



AMERICAN ACADEMY OF ALLERGY
ASTHMA & IMMUNOLOGY

We, the members of the American Academy of Allergy Asthma & Immunology (AAAAI) are very concerned about our ability as physicians to provide safe and effective care to our patients who require intravenous immunoglobulin (IVIG) for treatment of primary immunodeficiency (PI).

PI is caused by inherent defects of the immune system and results in recurrent, severe or unusual infections. Appropriately treating PI with IVIG preserves organ function, improves quality of life, prevents infection-related death, and increases lifespan. The long-term goal of IVIG therapy is to render the patient infection free, to the greatest extent possible.

An anonymous survey of the AAAAI membership ascertained that >95% of our physicians feel that current reimbursement standards present a risk to the health of their patients with PI. Thus, we would like to provide you with important information to help guide you in appropriately providing coverage for IVIG to patients whose lives depend upon it.

We outline 8 guiding principles for the safe, effective and appropriate use of IVIG for PI. These principles are listed below and are described in greater detail with supporting materials and specific references in the appendices to this letter.

- 1) **Indication** - IVIG therapy is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production. This is an FDA-approved indication for IVIG, for which all currently available products are licensed.
- 2) **Diagnoses** - There are a large number of PI diagnoses for which IVIG is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.
- 3) **Frequency of IVIG treatment** - IVIG is indicated as continuous replacement therapy for primary immunodeficiency. Treatment should not be interrupted once a definitive diagnosis has been established.
- 4) **Dose** - IVIG is indicated for patients with primary immunodeficiency at a starting dose of 400-600 mg/kg every 3-4 weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data.
- 5) **IgG trough levels** – IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should NOT be a consideration in access to IVIG therapy.
- 6) **Site of care** – The decision to infuse IVIG in a hospital, hospital outpatient, community office, or home based setting must be based upon clinical characteristics of the patient.
- 7) **Route** – Route of immunoglobulin administration must be based upon patient characteristics. The majority of patients are appropriate for intravenous and a subset for subcutaneous therapy.
- 8) **Product** - IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure patient safety. A change of IVIG product should occur only with the active participation of the prescribing physician.

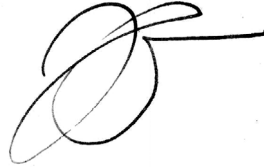
We encourage you to review the appendices to better understand the data and experience upon which these principals are based.

We hope that you will consider these principles and the evidence upon which they are based when making coverage determinations. This is essential in order to prevent poor outcomes in patients with PI.

Sincerely,

A handwritten signature in black ink, appearing to read "Stanley Goldstein". The signature is written in a cursive style with a long horizontal line extending to the right.

Stanley Goldstein, MD, FAAAAI

A handwritten signature in black ink, appearing to read "Jordan Orange". The signature is written in a cursive style with a large loop and a long horizontal line extending to the right.

Jordan Orange, MD, PhD, FAAAAI

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Appendix Five: Site of care guidelines for the provision of IVIG therapy. A guideline of the AAAAI, pending approval but to be published online as a sanctioned statement.

Appendix One

Background information on the American Academy of Allergy, Asthma and Immunology (AAAAI)

The AAAAI is the largest academic professional organization for allergists and clinical immunologists in the US. The AAAAI has over 6000 members and has the goals of providing safe and effective care to patients affected by allergic and immunologic diseases.

Above all else the AAAAI is committed to academic practice and education for its members, the medical community and public at large.

The AAAAI was founded in 1943. It has historically and currently serves as professional home for a significant portion of clinical immunologists caring for patients with primary immunodeficiency in the US. The AAAAI has always championed academic and clinical excellence in primary immunodeficiency. Examples include: 1) the numerous evidence reviews and practice statements over many years that have focused upon these diseases; 2) consistent inclusion of primary immunodeficiency in the Primer on Allergic and Immunologic diseases published every few years with the guidance of the AAAAI; 3) devotion of significant content and resources at the AAAAI annual meeting to education in primary immunodeficiency; 4) maintenance and active support of a subcommittee on primary immunodeficiency diseases composed of 30 experts in primary immunodeficiencies.

Further information about the AAAAI as well as an example of its public presence can be found at the following web address: www.AAAAI.org

Appendix Two: Detailed explanation of the eight guiding principals for safe, effective and appropriate use of IVIG. A sanctioned statement of the AAAAI.

Guiding Principal 1: Indication - IVIG therapy is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production. This is an FDA-approved indication for IVIG, which all currently available products are licensed.

Primary immunodeficiencies (PI) are a group of diseases caused by inherent defects of the immune system¹. These defects render a patient susceptible to a variety of infectious diseases. The infections in PI can occur repeatedly, severely and atypically damaging the organs, reducing quality of life and shortening lifespan. In many of these diseases the infectious susceptibility results from deficient antibody-producing components of the immune system leading to low quantity or quality of antibody.

In more severe cases of primary immunodeficiency associated with antibody defects, replacing the deficient antibodies using IVIG improves the quality of health and can be life-saving. In this regard every IVIG product approved by the US FDA is currently licensed for this indication. We appreciate that IVIG is an expensive therapy and precious resource. This fact, however, cannot present an impediment to our patients whose livelihood depends upon appropriate therapy with IVIG.

In appreciation of these concerns and with respect for the mission the AAAAI we have made guiding the appropriate usage of IVIG a priority. Although PI is perhaps the clearest indication for IVIG therapy, IVIG it represents a minority of total IVIG used in the US. To this end the AAAAI has recently completed two substantial projects directed at facilitating the rational use of IVIG and we provide them to you as resources in considering requests for IVIG therapy. The first is a Practice Paper entitled, "Practice paper on the appropriate use of intravenously administered immunoglobulin". This document is available as a free download from our website (http://www.aaaai.org/media/resources/academy_statements/practice_papers/) and is included in this package as Appendix Three.

The second project is a significantly broader review of evidence underlying the use of IVIG. This document entitled, "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. Published as a supplement to the Journal of Allergy and Clinical Immunology, April 2006, Volume 117, Pages S525 to S553. This paper reviews approximately 100 different uses of IVIG as well as practical considerations in IVIG therapy (provided in Appendix Four). Although there are only 6 FDA approved indications for IVIG, there are others, however, which are by clinical evidence. Unfortunately there are some indications that are not supported by data of the highest quality. Thus, we are concerned that use of IVIG in these diseases may deplete a precious resource from those whose lives truly depend upon IVIG therapy.

In both of these documents the evidence underlying specific-IVIG practices is reviewed, graded (using Cochrane database type standards), and specific recommendations provided. Based upon the evidence and perceived benefit of IVIG for a particular disease state, individual indications were ultimately given one of the following grades: Definitely beneficial, Probably beneficial, May provide benefit, unlikely to be beneficial. Although components of these documents apply to other of these 8 guiding principles and are discussed elsewhere, the cumulative evidence supporting the use of IVIG in PI are very clear.

Specifically IVIG therapy is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production. This statement carries the highest "Definitely beneficial" grade in the evidence review documents and all IVIG products currently licensed by the FDA are approved for use in patients with PI. Provision of IVIG to patients with PI on a regular basis is essential to prevent permanent bodily harm from infectious disease, and/or premature death.

Guiding Principal 2: Diagnoses - There are a large number of PI diagnoses for which IVIG is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.

As clinical immunologists we appreciate that our field is complex and expanding. According to the World Health Organization there are over 130 primary immunodeficiency diseases. To simplify the indication and use of IVIG our evidence review documents have focused on 3 overarching themes for which the use of IVIG is supported by the medical literature. These are:

- A) Primary immune defects with absent B cells.
- B) Primary immune defects with hypogammaglobulinemia and impaired specific antibody production.
- C) Primary immune defects with normogammaglobulinemia and impaired specific antibody production.

These themes are graded as beneficial indications for IVIG and any patient who fits these descriptions should receive regular IVIG therapy without interruption and without the need to continually re establish the diagnosis. As there are many individual primary immunodeficiency diagnoses that fall within this rubric¹, we believe it is easier and more appropriate to categorize patients in this manner.

Guiding Principal 3: Frequency of IVIG treatment - IVIG is indicated as continuous replacement therapy for primary immunodeficiency. Treatment should not be interrupted once a definitive diagnosis has been established.

There are a number of considerations that can be used to guide frequency of dosing IVIG for patients with PI. There no studies, however, that provide guidance other than that IVIG should be initially provided to patients with PI every 3 or 4 weeks. The dosing interval may need to be shortened to improve clinical efficacy and improve outcome. As there are no tests that can guide this decision it is currently based clinical status of the patient. For example, a PI patient who is repeatedly experiencing infections in the fourth week after IVIG treatment would be appropriate for treatment every 3 weeks. A recent anonymous survey of our membership in collaboration with the Immune Deficiency Foundation has determined that 87% routinely treat patients with IVIG every 4 weeks.

Frequencies of IVIG infusions of greater than every 4 weeks have not been adequately studied Using infusion intervals longer than every 4 weeks is not recommended in any of the FDA approved licensing materials and would be consistent with medical malpractice.

Importantly infusions should not be interrupted to learn about a patient's tolerance for frequency of infusion as this will place the patient in harm's way unnecessarily and also would be consistent with medical malpractice. IVIG is not indicated, or adequately studied in PI for use greater than every 4 weeks.

Guiding Principal 4: Dose - IVIG is indicated for patients with primary immunodeficiency at a starting dose of 400-600mg/kg every 3-4 weeks. Less frequent treatment of use of lower doses is not substantiated by clinical data.

Several studies comparing IVIG dose exist in the medical literature and are reviewed and considered in our review of evidence documents. The overwhelming data supports the use of higher doses of IVIG for the treatment of primary immunodeficiency². The dose ultimately needs to be adjusted to obtain clinical effect, but based upon the evidence a starting dose of less than 400mg/kg should not be considered. In the same light, doses of greater than 800mg/kg have not been rigorously studied.

Guiding Principal 5: IgG trough levels – IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should NOT be a consideration in access to IVIG therapy.

There have been a number of studies that have considered trough level of IgG in hypogammaglobulinemic patients who are being treated with hypogammaglobulinemia³⁻⁵. These data apply to only a subset of patients for whom IVIG is indicated as only a subset of diagnoses was included in the aforementioned studies. In those patients benefit was demonstrated to maintaining IgG trough over 500mg/dl. When specifically examined, greater benefit was demonstrated in maintaining the IgG trough level over 800mg/dl⁵. This is particularly germane for patients who have zero IgG at diagnosis. For these reasons maintaining IgG trough levels over these critical values is recommended as a part of good clinical care in our evidence review.

It is essential, however, that these values not be misinterpreted as benchmarks for therapy. Firstly trough levels only apply to subsets of and not all primary immunodeficiency patients. Secondly published studies of trough levels represent mean data and are not reflective of the dosing required by an individual patient. For example, a patient who is diagnosed with common variable immunodeficiency (ICD-9 279.06) and has an abnormally low IgG level of 521 with absent specific antibody will not be receiving adequate therapy if a trough dosing regimen with a goal of ≥ 500 mg/dl is applied as the patients IgG level is above 500mg/dl before therapy has begun. This patient, however, is susceptible to the ravages of infection because he has impaired antibody quality and fulfills criteria for common variable immunodeficiency. Similarly some patients have normal levels of IgG at diagnosis but have an inability to make any useful antibodies that will neutralize infection. As these patients can have IgG levels over 800 before starting therapy, trough dosing is completely irrelevant in this setting and would be consistent with medical malpractice.

Guiding Principal 6: Site of care – The decision to infuse IVIG in a hospital, hospital outpatient, community office, or home based setting must be based upon clinical characteristics of the patient.

The administration of IVIG is a complex undertaking⁶. In many cases patients with PI are chronically ill further complicating therapy. Furthermore, a majority of patients will experience some adverse event (AE) in the course of their therapy. There are also numerous severe IVIG-associated AEs many of which are acute and include thromboembolism, hypotension, seizures, aseptic meningitis syndrome, anaphylaxis, acute respiratory distress syndrome (ARDS), pulmonary edema, apnea and transfusion associated lung injury (TRALI). All IGIV products also include a black box warning regarding acute renal failure. The Immune Deficiency Foundation (IDF), which is the major patient oriented advocacy non-profit organization for those affected by PI has ascertained real world data regarding AEs in their 2002 survey of 1170 patients with PI⁷. They found that 61% of patients have infusion rate related AEs and 44% have had serious AEs. For these reasons it is critical to select patients who are appropriate for specific sites of care. In general a patients history of AEs is directly proportional to the medical supervision required. Thus the choice of site of care must account for the patients medical and IVIG history. For these reasons the AAAAI has generated a guideline to facilitate matching particular patients to specific sites of care (provided as Appendix 5).

Guiding Principal 7: Route – Route of immunoglobulin administration must be based upon patient characteristics. The majority of patients are appropriate for intravenous and a subset for subcutaneous therapy.

A product for the subcutaneous administration of immunoglobulin has recently been approved by the FDA. Although this route of therapy has been used by immunologists in the US as off label therapy for more than 20 years⁸ it is now a legitimate and approved therapy. The US licensing study as well as an earlier European cross-over trial have demonstrated that immunoglobulin administered subcutaneously to patients with PI is as effective as when immunoglobulin is administered intravenously⁹.

There are however many variables that need to be considered in effective subcutaneous immunoglobulin therapy and thus It is appropriate for some, but not all patients with PI¹⁰. As there are no specific data that currently guide physicians in choosing which patients should receive

immunoglobulin subcutaneously, the decision is a clinical one at this point. In fact there are many variables that a clinician must consider in deciding upon intravenous versus subcutaneous therapy. It is important to note however that the licensing information (package insert) for subcutaneous immunoglobulin specifies that to maintain a similar area under the curve (AUC) of serum IgG the transition dose from IV therapy needs to be increased by 37% for subcutaneous treatment. Despite this, subcutaneous therapy presents numerous benefits especially for patients experiencing severe and difficult to control adverse events, as well as those with poor intravenous access.

Guiding Principal 8: Product - IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure patient safety.

There are currently 11 IVIG products and one SCIG product licensed for use by the FDA. All of these are indicated for the treatment of primary immunodeficiency diseases. These products are not generic and there are notable differences amongst them¹¹. For these reasons they must be considered individual therapies and choice of or decision to change a particular IVIG product needs to be that of the physician^{11,12}. For example there are some products that are contraindicated in certain medical conditions. Some use glucose as a stabilizer and thus would not be recommended for diabetics. Others have high sodium content and would not be appropriate for individuals with cardiac conditions.

Also as the manufacture of the individual products is different, individual patients may experience adverse events in response to some, but not other products¹¹. For this reason the review of evidence document list the statement that “Product changes may improve adverse event profiles” as one of beneficence. The converse that a patient stably receiving a particular product should be maintained on that particular therapy is also important. In this light the aforementioned Immune Deficiency Foundation patient survey in 2002 found that 34% of all infusion related adverse events occur in the context of a product change⁷.

For these reasons, it is inappropriate for a patient to switch IVIG product without careful and due consideration. In addition, it is recommended in the site of care guideline (Appendix 5) that anytime a product needs to be changed that the highest precautions be taken in administering the infusion due to heightened concern for adverse events.

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