the same between SCID 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 IV preparations.

There are limitations to this procedure as well. 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 infusions has even been used successfully for a dermatomyositis patient who did not tolerate intravenous administration⁸⁸. The primary adverse events are local site reactions, including redness, swelling and pain. While these are almost universal at the start (91%) as infusions continue these become less problematic and seldom require return to intravenous infusion⁷⁷.

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 working or school time is also not an issue for patients receiving SCIG.

Though SCIG has clear advantages over IVIG, for pediatric use the increased number of needle sticks is a concern. Though it is easier to obtain access, the number of needle exposures is increased four-fold due to 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 two weeks using twice the dose. This can usually be tolerated, though a greater number of sites will be needed to accommodate the increased volume⁸⁹. Furthermore, a version of 10% IVIG solution (Gammagard or Kiovig, Baxter) 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 infusion⁹². The savings to the family and society are considerable as well, with SCIG infusions saving US\$10,100 per patient-year over intravenous infusion in 1997 in a study in Sweden⁷⁶. Similar impacts on quality of life were also found in a North American study⁹³. SCIG appears to be safe in pregnancy as well. 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 therapy⁹⁶. IgA-deficient patients, who are at risk for anaphylaxis due to contaminating IgA in IVIG, can be tolerized to IgA using subcutaneous infusion^{97,98}. While 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}.

References

1. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol* 2005;142:1. [PubMed: 16178850]
2. Mahadevia PJ. The pocketbook: Pharmacoeconomic issues related to intravenous immunoglobulin therapy. *Pharmacotherapy* 2005;25:94S. [PubMed: 16229680]
3. Nimmerjahn F, Ravetch JV. Anti-inflammatory actions of intravenous immunoglobulin. *Annu Rev Immunol* 2008;26:513. [PubMed: 18370923]
4. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525. [PubMed: 16580469]
5. Clynes R. Protective mechanisms of IVIG. *Curr Opin Immunol* 2007;19:646. [PubMed: 18032008]

6. Givner LB. Human immunoglobulins for intravenous use: comparison of available preparations for group B streptococcal antibody levels, opsonic activity, and efficacy in animal models. *Pediatrics* 1990;86:955. [PubMed: 2123536]
7. Lamari F, Anastassiou ED, Tsegenidis T, et al. An enzyme immunoassay to determine the levels of specific antibodies toward bacterial surface antigens in human immunoglobulin preparations and blood serum. *J Pharm Biomed Anal* 1999;20:913. [PubMed: 10746960]
8. Anonymous. Appropriate uses of human immunoglobulin in clinical practice: memorandum from an IUIS/WHO meeting. *Bull World Health Organ* 1982;60:43. [PubMed: 6979419]
9. Anonymous. Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives WHO Technical report Series No 786. Annex 1989:4.
10. Sewell WA, Jolles S. Immunomodulatory action of intravenous immunoglobulin. *Immunology* 2002;107:387. [PubMed: 12460182]
11. Siegel J. The product: All intravenous immunoglobulins are not equivalent. *Pharmacotherapy* 2005;25:78S. [PubMed: 16229678]
12. Schiff RI, Williams LW, Nelson RP, et al. Multicenter crossover comparison of the safety and efficacy of Intraglobin-F with Gamimune-N, Sandoglobulin, and Gammagard in patients with primary immunodeficiency diseases. *J Clin Immunol* 1997;17:21. [PubMed: 9049782]
13. Roifman CM, Schroeder H, Berger M, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. *Int Immunopharmacol* 2003;3:1325. [PubMed: 12890430]
14. Rosenfeld EA, Shulman ST, Corydon KE, et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. *J Pediatr* 1995;126:1000. [PubMed: 7776074]
15. Cunningham-Rundles C, Zhou Z, Mankarious S, et al. Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with anti-IgA antibodies. *J Clin Immunol* 1993;13:272. [PubMed: 8227286]
16. Stiehm ER. Human intravenous immunoglobulin in primary and secondary antibody deficiencies. *Pediatr Infect Dis J* 1997;16:696. [PubMed: 9239774]
17. Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. *Ann Allergy Asthma Immunol* 2007;99:281. [PubMed: 17910333]
18. Onigbanjo MT, Orange JS, Perez EE, et al. Hypogammaglobulinemia in a pediatric tertiary care setting. *Clin Immunol* 2007;125:52. [PubMed: 17631052]
19. Conley ME, Broides A, Hernandez-Trujillo V, et al. Genetic analysis of patients with defects in early B-cell development. *Immunol Rev* 2005;203:216. [PubMed: 15661032]
20. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34. [PubMed: 10413651]
21. Bacchelli C, Buckridge S, Thrasher AJ, et al. Translational mini-review series on immunodeficiency: molecular defects in common variable immunodeficiency. *Clin Exp Immunol* 2007;149:401. [PubMed: 17697196]
22. Bonilla FA, Geha RS. 12. Primary immunodeficiency diseases. *J Allergy Clin Immunol* 2003;111:S571. [PubMed: 12592303]
23. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? *Curr Allergy Asthma Rep* 2002;2:356. [PubMed: 12165200]
24. Dalal I, Reid B, Nisbet-Brown E, et al. The outcome of patients with hypogammaglobulinemia in infancy and early childhood. *J Pediatr* 1998;133:144. [PubMed: 9672529]
25. Moschese V, Graziani S, Avanzini MA, et al. A prospective study on children with initial diagnosis of transient hypogammaglobulinemia of infancy: results from the Italian primary immunodeficiency network. *Int J Immunopathol Pharmacol* 2008;21:343. [PubMed: 18547478]
26. Dorsey MJ, Orange JS. Impaired specific antibody response and increased B-cell population in transient hypogammaglobulinemia of infancy. *Ann Allergy Asthma Immunol* 2006;97:590. [PubMed: 17165264]
27. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. *J Clin Invest* 1993;91:602. [PubMed: 8432865]see comment

28. Driscoll DJ. Long-term results of the Fontan operation. *Pediatr Cardiol* 2007;28:438. [PubMed: 17768650]
29. Chehade M, Magid MS, Mofidi S, et al. Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr* 2006;42:516. [PubMed: 16707973]
30. Radhakrishnan K, Rockson SG. The clinical spectrum of lymphatic disease. *Ann N Y Acad Sci* 2008;1131:155. [PubMed: 18519969]
31. Schnaper HW. The immune system in minimal change nephrotic syndrome. *Pediatr Nephrol* 1989;3:101. [PubMed: 2702078]
32. Kemper MJ, Altrogge H, Ganschow R, et al. Serum levels of immunoglobulins and IgG subclasses in steroid sensitive nephrotic syndrome. *Pediatr Nephrol* 2002;17:413. [PubMed: 12107805]
33. Elizabeth FJ, Lejtenyi MC, Francisco JDN, et al. Secondary Hypogammaglobulinemia. *Immunology and allergy clinics of North America* 2001;21:141.
34. Wani MA, Haynes LD, Kim J, et al. Familial hypercatabolic hypoproteinemia caused by deficiency of the neonatal Fc receptor, FcRn, due to a mutant beta2-microglobulin gene. *Proc Natl Acad Sci U S A* 2006;103:5084. [PubMed: 16549777]
35. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007;7:715. [PubMed: 17703228]
36. Larsen B, Johnson G, van Loghem E, et al. Immunoglobulin concentration and Gm allotypes in a family with thirty-three cases of myotonic dystrophy. *Clin Genet* 1980;18:13. [PubMed: 7418249]
37. Pan Q, Hammarstrom L. Molecular basis of IgG subclass deficiency. *Immunol Rev* 2000;178:99. [PubMed: 11213812]
38. Paris K, Sorensen RU. Assessment and clinical interpretation of polysaccharide antibody responses. *Ann Allergy Asthma Immunol* 2007;99:462. [PubMed: 18051217]
39. Alachkar H, Taubenheim N, Haeney MR, et al. Memory switched B cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. *Clin Immunol* 2006;120:310. [PubMed: 16782407]
40. Carsetti R, Rosado MM, Wardmann H. Peripheral development of B cells in mouse and man. *Immunol Rev* 2004;197:179. [PubMed: 14962195]
41. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007;357:1608. [PubMed: 17881745]
42. Nichols KE, Ma CS, Cannons JL, et al. Molecular and cellular pathogenesis of X-linked lymphoproliferative disease. *Immunol Rev* 2005;203:180. [PubMed: 15661030]
43. Ochs HD, Slichter SJ, Harker LA, et al. The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes, and platelets. *Blood* 1980;55:243. [PubMed: 6444359]
44. Spector SA, Gelber RD, McGrath N, et al. Pediatric AIDS Clinical Trials Group. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. *N Engl J Med* 1994;331:1181. [PubMed: 7935655]
45. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. *N Engl J Med* 1991;325:73. [PubMed: 1675763]
46. Grisaru-Soen G, Lau W, Arneson C, et al. Randomized controlled trial of short-term withdrawal of i.v. immunoglobulin therapy for selected children with human immunodeficiency virus infection. *Pediatr Int* 2007;49:972. [PubMed: 18045306]
47. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev*. 2004CD001239
48. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. *Cochrane Database Syst Rev*. 2004CD000361
49. Kreymann KG, de Heer G, Nierhaus A, et al. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007;35:2677. [PubMed: 18074464]

50. Laupland KB, Kirkpatrick AW, Delaney A. Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. *Crit Care Med* 2007;35:2686. [PubMed: 18074465]
51. Trautmann M, Held TK, Susa M, et al. Bacterial lipopolysaccharide (LPS)-specific antibodies in commercial human immunoglobulin preparations: superior antibody content of an IgM-enriched product. *Clin Exp Immunol* 1998;111:81. [PubMed: 9472665]
52. Cunningham-Rundles C, Siegal FP, Smithwick EM, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. *Ann Intern Med* 1984;101:435. [PubMed: 6206756]
53. Eibl MM, Cairns L, Rosen FS. Safety and efficacy of a monomeric, functionally intact intravenous IgG preparation in patients with primary immunodeficiency syndromes. *Clin Immunol Immunopathol* 1984;31:151. [PubMed: 6421524]
54. Nolte MT, Pirofsky B, Gerritz GA, et al. Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol* 1979;36:237. [PubMed: 477026]
55. Liese JG, Wintergerst U, Tympner KD, et al. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992;146:335. [PubMed: 1543181]
56. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;134:589. [PubMed: 10228295]
57. Roifman CM, Gelfand EW. Replacement therapy with high dose intravenous gamma-globulin improves chronic sinopulmonary disease in patients with hypogammaglobulinemia. *Pediatr Infect Dis J* 1988;7:S92. [PubMed: 3399285]
58. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;1:1075. [PubMed: 2883406]
59. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med* 2001;135:165. [PubMed: 11487483]
60. Schiff RI, Rudd C. Alterations in the half-life and clearance of IgG during therapy with intravenous gamma-globulin in 16 patients with severe primary humoral immunodeficiency. *J Clin Immunol* 1986;6:256. [PubMed: 2424931]
61. Blaese RM, Strober W, Levy AL, et al. Hypercatabolism of IgG, IgA, IgM, and albumin in the Wiskott-Aldrich syndrome. A unique disorder of serum protein metabolism. *J Clin Invest* 1971;50:2331. [PubMed: 5096517]
62. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2002;109:1001. [PubMed: 12063531]
63. Ballou M. Safety of IGIV therapy and infusion-related adverse events. *Immunol Res* 2007;38:122. [PubMed: 17917017]
64. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003;17:241. [PubMed: 14571392]
65. Ahsan N. Intravenous immunoglobulin induced-nephropathy: a complication of IVIG therapy. *J Nephrol* 1998;11:157. [PubMed: 9650125]
66. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N Engl J Med* 1986;314:560. [PubMed: 3945295]
67. Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006;6:535. [PubMed: 16504916]
68. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994;121:259. [PubMed: 8037406]
69. Schleis TG. The process: New methods of purification and viral safety. *Pharmacotherapy* 2005;25:73S. [PubMed: 16229677]

70. Bjoro K, Froland SS, Yun Z, et al. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N Engl J Med* 1994;331:1607. [PubMed: 7526215]
71. Abrahamsen TG, Sandersen H, Bustnes A. Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics* 1996;98:1127. [PubMed: 8951264]
72. Alyanakian MA, Bernatowska E, Scherrmann JM, et al. Pharmacokinetics of total immunoglobulin G and immunoglobulin G subclasses in patients undergoing replacement therapy for primary immunodeficiency syndromes. *Vox Sang* 2003;84:188. [PubMed: 12670367]
73. Berger M, Cupps TR, Fauci AS. Immunoglobulin replacement therapy by slow subcutaneous infusion. *Ann Intern Med* 1980;93:55. [PubMed: 7396316]
74. Bjorkander J, Wadsworth C, Hanson LA. 1040 prophylactic infusions with an unmodified intravenous immunoglobulin product causing few side-effects in patients with antibody deficiency syndromes. *Infection* 1985;13:102. [PubMed: 4030106]
75. Chapel HM, Spickett GP, Ericson D, et al. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol* 2000;20:94. [PubMed: 10821460]
76. Gardulf A, Andersen V, Bjorkander J, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet* 1995;345:365. [PubMed: 7845120]
77. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. *J Clin Immunol* 2006;26:177. [PubMed: 16758340]
78. Gaspar J, Gerritsen B, Jones A. Immunoglobulin replacement treatment by rapid subcutaneous infusion. *Arch Dis Child* 1998;79:48. [PubMed: 9771252]
79. Ochs HD, Gupta S, Kiessling P, et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006;26:265. [PubMed: 16783465]
80. Remvig L, Andersen V, Hansen NE, et al. Prophylactic effect of self-administered pump-driven subcutaneous IgG infusion in patients with antibody deficiency: a triple-blind cross-over study comparing P-IgG levels of 3 g l-1 versus 6 g l-1. *J Intern Med* 1991;229:73. [PubMed: 1995766]
81. Ugazio AG, Duse M, Re R, et al. Subcutaneous infusion of gammaglobulins in management of agammaglobulinaemia. *Lancet* 1982;1:226. [PubMed: 6172685]
82. Waniewski J, Gardulf A, Hammarstrom L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol* 1994;14:90. [PubMed: 7515071]
83. Gardulf A, Borte M, Ochs HD, et al. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. *Clin Immunol* 2008;126:81. [PubMed: 17964220]
84. Gardulf A, Nicolay U. Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. *Curr Opin Allergy Clin Immunol* 2006;6:434. [PubMed: 17088648]
85. Cottler-Fox M, Lynch M, Pickle LW, et al. Some but not all benefits of intravenous immunoglobulin therapy after marrow transplantation appear to correlate with IgG trough levels. *Bone Marrow Transplant* 1991;8:27. [PubMed: 1655138]
86. Leen CL, Yap PL, McClelland DB. Increase of serum immunoglobulin level into the normal range in primary hypogammaglobulinaemia by dosage individualization of intravenous immunoglobulin. *Vox Sang* 1986;51:278. [PubMed: 3798863]
87. Ochs HD, Fischer SH, Wedgwood RJ, et al. Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. *Am J Med* 1984;76:78. [PubMed: 6424461]
88. Schleinitz N, Jean E, Benarous L, et al. Subcutaneous immunoglobulin administration: an alternative to intravenous infusion as adjuvant treatment for dermatomyositis? *Clin Rheumatol*. 2008

89. Gustafson R, Gardulf A, Hansen S, et al. Rapid subcutaneous immunoglobulin administration every second week results in high and stable serum immunoglobulin G levels in patients with primary antibody deficiencies. *Clin Exp Immunol* 2008;152:274. [PubMed: 18341618]
90. Bjorkander J, Nikoskelainen J, Leibl H, et al. Prospective open-label study of pharmacokinetics, efficacy and safety of a new 10% liquid intravenous immunoglobulin in patients with hypo- or agammaglobulinemia. *Vox Sang* 2006;90:286. [PubMed: 16635071]
91. Church JA, Leibl H, Stein MR, et al. Efficacy, safety and tolerability of a new 10% liquid intravenous immune globulin [IGIV 10%] in patients with primary immunodeficiency. *J Clin Immunol* 2006;26:388. [PubMed: 16705486]
92. Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. *Acta Paediatr* 2007;96:1474. [PubMed: 17850391]
93. Nicolay U, Kiessling P, Berger M, et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunodeficiency diseases receiving subcutaneous IgG self-infusions at home. *J Clin Immunol* 2006;26:65. [PubMed: 16418804]
94. Berger M, Cupps TR, Fauci AS. High-dose immunoglobulin replacement therapy by slow subcutaneous infusion during pregnancy. *Jama* 1982;247:2824. [PubMed: 7077789]
95. Gardulf A, Andersson E, Lindqvist M, et al. Rapid subcutaneous IgG replacement therapy at home for pregnant immunodeficient women. *J Clin Immunol* 2001;21:150. [PubMed: 11332654]
96. Arora R, Newton TC, Nelson MR. Subcutaneous immunoglobulin therapy in an 11-year-old patient with common variable immunodeficiency and von Willebrand disease. *Ann Allergy Asthma Immunol* 2007;99:367. [PubMed: 17941286]
97. de Albuquerque Campos R, Sato MN, da Silva Duarte AJ. IgG anti-IgA subclasses in common variable immunodeficiency and association with severe adverse reactions to intravenous immunoglobulin therapy. *J Clin Immunol* 2000;20:77. [PubMed: 10798611]
98. Sundin U, Nava S, Hammarstrom L. Induction of unresponsiveness against IgA in IgA-deficient patients on subcutaneous immunoglobulin infusion therapy. *Clin Exp Immunol* 1998;112:341. [PubMed: 9649200]
99. Quinti I, Soresina A, Agostini C, et al. Prospective Study on CVID Patients with Adverse Reactions to Intravenous or Subcutaneous IgG Administration. *J Clin Immunol*. 2008
100. Stiehm ER, Casillas AM, Finkelstein JZ, et al. Slow subcutaneous human intravenous immunoglobulin in the treatment of antibody immunodeficiency: use of an old method with a new product. *J Allergy Clin Immunol* 1998;101:848. [PubMed: 9648714]

Table 1
CAUSES OF HYPOGAMMAGLOBULINEMIA IN CHILDREN

DECREASED PRODUCTION

Primary antibody defects
?Transient hypogammaglobulinemia of infancy
*X-Linked Agammaglobulinemia
*Autosomal Recessive Agammaglobulinemia
*Hyper IgM Syndrome
*Common Variable Immunodeficiency
*Ataxia-telangiectasia
*Severe Combined Immunodeficiency
*Prematurity
?Malignancy
±Post transplant(solid organ, BMT)
?Chemotherapy

Drugs

INCREASED LOSS

Congenital heart disease
?Nephrotic syndrome
Intestinal lymphangiectasia
Burns

?Severe Atopic Dermatitis

INCREASED CATABOLISM

FcRN mutations
Myotonic dystrophy
Sepsis

Table 2**ADVERSE REACTIONS ASSOCIATED WITH IGIV THERAPY**

Mild to moderate	Severe
Flushing*	Renal failure
Chills*	Convulsions
Fever*	Thrombosis/ Stroke
Headache*	Pulmonary edema
Back pain	Hemolysis
Chest pain	Anaphylaxis
Bronchospasm	
Nausea	
Myalgia*	
Aseptic meningitis	
Transaminitis	
Increase creatininne	