

# A GUIDE FOR NURSES



on Immune Globulin Therapy

Prepared by  
The Immune Deficiency Foundation  
Nursing Advisory Committee

## Introduction

The mission of the Immune Deficiency Foundation is to improve the diagnosis and treatment of primary immune deficiency diseases through research, education and advocacy. Approximately 50,000 individuals in the United States are affected by primary immune deficiency diseases.

Intravenous immune globulin (IGIV) therapy is medically recommended for the majority of the primary immune deficiency diseases. The Immune Deficiency Foundation's national survey, "Treatment Experiences and Preferences of Patients with Primary Immune Deficiency Diseases," (June 2003) reveals that approximately 70% of patients reported treatment with IGIV.

According to the Immune Deficiency Foundation's 2003 survey, most IGIV infusions are given either at home (40%) or a hospital (30%), with nearly 90% of infusions administered by nurses. Therefore, nursing professionals administering IGIV have a unique opportunity to improve treatment experiences and the quality of life of primary immune deficiency patients by providing reliable information on IGIV therapy and recognizing that immune globulin products and treatment regimens may need to be determined on an individual basis.

## Survey Highlights

Among the patients currently being treated, there appears to be a wide range of treatment practices related to frequency, dosing, length and location of administration of immune globulin therapy. Many patients discriminate among immune globulin products, citing differences in tolerability, side effects, and product preferences.

- Approximately, 30% of patients experienced rate-related reactions to immune globulin
- 22% reported non-rate related, serious side effects IGIV
- The most commonly reported side effects included headaches, fever, nausea, vomiting and chills
- 75% of patients report major or moderate concerns regarding IGIV safety
- 87% report major or moderate concerns regarding IGIV supply

The Immune Deficiency Foundation's Nursing Advisory Committee developed this educational booklet to provide essential and current information on immune globulin therapy with the goal of improving the quality of care for primary immune deficient patients and others reliant on this life saving therapy.

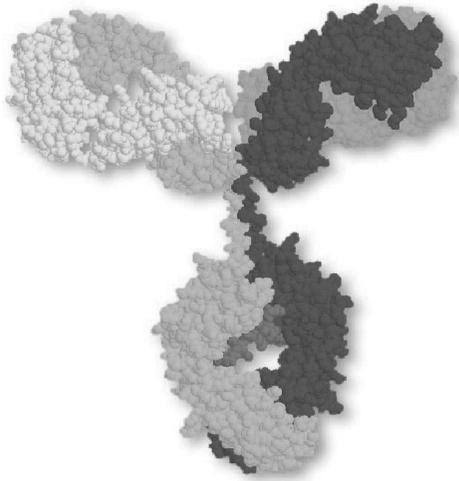
**“Nearly 90% of IGIV infusions are administered by nurses.”**

## Clinical Uses for IGIV Therapy

Immune Globulin Intravenous (IGIV) is used for multiple clinical conditions. For years IGIV has been successfully used to prevent or attenuate viral infections, as a replacement for deficient or malfunctioning antibody syndromes; and in the treatment of autoimmune and inflammatory diseases. In addition, IGIV continues to be in clinical trials for several indications currently considered to be off-label use. Clinical uses of IGIV can be grouped into two main categories: Replacement therapy and immune modulation therapy.

**Replacement therapy:** IGIV is given for various primary and secondary immune deficiency conditions in which the patient does not make adequate amounts of antibodies or the antibody that is made does not function correctly.

**Immune modulation:** IGIV has also been used to treat several diseases mediated by autoantibodies or believed to be mediated by aggressive T cells. However, the beneficial effects of IGIV have been established in only a few of these disorders.



Antibody image courtesy of Bayer Healthcare.

## Replacement Therapy

<b>Recognized Indications for Replacement Therapy: Primary diseases</b>
Ataxia Telangiectasia
Common Variable Immune Deficiency
DiGeorge Anomaly
Dysgammaglobulinemia
Failure to B-Cell engraft post BMT
Hyper IgM Syndrome
Hypogammaglobulinemia
Idiopathic T-Cell Lymphopenia
Severe Combined Immunodeficiency
Transient Hypogammaglobulinemia of infancy
Wiskott-Aldrich Syndrome
X-linked Agammaglobulinemia
Severe Combined Immunodeficiency
X-Linked Lymphoproliferative Syndrome

<b>Recognized Indications for Replacement Therapy: Secondary diseases</b>
Burn Patients
CLL and B-Cell Lymphoma with Hypogammaglobulinemia
HIV with inadequate antibody
Intestinal Lymphangiectasia
Low birth-weight babies at risk for sepsis
Myeloma and specific antibody deficiency
Non B-Cell reconstitution post Rituxan Therapy for Lymphoproliferative Disorders

## Immune Modulation

### **Immune modulation recognized treatments:**

Corticosteroid Resistant Dermatomyositis

Graft Versus Host Disease

Guillain-Barre Syndrome

Idiopathic Demyelinating Polyradiculoneuropathy (chronic)

Idiopathic Thrombocytopenic Purpura

Kawasaki's Disease

Multifocal Motor neuropathy

Myasthenia Gravis

Stiff Man Syndrome

### **Treatments still under investigation:**

Autoantibody Positive Vasculitis

Autoimmune Uveitis

Antineutrophil Cytoplasmic Antibody Vasculitis

Childhood Epilepsy

Chronic Polymyositis

Diabetes

Multiple Sclerosis

Pure Red Cell Aplasia

Recurrent Spontaneous Abortion

Rheumatoid Arthritis

Systemic Lupus Erythematosus

## IGIV Preparations

There are nine licensed and currently distributed IGIV products (See Table 1) and numerous hyperimmune products for use in the United States. Each supplier and/or institution will have a limited number of preparations on their formulary. Key points to be aware of regarding the products on the formulary at a specific institution are:

**Product form:** Whether preparations are lyophilized or liquid. Lyophilized preparations may have indications to be prepared at more than one concentration.

**Stabilizers:** Sugars, including sorbitol and sucrose, are the major stabilizing agents. Products that contain sucrose have been identified as potentially exacerbating renal disease in the elderly and in patients with underlying renal disease and other conditions noted in the label.

**IgA levels:** Products vary in the level of IgA. The IgA level is of concern in those patients with IgA deficiency. These patients can develop antibodies to IgA. With the development of antibodies the patient is at increased risk for severe life-threatening reactions. Products are considered to be low in IgA when the measured level is less than 10 micrograms/mL.

**Documentation:** With each infusion the product given, lot number, and dosage should be recorded either in the patients' record, in a central database, or preferably both. Documentation is important to look for trends with patient tolerance or if there is a recall of a particular lot of IGIV. Additional comments on product form, stabilizers, and IgA level can be found in the side effects section of this booklet.

**Product Integrity:** All products should be inspected prior to the beginning of the infusion for any evidence of tampering to the packaging of the product, including the carton as well as the vial and its closures. In addition the product, once in solution, should be inspected for clarity. Any evidence of tampering should be reported to the supplier and/or producer. No product should be infused if there is evidence of particulate matter, precipitants, or cloudiness.

## Delivery of IGIV

The delivery of IGIV can refer to either the protocol for or route of delivery for the patient, or the place where IGIV is administered to the patient. Beginning in the early 1950's immune globulin was only available in an intramuscular preparation. Immunodeficient patients required large frequent doses in order to achieve increased serum levels. This method was very painful and patients seldom reached therapeutic serum IgG levels. In the early 1980's, new manufacturing processes were developed to make immune globulin preparations in a purified form that could be given intravenously, IGIV. This allowed immunodeficient patients to maintain normal serum IgG levels. A dose of IGIV given every three to four weeks helps immunodeficient patients to remain healthy and infection free.

Rapid infusion of IGIV is a new option for immunodeficient patients receiving IGIV. Patients who are tolerating routine infusions with few to no side effects may be candidates for this therapy. Protocols for rapid infusion vary. In general the transition time to a rapid infusion protocol is 6 to 12 months. Infusion time can be as quick as 30 minutes rather than 2 to 4 hours. Rapid infusion of IGIV can provide benefits to both patients and healthcare providers by enhancing efficiency, lowering costs and allowing flexibility in treatment schedules.

Subcutaneous Immune Globulin, SubQ IG, is an option for immunodeficient patients who are not suitable candidates for IGIV. These patients may have poor venous access or have experienced adverse reactions to IGIV. The immunoglobulin is given through a small needle just under the skin over several hours. The subcutaneous method is a common method of administration in Europe. In the United States the method is currently considered off-label; however, clinical trials started in 2001 are awaiting FDA review and approval.

Immune globulin can be administered under several models or situations. Each has advantages and disadvantages. Each patient should be considered individually as to the best model and given choice of where their treatments should be administered. Most of the time IGIV will be a lifelong treatment for immunodeficient patients and through their life cycle the model of administration may need to be modified. Rates of administration are product specific and can be found in the products' package inserts. Most of the time it is not where but who is administering the IGIV that is important. For best patient outcomes, consistency with

someone who is knowledgeable about immune deficiencies and appropriate administration of IGIV is needed. IGIV administration most often occurs in one of the following places:

Hospital

Physician's office

Infusion suite (hospital, physician's or free standing)

Home

- Nurse Administered
- Self-infusion (patient obtains venous access and self-administers IGIV product)



## Side Effects of IGIV

A number of adverse events have been associated with the use of IGIV in both children and adults. Up to 15% of recipients experience some type of reaction. The severity of reactions can range from mild to severe, depending on the type. Most reactions occur during the initial 30 to 60 minutes of the infusion and are mild and self-limited. Severe anaphylactic reactions are rare. There are risk factors that may identify persons at greater risk for having a reaction to IGIV. It is advised to read the specific package insert for the IGIV product used as the incidence and type of adverse events varies from product to product.

### Types of Adverse Reactions and Management

**Pyrogenic reactions:** These reactions are marked by a significant rise in temperature and are usually accompanied by systemic symptoms. Fever is the most common side effect in children.

**Allergic reactions:** Reactions that are associated with an allergic mechanism can be recognized when a patient presents with an uncomfortable feeling, especially a tightening in or around the neck, chest, or abdomen. There may be difficulty swallowing, a choking sensation, or difficulty breathing. Other symptoms of anaphylaxis include wheezing, rash or hives, rapid or weak pulse, sweating, or an upset stomach with or without diarrhea. Management of symptoms associated with an allergic reaction start by immediately turning off the infusion. The patient may be given an antihistamine. Usually, the symptoms resolve with these measures. The patient's health care provider should be notified. If the symptoms do not resolve, the patient should lie flat and be given a single dose of adrenaline (Epi-pen) and arrangements should be made for the patient to be evaluated by a health care provider. These reactions are very uncommon, and although severe, may not preclude future use of IGIV.

**Reactions in IgA Deficient Patients:** Selecting a product that has been IgA depleted can reduce the risk of reaction in patients with IgA deficiencies and antibodies to IgA. Products are considered to be low in IgA when the IgA content is less than 10 micrograms/mL.

**Minor systemic reactions:** These reactions most commonly include headache, dizziness, or lightheadedness. Patients can also experience chills, nausea, vomiting, back or hip pain, malaise and myalgia.

The most frequent cause of an adverse reaction is infusion at a rate that is too rapid. Flushing marks these reactions and warmth of the skin, chills, headache, dizziness, nausea, vomiting, and muscle aches. Management of a minor reaction begins with temporarily stopping the infusion by closing off the clamp.

The infusion can be restarted when the symptoms begin to subside, usually within 30 minutes. Restart at one-half of the previous rate and gradually increase until the recommended rate is reached. It is important to remember that individuals require varying rates of infusion, although most can tolerate administration of IGIV over three to four hours. It may be helpful for someone who has experienced a reaction to prepare for the infusion by taking a premedication, usually acetaminophen or diphenhydramine, or both approximately one hour prior to beginning the infusion. If the patient requires a longer duration of infusion, the premedication can be readministered four hours into the infusion.

Patients who continue to have reactions in spite of precautionary measures such as decreasing the rate and volume of the infusion, or premedicating with acetaminophen and diphenhydramine may benefit from adding hydrocortisone (1-2 mg/kg intravenously 1/2 hour prior to infusion) to the premedication regimen.

**Vasomotor symptoms with or without additional cardiac manifestations:** Blood pressure can either increase or decrease, and may be accompanied by flushing or tachycardia. Patients experiencing such reactions may report shortness of breath or tightness in the chest.

**Transmission of Blood-borne Pathogens:** IGIV products are manufactured from plasma collected from large numbers of carefully screened human donors who have been tested for the absence of hepatitis B surface antigen, HCV antibody and HIV antibody and by nucleic acid testing for HIV and HCV. The products are produced using techniques to remove or inactivate potentially contaminating viral pathogens. It is uncertain whether there are unrecognized infectious agents that can contribute to safety problems in the future. However, favorable studies have been performed by some manufacturers regarding clearance of prion agents which cause Variant Creutzfeldt-Jakob disease.

**Anemia Associated with WinRho SD:** Patients who are receiving the WinRho SD preparation benefit from the platelet preserving properties of the product, however, selective destruction of red blood cells may result in significant anemia. Patients should be monitored for decreases in red blood cell counts, especially if they are taking other medications known to cause anemia.

**Renal Adverse Events:** There have been rare reports of increased serum creatinine, oliguria, and acute renal failure occurring within seven days of IGIV administration. Hyperosmolality and differences in stabilizer sugars [maltose, glucose, or especially sucrose (in Carimune NF and Gammar PIV)] have been implicated as factors contributing to renal adverse events. Additionally, patients who are not adequately hydrated prior to onset of the infusion, or who have diabetes mellitus, any pre-existing renal insufficiency, receiving nephrotoxic antibiotics, have paraproteinemia or who are over age 65 are at greater risk.

**Aseptic Meningitis:** Aseptic meningitis has developed in patients who have received standard and high-dose (2 gm/kg) IGIV. The symptoms develop within 24 hours of the infusion. Patients with aseptic meningitis develop severe headache with nuchal rigidity, drowsiness, fever, lethargy, photophobia, painful eye movements, nausea and vomiting. A previous history of migraine headaches has been noted to be a risk factor. Symptoms are not relieved by slowing or stopping the infusion, and the headache does not resolve with acetaminophen or nonsteroidal anti-inflammatory agents. Using a different IGIV preparation may be helpful in preventing the recurrence of aseptic meningitis, and severe cases requiring discontinuation of therapy are rare.

**Post-infusion reactions:** These reactions can occur immediately up to 48 hours post-infusion. These reactions are usually less severe in nature. Common post-infusion reactions are headache, low-grade fever, nausea, arthralgias, and generalized malaise. These types of reactions are managed with over-the-counter analgesics, antihistamines, and low dose systemic steroids.

## Concomitant Medications



IGIV is only compatible with Normal Saline, sterile water, or D5W as recommended by the manufacturer's insert. If medications are required prior to or during an infusion, it is recommended to flush the line with at least 5 to 10 mL of compatible fluid prior to administering the medication.

Medications will precipitate in the line, especially Lasix or Valium. No medications should be directly administered into the same line as the IGIV is being administered. If multiple medications are required, a second IV line should be placed as not to interfere with the infusion. Other options could be to have a main line of compatible fluid and piggyback the IGIV in to the line at the closest port so that a flush system is readily available.

IGIV should be administered at room temperature. If the product is initially refrigerated, it should be allowed to slowly warm to room temperature over at least one to two hours. Patients may have side effects of chills, headaches or backaches if the product is administered cold.

Once the infusion line is primed the infusion should be administered within 4 hours to reduce the risk of the growth of bacterial pathogens. There may be variations from product to product and the specific product insert should be reviewed prior to administration.

**Table 1: Characteristics of Available IGIV Products  
Licensed for Use in the United States - October 2004**

BRAND NAME	Polygam S/D		Panglobulin	Gammagard S/D		Iveegam EN
	5%	10%		5%	10%	
Manufacturer or Distributor	American Red Cross		American Red Cross	Baxter Corporation/ BioScience Division		Baxter Corporation/ BioScience Division
Method of Production (Including Viral Inactivation)	Cohn-Oncley fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment		Kistler Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration	Cohn-Oncley fractionation, ultra-filtration, ion-exchange chromatography, solvent detergent treatment		Cold ethanol fractionation, PEG, trypsin treatment
Form	Lyophilized		Lyophilized	Lyophilized		Lyophilized
Shelf-Life	24 Months		24 Months	24 Months		24 Months
Reconstitution Time	<5 minutes at room temperature >20 minutes if cold		Several minutes	<5 minutes at room temperature >20 minutes if cold		≤10 minutes at room temperature
Available Concentrations	5%	10%	3 to 12%	5%	10%	5%
Maximum Recommended Infusion Rate	4 mL/kg/hour	8 mL/kg/hour	>2.5 mL/kg/hour	4 mL/kg/hour	8 mL/kg/hour	1.8 mL/kg/hour
Time to Infuse 35 gms <sup>1</sup>	2.5 hours	0.6 hours	<3.3 hours (6% solution)	2.5 hours	0.6 hours	5.6 hours
Sugar Content	20 mg/mL glucose	40 mg/mL glucose	1.67 gm sucrose per gram of protein	20 mg/mL glucose	40 mg/mL glucose	50 mg/mL glucose
Sodium Content	8.5 mg/mL sodium chloride	17 mg/mL sodium chloride	<20 mg sodium chloride per gram of protein	8.5 mg/mL sodium chloride	17 mg/mL sodium chloride	3 mg/mL sodium chloride
Osmolarity/Osmolality	636 mOsm/L	1250 mOsm/L	192 - 1074 mOsm/kg	636 mOsm/L	1250 mOsm/L	≥240 mOsm/L
PH	6.4 - 7.2		6.4 - 6.8	6.4 - 7.2		6.4 - 7.2
IgA Content	< 2.2 µg/mL in a 5% solution		720 µg/mL	< 2.2 µg/mL in a 5% solution		<10 µg/mL

<sup>1</sup>0.5 gm/kg for a 70 kg adult = 35 gms; 5% Concentrations: 1g = 20 mL; 10% Concentrations: 1g = 10 mL  
The time to infuse is based on the maximal infusion rate.

Check product label for storage temperatures, which vary among IGIV brands.

**Table 1: Characteristics of Available IGIV Products  
Licensed for Use in the United States - October 2004**

BRAND NAME	Gamunex	Flebogamma 5%	Octagam	Carimune NF	Gammar-P I.V.
Manufacturer or Distributor	Bayer HealthCare/ Biologic Products Division	Grifols	Octapharma	ZLB Behring	ZLB Behring
Method of Production (Including Viral Inactivation)	Cohn-Oncley fractionation, caprylate/ chromatography purification, cloth and depth filtration, final container low pH incubation	Cold alcohol fractionation, PEG ion-exchange chromatography, pasteurized at 60° C for 10 hours	Cohn-Oncley cold ethanol fractionation, ultra-filtration, chromatography, solvent detergent treatment	Kistler Nitschmann fractionation, pH 4.0, trace pepsin, nanofiltration	Cohn-Oncley fractionation, ultra-filtration pasteurization at 60° C for 10 hours
Form	Liquid	Liquid	Liquid	Lyophilized	Lyophilized
Shelf-Life	36 Months	24 Months	24 Months	24 Months	24 Months
Reconstitution Time	None (Liquid Solution)	None (Liquid Solution)	None (Liquid Solution)	Several minutes	<20 minutes
Available Concentrations	10%	5%	5%	3 to 12%	5%
Maximum Recommended Infusion Rate	4.8 mL/kg/hour	6.0 mL/kg/hour	<4.2mL/kg/hour	>2.5 mL/kg/hour	3.6 mL/kg/hour
Time to Infuse 35 gms <sup>1</sup>	1.0 hour	1.6 hours	2.5 hours	<3.3 hours (6% Solution)	2.8 hours
Sugar Content	None	50 mg/mL D-Sorbitol	100 mg/mL maltose	1.67 gm sucrose per gram of protein	50 mg/mL sucrose
Sodium Content	Trace Amounts	<3.2 mEq/L	≤30 mMol/L	<20 mg sodium chloride per gram of protein	5 mg/mL sodium chloride
Osmolarity/ Osmolality	258 mOsm/kg	240 - 350 mOsm/L	310 - 380 mOsm/kg	192 - 1074 mOsm/kg	309 mOsm/L
PH	4.0 - 4.5	5.0 - 6.0	5.1 - 6.0	6.4 - 6.8	6.4 - 7.2
IgA Content	46 µg/mL	<50 µg/mL	<100 µg/mL	720 µg/mL	<25 µg/mL

<sup>1</sup>0.5 gm/kg for a 70 kg adult = 35 gms; 5% Concentrations: 1g = 20 mL; 10% Concentrations: 1g = 10 mL  
The time to infuse is based on the maximal infusion rate.

Check product label for storage temperatures, which vary among IGIV brands.

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## Resources

The members of the Immune Deficiency Foundation's (IDF) Nursing Advisory Committee are available as a resource for nurses administering IGIV or treating patients with primary immune deficiency diseases.

Please contact IDF at 800-296-4433 or [idf@primaryimmune.org](mailto:idf@primaryimmune.org) and the staff will assist you in contacting a member of the Nursing Advisory Committee.

Additional resource information can also be found on the IDF website: [www.primaryimmune.org](http://www.primaryimmune.org).

The Patient Notification System (PNS) is a free, confidential, 24-hour communication system providing information on plasma-derived and recombinant product withdrawals and recalls. Led by the Plasma Protein Therapeutics Association (PPTA), the Patient Notification System was developed by the producers and distributors of plasma products with direct input from consumers.

Log on to [www.patientnotificationsystem.org](http://www.patientnotificationsystem.org) for more information.

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