



Work Group Report on the appropriate use of intravenously administered immunoglobulin (IGIV)

Generated by the primary immunodeficiency committee of the American Academy of Allergy, Asthma and Immunology.

Participants:

Jordan S. Orange MD, PhD (editor)

Assistant Professor of Pediatrics

University of Pennsylvania School of Medicine

The Children's Hospital of Philadelphia

3615 Civic Center Blvd – ARC 1216F

Philadelphia, PA 19104

Mark Ballow, MD

Professor of Pediatrics

State University of New York at Buffalo, School of Medicine and Biomedical Sciences

Women's and Children's Hospital of Buffalo

219 Bryant St.

Buffalo, NY 14222

Melvin Berger MD, PhD

Professor of Pediatrics and Pathology

Case Western Reserve University School of Medicine

Rainbow Babies and Children's Hospital

11100 Euclid Avenue Mail Stop 6008B, Cleveland, OH

Rebecca H. Buckley, M.D.

J. Buren Sidbury Professor of Pediatrics

Professor of Immunology

Duke University Medical Center

Durham, NC 27710

Javier Chinen, MD, PhD

Associate Investigator

NHGRI-NIH

Bldg 10-CRC, East Wing Rm 6-3340

10 Center Dr. MSC 1611

Bethesda, MD 20892-1611

Charlotte Cunningham-Rundles MD/PhD

Professor, Medicine / Clinical Immunology

Mount Sinai School of Medicine

One Gustave L. Levy Place

Box 1089 New York, NY 10029

Yehia El-Gamal, MD, PhD

President of the Egyptian Society of Pediatric Allergy & Immunology (ESPAI)

Professor of Pediatrics

Pediatric Allergy and Immunology Unit

Children's Hospital, Ain Shams University

Cairo 11566, Egypt

Elham Hossny, MD, PhD

Professor of Pediatrics,

Pediatric Allergy and Immunology Unit

Children's Hospital, Ain Shams University

Cairo 11566, Egypt

Bruce D. Mazer MD

Division Head,

Allergy and Immunology

Montreal Children's Hospital

Associate Professor of Pediatrics

McGill University

Robert P. Nelson, Jr. M.D.

Associate Professor of Medicine

Division of Hematology/Oncology

Hematological Malignancy Program/Immunology

Indianapolis, IN

Dhaval Kumar D. Patel, MD, PhD

Professor of Medicine and Microbiology and Immunology

Director, Thurston Arthritis Research Center

Chief, Division of Rheumatology, Allergy and Immunology

University of North Carolina @ Chapel Hill

CB# 7280, 3330 Thurston Building

Chapel Hill, NC 27599-7280

Elizabeth Secord MD, PhD

Assistant professor of Pediatrics

Wayne State University

Children's Hospital of Michigan

3901 Beaubien

Detroit MI 48201

Ricardo U. Sorensen, M.D.

Department of Pediatrics

Louisiana State University Health Science Center

1542 Tulane Avenue

New Orleans, Louisiana 70112-2822

Richard L. Wasserman, M.D, Ph.D.

Clinical Associate Professor

Department of Pediatrics

University of Texas Southwestern Medical School

7777 Forest Lane, B-332

Dallas, Texas 75230

Catherine R. Weiler, MD, PhD

Assistant Professor of Medicine

W-15 Mayo Bldg

Division of Allergy

Mayo Clinic College of Medicine

Rochester, MN 55905

Introduction

Immunoglobulin (IG) for intravenous (IV) administration, or IGIV (also commonly referred to as IVIG, although officially designated in the US as IGIV) is currently approved by the US Food and Drug Administration (FDA) for 6 indications: 1) treatment of primary immunodeficiencies; 2) prevention of bacterial infection in patients with hypogammaglobulinemia due to B cell chronic lymphocytic leukemia; 3) prevention of coronary artery aneurysms in Kawasaki disease; 4) prevention of infections and graft versus host disease after bone marrow transplantation; 5) reduction of serious bacterial infection in HIV-infected children; and 6) increasing platelet count in idiopathic thrombocytopenic purpura to prevent bleeding. Not all currently available products are approved for each of these indications and physicians should review specific product information. The use of IGIV for these purposes can be variable and there are notable disparities in current clinical practices. Furthermore, there have been developments regarding IGIV usage, which warrant consideration.

IGIV has been utilized for other conditions without FDA approval. Some of these uses are based entirely upon theory and/or anecdotal reports, while others are based upon quality evidence. A comprehensive review of the evidence supporting the use of IGIV in specific indications is beyond the scope of this document, but was reviewed in detail in its preparation. The entire summary of evidence and detailed recommendations regarding the use of IGIV will be published elsewhere and the reader is referred to that document as well as other more comprehensive discussions of IGIV usage.¹

In this position statement the major uses of IGIV are reviewed and specific recommendations are provided where appropriate (Table 1). These recommendations should not be considered absolute, but should help prompt each prescribing physician to

consider and review the data supporting any particular use of IGIV. The indications discussed are: primary immunodeficiency; secondary immunodeficiency; autoimmune disease; asthma; neurologic disorders; transplantation; infectious disease; Kawasaki disease; and other uses. Practical considerations in using IGIV are also raised.

Primary Immunodeficiency

IGIV is indicated to reduce the susceptibility to infections in patients with primary immunodeficiencies affecting the quantity and/or quality of humoral immunity. Primary humoral immunodeficiencies include agammaglobulinemia, hyper IgM syndrome, common variable immunodeficiency as well as other deficiencies of immunoglobulin and specific antibody production (hyper IgE syndrome, Wiskott-Aldrich Syndrome and specific antibody deficiency).² Patients markedly deficient in humoral immunity are dependent on IGIV for survival. Benefits of IGIV in patients not able to produce antibodies normally include: a reduction of the severity and frequency of infections,³ prevention of chronic lung disease⁴ and prevention of enteroviral meningoencephalitis.³ The decision to administer IGIV to patients with primary deficiencies in antibody production should be based on: 1) abnormalities of serum immunoglobulin concentrations; 2) clinical history of infections; and, when appropriate, 3) the demonstrated inability to produce antibody normally following antigenic stimulation. IGIV is not indicated for treatment of selective IgA deficiency, per se, but may be useful in patients in whom IgA deficiency is accompanied by defects in IgG production.

An additional consideration is the route of administration. In the United States, at the present time, available immunoglobulin products are licensed only for administration by the intravenous or intramuscular route. Subcutaneous administration of intravenous or intramuscular preparations of immunoglobulin which is widely employed in Europe, has therapeutic equivalence with intravenous therapy.^{5, 6}

Secondary immunodeficiency

IGIV has also been used in a number of diseases that result in secondary immunodeficiency. IGIV administration may be appropriate for selected patients with B cell chronic lymphocytic leukemia.⁷ A well controlled trial of IGIV in HIV infected children demonstrated a significant reduction in bacterial infections but the benefit of IGIV was not seen in patients treated with trimethoprim/sulfamethoxazole for *Pneumocystis* pneumonia prophylaxis.⁸ The use of IGIV as an adjunct to enhance the antibacterial defenses of premature newborn infants remains controversial, but may diminish the incidence of sepsis.⁹ Other uses of IGIV for secondary immunodeficiencies, including sepsis beyond the neonatal period, multiple trauma and post-operative wounds are not well supported by published data.

Autoimmune Diseases

IGIV remains an important treatment modality in immune thrombocytopenic purpura, and it has been shown to improve platelet counts in controlled studies.¹⁰ Despite the lack of vigorous scientific evidence for benefit in post-transfusion purpura, IGIV administration is recommended given the potential life threatening nature of the disease.¹¹ Anecdotal reports also suggest utility for IGIV in autoimmune neutropenia, autoimmune hemolytic anemia, Evans syndrome and acquired hemophilia especially when other therapeutic modalities fail.^{12, 13}

IGIV has been used with varying efficacy in several other autoimmune diseases. The results in rheumatoid arthritis are controversial, but some benefit was suggested from case reports and open label trials.¹⁴ Although high dose IGIV was reported to improve specific organ-related complications of systemic lupus erythematosus including nephritis, myocarditis, polyradiculopathy, and bone marrow suppression, its potential

prothromboembolic effects necessitate extreme caution in its therapeutic application.¹⁵ IGIV also anecdotally helped patients with antiphospholipid antibody syndrome experiencing recurrent spontaneous abortion and those undergoing *in vitro* fertilization.¹⁶ Some case reports and open label studies additionally report benefit from IGIV as an alternative therapeutic agent in patients with anti-neutrophil cytoplasmic antibody disorders,¹⁷ systemic sclerosis/scleroderma,¹⁸ and Still's disease.¹⁹ IGIV has been successfully used in some other organ specific autoimmune diseases including Graves' ophthalmopathy,²⁰ autoimmune uveitis,²¹ and autoimmune chronic active hepatitis,²² but lack of convincing evidence prevents a recommendation for its routine use.

Asthma

Asthma is a disease of pulmonary inflammation, which is effectively treated in most individuals with regimens that include low to moderate doses of inhaled corticosteroids, or non-steroidal anti-inflammatory agents. In some patients, very high doses of inhaled and oral steroids are required to control asthma symptoms, leading to intolerable adverse effects. In this setting, IGIV has been employed as a steroid-sparing agent in open trials.²³⁻²⁶ Two placebo-controlled studies have had contradictory results; one failed to show any benefit of IGIV,²⁷ while the other demonstrated decreases in steroid requirements in steroid-dependent asthmatics.²⁸ Other smaller studies that have used low doses of IGIV, or that have only evaluated patients requiring inhaled steroids have not shown significant differences.^{26, 29}

The inconsistent data from randomized controlled studies combined with the cost and availability of IGIV, does not support a recommendation for routine use in severe asthma. The efficacy in select groups, suggests that it may be used as a treatment for carefully defined asthmatic patients with persistent requirements for high doses of systemic steroids. Although, IGIV cannot be presently recommended for routine treatment

of asthma, individuals with antibody deficiency who have asthma-like symptoms can benefit from IGIV therapy through its ability to decrease the incidence of infections that may trigger bronchospasm.

Neurological Disorders

IGIV has demonstrated effectiveness in inflammatory demyelinating disorders of the peripheral and central nervous systems.^{30, 31} Despite the lack of an FDA indication, IGIV has become first-line therapy for demyelinating neuropathies such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy, and has demonstrated similar efficacy with less adverse effects than plasma exchange or corticosteroids.³²⁻³⁴ In myasthenia gravis³⁵ and Lambert Eaton myasthenic syndrome,³⁶ IGIV may be used as an alternative treatment when patients fail to respond or do not tolerate other treatments. IGIV may also be a potentially effective second line treatment in relapsing-remitting multiple sclerosis, although the optimal dosage remains to be established.³⁷ IGIV may also be extremely useful in the inflammatory myopathies, polymyositis and dermatomyositis,³⁸ but it is unlikely to be beneficial in inclusion body myositis³⁹ and thus a specific recommendation for use in the latter disease in particular is not possible.

Due to the paucity of reliable studies that demonstrate substantial efficacy of IGIV in intractable childhood epilepsy syndromes, its routine use cannot be recommended for these patients. However, the poor prognosis and quality of life of children who do not improve with anti-epileptic drugs and corticosteroids would justify a role for IGIV especially in patients who may be candidates for surgical resection.^{40, 41} Many case reports exist in which IGIV therapy was tried with varying success in other less common neurological disorders but more clinical research is needed to establish its usefulness.

Hematopoietic Stem Cell and Solid Organ Transplantation

IGIV is currently indicated as an adjunct treatment for selected patients undergoing allogeneic hematopoietic stem cell transplantation for the treatment of hematologic malignancy.⁴² Treatment is provided to prevent infection during the period in which patients are rendered most immunodeficient due to chemoablation, typically during the first 100 days. Similarly IGIV is effective in the management of primary immunodeficient patients undergoing allogeneic transplantation.⁴³ In particular, IGIV offers protection against interstitial pneumonia secondary to CMV, especially when given in conjunction with antiviral chemoprophylaxis.⁴⁴

The benefit of IGIV as adjunct therapy for patients transplanted in the era of improved molecular HLA matching, anti-CMV chemoprophylaxis, gram-negative antimicrobial prophylaxis, nonablative conditioning regimens and improvements in graft versus host immunoprophylaxis is not known. Thus, a re-evaluation of practices is warranted. In this regard a recent double-blind placebo-controlled multi-center trial of IGIV in allogeneic bone marrow transplantation failed to demonstrate utility of IGIV administration.⁴⁵ As a result, its routine use in patients undergoing allogeneic matched related bone marrow transplantation may not be necessary.

IGIV had also been considered to reduce the incidence and severity of acute graft versus host disease (GVHD).⁴⁶ More recent studies, however have failed to demonstrate this benefit, thus preventing a recommendation of IGIV for this indication.^{42, 45} In contrast, data have never supported the use of IGIV to prevent chronic GVHD.⁴⁷ Further trials are needed to resolve data supporting contrasting practices. Studies are also needed to determine whether IGIV is beneficial in the case of HLA-matched unrelated donor bone marrow or cord blood transplants.

IGIV can be useful for solid organ transplant recipients who experience acute rejection, or who are HLA-sensitized for acute rejection, and may be justified for

appropriately selected renal transplantation.⁴⁸ Although less data exist, there may also be a role for IGIV in autoimmune cytopenias that can occur post-transplant.⁴⁹

Kawasaki Disease (KD)

KD is an acute febrile vasculitis of medium-sized vessels that commonly affects the coronary arteries and is believed to have a post-infectious origin. IGIV (single dose of 2g/kg) in conjunction with aspirin is the standard of care for patients with KD during the first 10 days of the syndrome to prevent the development of coronary aneurysms.⁵⁰ Although there are some data suggesting that there may be benefit to treatment on or prior to day 5,⁵¹ they have been challenged.⁵² Most importantly, therapy should be provided when the diagnosis is established in attempt to prevent coronary aneurysm, even after 10 days of onset of fever.

Treatment of infectious disease

Although IGIV does not have a major role in the treatment of infections, a beneficial role has been shown in the following settings. Adjunct treatment of established bacterial septic shock and neonatal group B streptococcal disease with IGIV provides benefit and reduces mortality.⁵³⁻⁵⁷ High dose IGIV administered intravenously or intrathecally may be useful for treatment of meningoencephalitis caused by enteroviral infection in patients with agammaglobulinemia.⁵⁸ Orally administered IGIV can reduce the duration of diarrhea, viral shedding and hospitalization in children with acute rotaviral gastroenteritis.⁵⁹ Treatment of pneumonitis caused by CMV with high dose IGIV,⁶⁰ or high-titer anti-CMV IGIV⁴⁴ combined with ganciclovir has resulted in improved outcomes. IGIV or hyperimmune respiratory syncytial virus (RSV) IGIV has provided some benefit in combination with ribavirin to treat RSV pneumonitis in immunodeficient patients.^{61, 62} IGIV has also been effectively administered in anemia caused by chronic erythrovirus B-19 infection,⁶³ *Campylobacter*

jejuni infection,⁶⁴ and in pseudomembranous colitis caused by *Clostridium difficile*,⁶⁵ but its widespread use in these conditions is not supported by extensive data.

Other Uses

Conflicting reports exist regarding the efficacy of IGIV in toxic epidermal necrolysis and Stevens-Johnson syndrome, but given the risk of mortality, the majority of evidence support the use of high-dose IGIV as an early therapeutic intervention.⁶⁶ The evidence for IGIV use in the autoimmune blistering disorders, such as bullous pemphigoid, is outlined in a consensus statement published by the American Academy of Dermatology,⁶⁷ and is primarily based on case reports or prospective studies of “last resort” treatment. There has been an open trial of IGIV use for delayed pressure urticaria and two thirds of the patients had remission, or some benefit.⁶⁸ The evidence for IGIV use in other chronic urticarias is unclear and does not currently support its use.^{69, 70} Likewise the data for atopic dermatitis, which includes one small, randomized, evaluator blinded trial, does not support the use of IGIV.⁷¹ There are case reports, but no controlled trials supporting the use of IGIV in psoriasis.⁷²

Several neurocognitive disorders are proposed to have immunological components including childhood autism, chronic fatigue syndrome and the pediatric autoimmune neuropsychiatric disorders with associated streptococcal infection (PANDAS). Despite the abundance of anecdotal reports of IGIV utility in these disorders, a double-blind placebo controlled trial has only been performed in chronic fatigue syndrome and demonstrated a lack of efficacy.⁷³ In PANDAS, a single case controlled prospective trial did demonstrate efficacy of 1g/kg/d treatment with IGIV on 2 consecutive days for rigorously defined patients.⁷⁴ In contrast, studies of IGIV in autism have at best, been case series and have not provided suggestion of benefit.⁷⁵

IGIV has also been evaluated in certain other organ specific diseases. In selected patients with cystic fibrosis there have been some encouraging observations regarding IGIV therapy, but effects are marginal and probably do not justify the resources and risk.⁷⁶ High dose IGIV treatment appeared promising in numerous case reports of acute myocarditis,⁷⁷ but has been found ineffective in treatment of the carditis of acute rheumatic fever⁷⁸ as well as in recently diagnosed dilated cardiomyopathy,⁷⁹ as determined by randomized placebo controlled trials. Finally, IGIV has been suggested to promote successful pregnancy in women who experience recurrent spontaneous abortion, but meta-analysis of existing randomized controlled trials failed to demonstrate any benefit⁸⁰ and thus therapy is not recommended for this indication.

IGIV Products

There are currently a number of IGIV products that provide chemically unmodified lyophilized or liquid forms of IgG produced from plasma recovered from whole blood donations or from plasmapheresis donors (Table 2). Lots may contain plasma obtained from more than 50,000 donors, which is pooled and then treated to precipitate the immunoglobulin-containing fraction. The resulting solutions may contain sodium, maltose, albumin, polyethylene glycol, D-mannitol, D-sorbitol, sucrose, glucose, and/or albumin among other substances to prevent aggregation. Donors are screened and tested for multiple infectious agents to reduce the risk of pathogen contamination. In addition, several different pathogen inactivation steps are also utilized in the preparation of the various IGIV products and can include solvent/detergent treatment, acid incubation, pasteurization, filtration, and precipitation/chromatography. IGIV solutions have final IgG concentrations of 3,5,6,10 or 12% depending on the product. The osmolarity of these solutions lies between 253 mOsm/L and 1250 mOsm/L. The IgA content of current brands varies between <0.4µg/ml to 720 µg/ml.

IGIV dosing

For antibody replacement IGIV therapy is typically administered every 3 to 4 weeks starting with as much as 400-600 mg/kg.⁸¹ The dose or dosing interval should be adjusted (based on the clinical response and patient's catabolism of IgG or known protein loss) to achieve optimal clinical results. Some studies suggest that doses as high as 800 mg/kg/month may be useful, particularly in primary immunodeficiency patients with chronic lung disease.^{82, 83} Measurement of trough IgG levels may be helpful. Trough levels greater than 500 mg/dl are associated with fewer infections and improved outcomes.^{3, 84} The target trough level for patients with pre-treatment IgG levels between 200 and 500mg/dl should be at least the pre-treatment IgG plus 300. Higher trough levels (>800 mg/dL) have the potential to further reduce the incidence of infection.³ Patients with normal IgG levels, but impaired specific antibody production may also benefit from doses ≥ 400 mg/kg.⁸⁵ Ultimately, the dose must be individualized and titrated to achieve clinical benefit for the patient being treated. Immunomodulatory doses are typically higher than those used for antibody replacement and range between 400 mg/ kg for 5 days, or a more rapid course of 1 or 2 g/kg given in one or two days.

Infusion methods

The first infusion in an immunodeficient patient should be given in a setting with cardiovascular and pulmonary monitoring and should be administered slowly, starting with a rate of 0.4 mg/Kg/min. After 15 to 30 minutes the rate can be increased to 1.2 to 1.6 mg/Kg/min, and increased as tolerated to a maximum of 3.3 mg/kg/min (certain IGIV products are licensed for greater rates of infusion). Considerations of the sodium or sucrose content, total volume to be administered, and the osmolarity of the product are important in patients with pre-existing medical conditions such as renal⁸⁶ or

cardiovascular disease.^{31, 87-89} IGIV preparations should not be considered to be generically equivalent, and substitution should generally not be allowed without careful monitoring of the patient. Infusions of IGIV are commonly given in outpatient infusion centers, outpatient clinics, or in the home. The latter is facilitated by the involvement of home care nurses, but alternatively can be provided by self infusion.⁹⁰ The placement and use of indwelling venous access for IGIV administration should be carefully weighed against the thrombotic and infectious risks inherent to these devices that may be further amplified in immunodeficient patients, or by administration of IGIV. In most cases the IV route is used, but subcutaneous infusion (not yet FDA approved), has been found similarly satisfactory at least in primary immunodeficiency.⁹¹ This route may be especially useful in patients with difficult venous access. Although a number of protocols are applicable for subcutaneous immunoglobulin replacement therapy, 100mg/kg/wk is an acceptable option as a starting dose. Typically, up to 20cc of IGIV (or intramuscular IG) is infused into a single site at rates approximating 10cc/hr. Multiple sites may be used simultaneously as well as the more concentrated preparations of IGIV to allow for an efficient infusion process. The subcutaneous route of administration, however, has not been well documented for indications other than primary immunodeficiency and should be avoided for the treatment of other diagnoses until better data are available.

Adverse effects

Mild adverse reactions, myalgias, chills, low grade fever, and/or headache are relatively common. They occur more commonly in the first few infusions and are treated by slowing or stopping the infusion for 15 to 30 minutes. Pre-treatment with diphenhydramine, acetaminophen, aspirin or ibuprofen, or IV hydration may also be helpful. Prophylaxis of more severe reactions can be provided with 1mg/kg IV hydrocortisone. Serious adverse events are rare, but include aseptic meningitis, renal

failure, thrombosis, and perhaps neurodegeneration amongst others.⁹² Of these, renal failure has been associated with the sucrose content of a given product and thrombosis may be associated with high osmolarity products or high viscosity states.^{90, 93} There is also a risk of reactions from anti-IgA antibodies generated in patients with complete IgA deficiency,⁹⁴ including true IgE-mediated anaphylactic reactions against IgA,⁹⁵ but the latter are extremely rare. The risk of these reactions and/or the risk of sensitization of IgA deficient patients with some preserved antibody production may be minimized by selection of IGIV products with low IgA content. Finally, the theoretical and actual possibility of transmission of blood-borne infection needs to be considered. Thus, the risks of IGIV administration must be carefully weighed against potential benefits. The appropriate use of IGIV, however, can be life-saving and should not be withheld for patients in justifiable need.

Literature cited

Table 1: Selected uses of IGIV*

Benefit*	Disease	Evidence category***	Reference
Definitely beneficial	Primary immunodeficiency	IIb	2,3
	Idiopathic thrombocytopenic purpura	Ia	10
	Graves' ophthalmopathy	Ib	20
	Demyelinating polyneuropathies	Ia	30, 32-34
	Kawasaki Disease	Ia	50
Probably beneficial	Chronic lymphocytic leukemia with reduced IgG and history of infections	III	7
	Prevention of bacterial infection in HIV-infected children	Ib	8
	Dermatomyositis and polymyositis	IIa	38
	Myasthenia Gravis and Eaton-Lambert myasthenia	Ib	35,36
	Established bacterial sepsis	Ia	53-57
	Toxic epidermal necrolysis and Stevens-Johnson Syndrome	IIa	66
May provide benefit	Prevention of neonatal sepsis	Ia	9
	Post transfusion purpura	III	11
	Autoimmune cytopenias	III	12
	Systemic Lupus	III	15
	Severe rheumatoid arthritis	IIb	14
	Antiphospholipid antibody syndrome in pregnancy	III	16
	Anti-neutrophil cytoplasmic antibody syndromes	III	17
	Severe persistent high dose steroid-dependent asthma	Ib	23-27
	Multiple sclerosis (relapsing-remitting)	Ia	37
	Intractable childhood epilepsy	Ia	40, 41
	Prevention of infection and acute graft versus host disease post-hematopoietic stem cell transplantation	Ib	42, 43, 45, 46
	Prevention of acute humoral rejection in renal transplantation	III	48

Benefit*	Disease	Evidence category***	Reference
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)	IIb	74
Unlikely to be beneficial	Inclusion body myositis	Ib	39
	Non steroid-dependent asthma	Ib	26-29
	Atopic Dermatitis	IIa	71
	Chronic non-pressure urticarias	IIb	69, 70
	Chronic fatigue syndrome	Ia	73
	Autistic disorders	III	75

*Indications for which certain IGIV products have approval from the US Food and Drug Administration are listed in boldface italics.

**The recommendation of benefit is based upon the available evidence. As additional studies become available and as the category of evidence listed for a given indication changes it is possible that the benefit category will change. The strength of a recommendation within a given category should be considered directly proportional to the category of evidence.

***Evidence categorization is as follows: Ia – from meta-analysis of randomized controlled studies; Ib – from at least one randomized controlled study; IIa – from at least one controlled trial without randomization; IIb - from at least one other type of quasi-experimental study; III – from non-experimental descriptive studies such as comparative, correlation or case-control studies; IV – from expert committee reports or opinions or clinical experience of respected authorities or both. It should be clear that this scale is non-linear and recommendations based on category I evidence should be given the greatest value.

Table 2: Currently Available IGIV Products and Their Properties

Product	Dosage Form	Diluent	Refrigeration	Filter Required	Osmolality (mOsm/L)	Sodium Content	pH after Reconstitution	IgA content	Stabilizer, or added regulator	Indication****
Carimune NF	Lyophilized powder	0.9% sodium chloride	No	No	498 (3%) 690 (6%) 1,074 (12%)	0.01 mEq/mL (3% solution) 0.02 mEq/mL (6% solution) 0.041 mEq/mL (12% solution)	6.6	720µg/ml	Sucrose	PI, ITP
Carimune NF	Lyophilized powder	Sterile Water for Injection	No	No	192 (3%) 384 (6%) 576 (9%) 768 (12%)	none	6.6	720µg/ml	Sucrose	PI, ITP
Flebogamma	5% Liquid	NA	No***	Optional	240-350	<0.032 mEq/ml	5-6	<0.05mg/ml	D-sorbitol	PI
Gamimune N 10%*	10% liquid	NA Incompatible with saline	Yes	No	274	Trace	4.25		Glycine	PI, ITP, BMT, HIV
Gammagard 5% S/D	Lyophilized powder	Sterile Water for Injection	No	Yes	636 (5%)	0.145 mEq/mL	6.8	<2.2µg/ml	2% Glucose	PI, ITP, CLL, KD
Gammagard 10% S/D	Lyophilized powder	Sterile Water for Injection	No	Yes	1,250 (10%)	0.145 mEq/mL	6.8	270µg/ml	4% Glucose	PI, ITP, CLL, KD
Gammar-P	Lyophilized powder	Sterile Water for Injection	No	No	309 (5%) 600 (10%)	0.085 mEq/mL	6.8	<25µg/ml	Sucrose	PI
Gamunex	10% Liquid	NA Incompatible with saline	No**	No	258	Trace	4 to 4.5	46µg/ml	Glycine	PI
Iveegam EN**	Lyophilized powder	Sterile Water for Injection	Yes	Yes	≥ 240	0.05 mEq/mL	6.4 to 7.2	<10µg/ml	Glucose	PI, KD
Octagam	5% liquid	NA	No***	No	310-380	0.03 mEq/ml	5.1-6.0	<0.1mg/ml	Maltose	PI
Panglobulin NF	Lyophilized powder	(0.9% sodium chloride, 5% dextrose.) Sterile Water for Injection	No	No	With water: 192 (3%)* 384 (6%)* 576 (9%)* 768 (12%)*	0.01 mEq/mL (3% solution) 0.02 mEq/mL (6% solution) 0.031 mEq/mL (9% solution) 0.041 mEq/mL (12% solution) or none	6.6	720µg/ml	Sucrose	PI, ITP
Polygam S/D	Lyophilized powder	Sterile Water for Injection	No	Yes	636 (5%) 1,250 (10%)	0.145 mEq/mL (5% solution) 0.28 mEq/mL (10% solution)	6.8	<2.2µg/ml	Glucose	PI, ITP, CLL, KD

*Gamimune N has been discontinued but may still be offered by suppliers as inventories may still exist.

**Iveegam EN is currently only available for patients who have been maintained on this product.

***not required

****US Food and Drug Administration Licensed indications for the specific product. Abbreviations are: PI, primary immunodeficiency; ITP – immune thrombocytopenic purpura; BMT – bone marrow transplantation; KD – Kawasaki disease; HIV – pediatric HIV infection; CLL – B-cell chronic lymphocytic leukemia. For specifics of each indication please see the text and the manufacturers product information.

NA – Not applicable

1. Sacher RA. Intravenous immunoglobulin consensus statement. *J Allergy Clin Immunol* 2001; 108:S139-46.
2. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med* 1991; 325:110-7.
3. Quartier P, Debre M, De Blic J, de Sauevzac R, Sayegh N, Jabado N, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999; 134:589-96.
4. 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; 109:1001-4.
5. Gardulf A, Andersen V, Bjorkander J, Ericson D, Froland SS, Gustafson R, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet* 1995; 345:365-9.
6. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol* 2000; 20:94-100.
7. Cooperative group for the study of immunoglobulin in chronic lymphocytic leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. *N Eng J med* 1988; 319:902-7.
8. Mofenson LM, Moye J, Jr., Korelitz J, Bethel J, Hirschhorn R, Nugent R. Crossover of placebo patients to intravenous immunoglobulin confirms efficacy for prophylaxis of bacterial infections and reduction of hospitalizations in human immunodeficiency virus-infected children. The National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *Pediatr Infect Dis J* 1994; 13:477-84.
9. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev* 2004; 1:CD001239.
10. Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; 359:23-9.
11. Mueller-Eckhardt C, Kiefel V. High-dose IgG for post-transfusion purpura-revisited. *Blut.* 1988; 57:163-7.
12. Flores G, Cunningham-Rundles C, Newland AC, Bussel JB. Efficacy of intravenous immunoglobulin in the treatment of autoimmune hemolytic anemia: results in 73 patients. *Am J Hematol* 1993; 44:237-42.
13. Bossi P, Cabane J, Ninet J, Dhote R, Hanslik T, Chosidow O, et al. Acquired hemophilia due to factor VIII inhibitors in 34 patients. *American Journal of Medicine* 1998; 105:400-8.
14. Ballou M. Mechanisms of action of intravenous immunoglobulin therapy and potential use in autoimmune connective tissue diseases. *Cancer* 1991; 68:1430-6.
15. Arnal C, Piette JC, Leone J, Taillan B, Hachulla E, Roudot-Thoraval F, et al. Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. *J Rheumatol* 2002; 29:75-83.
16. Galli M, Cortelazzo S, Barbui T. In vivo efficacy of intravenous gammaglobulins in patients with lupus anticoagulant is not mediated by an anti-idiotypic mechanism. *Am J Hematol* 1991; 38:184-8.
17. Jayne DR, Esnault VL, Lockwood CM. ANCA anti-idiotypic antibodies and the treatment of systemic vasculitis with intravenous immunoglobulin. *Journal of Autoimmunity* 1993; 6:207-19.
18. Rutter A, Luger TA. Intravenous immunoglobulin: an emerging treatment for immune-mediated skin diseases. *Curr Opin Investig Drugs* 2002; 3:713-9.
19. Prieur AM. Intravenous immunoglobulins in Still's disease: still controversial, still unproven. *J Rheumatol* 1996; 23:797-800.
20. Kahaly G, Pitz S, Muller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in Graves' ophthalmopathy. *Clin Exp Immunol* 1996; 106:197-202.
21. Rosenbaum JT, George RK, Gordon C. The treatment of refractory uveitis with intravenous immunoglobulin. *Am J Ophthalmol* 1999; 127:545-9.
22. Carmassi F, Morale M, Puccetti R, Pistelli F, Palla R, Bevilacqua G, et al. Efficacy of intravenous immunoglobulin therapy in a case of autoimmune-mediated chronic active hepatitis. *Clin Exp Rheumatol* 1992; 10:13-7.

23. Mazer BD, Gelfand EW. An open-label study of high-dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991; 87:976-83.
24. Haque S, Boyce N, Thien FC, O'Hehir RE, Douglass J. Role of intravenous immunoglobulin in severe steroid-dependent asthma. *Intern Med J* 2003; 33:341-4.
25. Landwehr LP, Jeppson JD, Katlan MG, Esterl B, McCormick D, Hamilos DL, et al. Benefits of high-dose i.v. immunoglobulin in patients with severe steroid-dependent asthma. *Chest* 1998; 114:1349-56.
26. Jakobsson T, Croner S, Kjellman NI, Pettersson A, Vassella C, Bjorksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma. *Allergy* 1994; 49:413-20.
27. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999; 91:126-33.
28. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial. *J Allergy Clin Immunol* 1999; 103:810-5.
29. Niggemann B, Leupold W, Schuster A, Schuster R, v Berg A, Grubl A, et al. Prospective, double-blind, placebo-controlled, multicentre study on the effect of high-dose, intravenous immunoglobulin in children and adolescents with severe bronchial asthma. *Clin Exp Allergy* 1998; 28:205-10.
30. Singhi SC, Jayshree M, Singhi P, Banerjee S, Prabhakar S. Intravenous immunoglobulin in very severe childhood Guillain-Barre syndrome. *Ann Trop Paediatr* 1999; 19:167-74.
31. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; 291:2367-75.
32. Shanbag P, Amirtharaj C, Pathak A. Intravenous immunoglobulins in severe Guillain-Barre syndrome in childhood. *Indian J Pediatr* 2003; 70:541-3.
33. Leger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001; 124:145-53.
34. Perez Nellar J, Dominguez AM, Llorens-Figueroa JA, Ferra-Betancourt A, Pardo A, Quiala M, et al. [A comparative study of intravenous immunoglobulin and plasmapheresis preoperatively in myasthenia]. *Rev Neurol* 2001; 33:413-6.
35. Rich MM, Teener JW, Bird SJ. Treatment of Lambert-Eaton syndrome with intravenous immunoglobulin. *Muscle Nerve* 1997; 20:614-5.
36. Gray O, McDonnell G, Forbes R. Intravenous immunoglobulins for multiple sclerosis. *Cochrane Database Syst Rev* 2003; 4:CD002936.
37. Illum N, Taudorf K, Heilmann C, Smith T, Wulff K, Mansa B, et al. Intravenous immunoglobulin: a single-blind trial in children with Lennox-Gastaut syndrome. *Neuropediatrics* 1990; 21:87-90.
38. Cherin P, Piette JC, Wechsler B, Blety O, Ziza JM, Laraki R, et al. Intravenous gamma globulin as first line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. *J Rheumatol* 1994; 21:1092-7.
39. Dalakas MC, Koffman B, Fujii M, Spector S, Sivakumar K, Cupler E. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. *Neurology* 2001; 56:323-7.
40. Assa A, Watemberg N, Bujanover Y, Lerman-Sagie T. Demyelinative brainstem encephalitis responsive to intravenous immunoglobulin therapy. *Pediatrics* 1999; 104:301-3.
41. Zivkovic SA, Heyman R, Pless M. Subacute rhombencephalitis optica responsive to intravenous immunoglobulins. *Eur J Neurol* 2003; 10:83-6.
42. Winston DJ, Antin JH, Wolff SN, Bierer BE, Small T, Miller KB, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001; 28:187-96.
43. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med* 1999; 340:508-16.
44. Reed EC, Bowden RA, Dandliker PS, Lilleby KE, Meyers JD. Treatment of cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. *Ann Intern Med* 1988; 109:783-8.
45. Cordonnier C, Chevret S, Legrand M, Rafi H, Dhedin N, Lehmann B, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. *Ann Intern Med* 2003; 139:8-18.
46. Sullivan KM, Kopecky KJ, Jocom J, Fisher L, Buckner CD, Meyers JD, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation.[see comment]. *New England Journal of Medicine* 1990; 323:705-12.
47. Sullivan KM, Storek J, Kopecky KJ, Jocom J, Longton G, Flowers M, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host

- disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. *Biol Blood Marrow Transplant* 1996; 2:44-53.
48. Jordan S, Cunningham-Rundles C, McEwan R. Utility of intravenous immune globulin in kidney transplantation: efficacy, safety, and cost implications. *Am J Transplant* 2003; 3:653-64.
 49. Riechsteiner G, Speich R, Schanz U, Russi EW, Weder W, Boehler A. Haemolytic anaemia after lung transplantation: an immune-mediated phenomenon? *Swiss Med Wkly* 2003; 133:143-7.
 50. Sundel RP. Update on the treatment of Kawasaki disease in childhood. *Curr Rheumatol Rep* 2002; 4:474-82.
 51. Tse SM, Silverman ED, McCrindle BW, Yeung RS. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. *J Pediatr* 2002; 140:450-5.
 52. Muta H, Ishii M, Egami K, Furui J, Sugahara Y, Akagi T, et al. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. *J Pediatr* 2004; 144:496-9.
 53. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002:CD001090.
 54. Friedman CA, Wender DF, Temple DM, Rawson JE. Intravenous gamma globulin as adjunct therapy for severe group B streptococcal disease in the newborn. *American Journal of Perinatology* 1990; 7:1-4.
 55. Jackson MA, Colombo J, Boldrey A. Streptococcal fasciitis with toxic shock syndrome in the pediatric patient. *Orthop Nurs* 2003; 22:4-8.
 56. Werdan K, Pilz G. Supplemental immune globulins in sepsis: a critical appraisal. *Clin Exp Immunol* 1996; 104 Suppl 1:83-90.
 57. Jenson HB, Pollock BH. The role of intravenous immunoglobulin for the prevention and treatment of neonatal sepsis. *Semin Perinatol* 1998; 22:50-63.
 58. Quartier P, Foray S, Casanova JL, Hau-Rainsard I, Blanche S, Fischer A. Enteroviral meningoencephalitis in X-linked agammaglobulinemia: intensive immunoglobulin therapy and sequential viral detection in cerebrospinal fluid by polymerase chain reaction. *Pediatr Infect Dis J* 2000; 19:1106-8.
 59. Guarino A, Canani RB, Russo S, Albano F, Canani MB, Ruggeri FM, et al. Oral immunoglobulins for treatment of acute rotaviral gastroenteritis. *Pediatrics* 1994; 93:12-6.
 60. Ljungman P, Engelhard D, Link H, Biron P, Brandt L, Brunet S, et al. Treatment of interstitial pneumonitis due to cytomegalovirus with ganciclovir and intravenous immune globulin: experience of European Bone Marrow Transplant Group. *Clin Infect Dis* 1992; 14:831-5.
 61. Ghosh S, Champlin RE, Englund J, Giralt SA, Rolston K, Raad I, et al. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant* 2000; 25:751-5.
 62. DeVincenzo JP, Hirsch RL, Fuentes RJ, Top FH, Jr. Respiratory syncytial virus immune globulin treatment of lower respiratory tract infection in pediatric patients undergoing bone marrow transplantation - a compassionate use experience. *Bone Marrow Transplant* 2000; 25:161-5.
 63. Mareschal-Desandes R, Andre JL, Lesesve JF, Krier MJ, Bordigoni P, Humbert JC. Successful treatment of chronic parvovirus B19 infection by high-dose immunoglobulin. *Clin Nephrol* 2003; 59:311-2.
 64. Hammarstrom V, Smith CI, Hammarstrom L. Oral immunoglobulin treatment in *Campylobacter jejuni* enteritis. *Lancet* 1993; 341:1036.
 65. Salcedo J, Keates S, Pothoulakis C, Warny M, Castagliuolo I, LaMont JT, et al. Intravenous immunoglobulin therapy for severe *Clostridium difficile* colitis. *Gut* 1997; 41:366-70.
 66. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience.[see comment]. *Archives of Dermatology* 2003; 139:39-43.
 67. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Archives of Dermatology*. 2003; 139:1051-9.
 68. Dawn G, Urcelay M, Ah-Weng A, O'Neill SM, Douglas WS. Effect of high-dose intravenous immunoglobulin in delayed pressure urticaria. *British Journal of Dermatology* 2003; 149:836-40.
 69. O'Donnell BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *British Journal of Dermatology*. 1998; 138:101-6.
 70. Asero R. Are IVIG for chronic unremitting urticaria effective? *Allergy* 2000; 55:1099-101.
 71. Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002; 147:518-22.
 72. Gurmin V, Mediwake R, Fernando M, Whittaker S, Rustin MH, Beynon HL. Psoriasis: response to high-dose intravenous immunoglobulin in three patients. *British Journal of Dermatology* 2002; 147:554-7.
 73. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, Tymms K, Wakefield D, Dwyer J, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med* 1997; 103:38-43.

74. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 1999; 354:1153-8.
75. Plioplys AV. Intravenous immunoglobulin treatment of children with autism.[see comment]. *Journal of Child Neurology*. 1998; 13:79-82.
76. Winnie GB, Cowan RG, Wade NA, Cairo MS. Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. *Journal of Pediatrics* 1989; 114:309-14.
77. Kishimoto C, Shioji K, Kinoshita M, Iwase T, Tamaki S, Fujii M, et al. Treatment of acute inflammatory cardiomyopathy with intravenous immunoglobulin ameliorates left ventricular function associated with suppression of inflammatory cytokines and decreased oxidative stress. *Int J Cardiol* 2003; 91:173-8.
78. Voss LM, Wilson NJ, Neutze JM, Whitlock RM, Ameratunga RV, Cairns LM, et al. Intravenous immunoglobulin in acute rheumatic fever: a randomized controlled trial. *Circulation* 2001; 103:401-6.
79. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001; 103:2254-9.
80. Daya S, Gunby J, Porter F, Scott J, Clark DA. Critical analysis of intravenous immunoglobulin therapy for recurrent miscarriage. *Human Reproduction Update*. 1999; 5:475-82.
81. 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; 6:256-64.
82. Eijkhout HW, van Der Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, 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; 135:165-74.
83. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987; 1:1075-7.
84. de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol* 2004; 4:745-53.
85. Liese JG, Wintergerst U, Tympner KD, Belohradsky BH. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992; 146:335-9.
86. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J* 2000; 93:901-4.
87. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; 17:241-51.
88. Brennan VM, Salome-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. *Clin Exp Immunol* 2003; 133:247-51.
89. Akhtar I, Bastani B. Acute renal failure and myocarditis associated with intravenous immunoglobulin therapy. *Ann Intern Med* 2003; 139:W65.
90. Eibl MM. Intravenous immunoglobulins in neurological disorders: safety issues. *Neurol Sci* 2003; 24 Suppl 4:S222-6.
91. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004; 112:1-7.
92. Wittstock M, Benecke R, Zettl UK. Therapy with intravenous immunoglobulins: complications and side-effects. *European Neurology* 2003; 50:172-5.
93. Renal insufficiency and failure associated with immune globulin intravenous therapy--United States, 1985-1998. *MMWR Morb Mortal Wkly Rep* 1999; 48:518-21.
94. Bjorkander J, Hammarstrom L, Smith CI, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol* 1987; 7:8-15.
95. 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; 314:560-4.