

History of Immunoglobulin Replacement

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- Immunoglobulin • IVIg treatment • Primary immunodeficiency
- Antibody deficiency • Immune modulation

HISTORY OF IMMUNOGLOBULIN TREATMENT

In 1890, von Behring and Kitasato¹ proved that “bloodserum” of rabbits immunized with tetanus toxin contained activity against “tetanus poison,” and such blood serum transferred to rabbits protected these normal (naive) animals against tetanus. In 1901, von Behring was awarded the first Nobel Prize in Medicine or Physiology for his work in this field. Ehrlich² demonstrated that protection could be quantitatively correlated to the amount of antitoxin in the blood.

In 1910, Dr. A. Wolff-Eisner, a 33-year-old physician in Berlin, published “Curative Serum Therapy and Experimental Therapy,” a handbook for clinic and medical practice.³ His intention—not so far from our own current intentions—was to convey to clinicians and practitioners “the advances of biological science as they relate to therapy. The theoretic [the science] should only be included as far as necessary for the understanding of treatment.” Several infectious diseases and conditions such as allergy and cancer were treated with curative serum. Serum therapy of diphtheria and tetanus was already common practice.⁴

In Germany alone, five companies, including Höchster Farbwerke, Merck-Darmstadt, and Behring-Höchst, produced curative serum; products from Schering and Parke-Davis were also available. There was international cooperation: Calmette⁵ in Lille, France worked on the treatment of snake venom; Wolff-Eisner in Berlin concentrated on serum therapy of hay fever and treatment of bacterial diseases. Serum therapy was introduced in the treatment of staphylococcal disease (van de Velde, Holland), streptococcal infection (R. Freund, Berlin), and meningococcal disease (Flexner, New York).^{6–8} Curative (mainly antitoxic) sera were produced in different animal species because serum sickness already was recognized as one of the feared complications of therapy. Convalescent human sera had great advantages compared

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with sera of immunized animals, because human serum could be applied without the risk of anaphylaxy and serum sickness.

In 1907, Cenci⁹ (Italy) applied convalescent human sera for the prevention of measles. McKhann and Chu¹⁰ followed in the same indication with material obtained from the globulin fraction of placenta in 1933. Treatment with curative sera was performed successfully and saved the lives of many individuals in the first third of the twentieth century,⁵ mainly children with diphtheria and soldiers with tetanus in World War I. Treatment was also widely applied in pneumococcal disease.

Although antibody treatment had been widely used,¹¹ information on serum protein composition was incomplete until the 1930s. The proof that antibodies localized to the immunoglobulin (Ig) compartment of human serum came in the 1930s. Initially fractionation was performed by precipitation with different salt concentrations (such as ammonium sulfate).

In 1938, Karelitz,¹² an associate of Schick, published prophylaxis against measles with the globulin fraction of immune adult serum in *The American Journal of Diseases of Children*, but profound understanding on serum proteins became available only after Tiselius and Kabat¹³ published their pioneering work on electrophoresis of immune serum in *Science* in 1938. Just 2 years later, Cohn and his group^{14,15} reported on preparation and properties of serum and plasma proteins, which opened the way for Ig prophylaxis and treatment of infectious diseases.

Fractionation of Serum Proteins

Techniques developed by Cohn and his coworkers^{14,15} in Boston at the beginning of World War II led to the development of the separation of plasma proteins into individual stable fractions with different biologic functions. The basis for Cohn's fractionation was to use low concentrations of alcohol by reducing the pH and lowering ionic strength. The procedure was performed at low temperature, which reduced the likelihood of contamination and made large-scale fractionation possible. This method, further refined in cooperation with J.L. Oncley,¹⁵ is basically still in use and, with some additional steps, yields Ig for intramuscular and subcutaneous use. By the mid-1940s, however, Cohn¹⁴ realized that an Ig product that could be applied intravenously was desirable. He recognized that the removal of depressor substances was necessary and would require new technology.

In the following years, numerous cooperations were established between Cohn and others,¹⁶ including Elliot Robinson at the Massachusetts Antitoxin and Vaccine Laboratory, Charles Janeway¹⁷ (Sen.) and John Enders at Harvard, and clinical trials to prevent viral diseases (eg, measles and hepatitis) were initiated. Because of the limited availability of blood, Ig products were also prepared from placentas. During and after World War II, the supply of gammaglobulin increased as plasma from the American Red Cross became available.

The first Ig products were mainly given to prevent and treat infections: polymyelitis, measles, mumps, pertussis, and hepatitis A.^{18,19} These Ig disappeared as soon as the respective diseases could be and were prevented by vaccination. Other Ig products with defined specificities were developed subsequently and continue to be used currently (eg, tetanus Ig,²⁰ RHo(D) Ig,²¹ rabies Ig, hepatitis B Ig,²² and varicella zoster Ig²³). Respiratory syncytial virus hyperimmunoglobulin²⁴ was licensed but later replaced by a respiratory syncytial virus monoclonal antibody,^{25,26} one of the few monoclonal antibodies that made its way into clinical application in the prevention of an infectious disease—pneumonia caused by respiratory syncytial virus, a dangerous, potentially fatal disease in premature infants and newborns.

Early Treatment of Primary Immunodeficiency with Immunoglobulin

The first patient who had primary immunodeficiency (PID) described by Bruton²⁷ in 1952 had recurrent infections and multiple episodes of sepsis. Testing his serum revealed the absence of specific antibodies, and serum electrophoresis indicated that Ig were lacking. The boy was treated with subcutaneous gammaglobulin and was free of sepsis and severe infections thereafter. The clinical history of the patient indicated that in addition to life-threatening bacterial infections, he had mumps four times but managed to recover from the disease without problems or complications. That finding, which was an experiment of nature, indicated that antibodies are important to prevent the disease, but T-cell immunity is sufficient to clear this viral infection. Parallel to this observation, numerous patients with agammaglobulinemia were identified and treated by Janeway and others.^{17,28} In the early days, however, especially if a product had not been prepared in the cold, contamination by bacterial toxins occurred despite the fact that the product passed tests of sterility and pyrogenicity. Although Janeway¹⁷ also preferred the subcutaneous route, intramuscular administration of "immune serum globulin" became state-of-the-art for the years to come.

Immune serum globulin became standard treatment of patients with antibody deficiency syndromes (agammaglobulinemia and hypogammaglobulinemia) in the 1950s and was widely used with this indication for at least the next two decades.^{29–39} Its efficacy has been well documented. The products contained mainly IgG traces of IgM and differing amounts of IgA. Ig treatment substantially improved the prognosis of patients with agammaglobulinemia, hypogammaglobulinemia, and other forms of severe antibody deficiencies. The recommended dose was 25 mg/kg/wk. After the efficacy of IgG (for intramuscular use) had been clearly proven in primary immunodeficiencies in the early 1950s, the British Medical Research Council set up a working party to find the optimal dose for the treatment of patients with antibody deficiency⁴⁰ (hypogammaglobulinemia). Based on the results, a 50 mg/kg/wk dose was regarded as adequate, but it was felt that the previously accepted dose of 100 mg/kg/mo might be justified in view of the discomfort the injection caused and with regard to the high expense of treatment. In 1966, Janeway¹⁷ considered a raise in serum levels of 200 mg/dL necessary to prevent invasive bacterial infections and suggested 300 mg/kg as an initial dose to be followed by 100 mg/kg/mo.

Products of intramuscular Ig of different manufacturers were similar in composition and activity as long as the plasma of at least 1000 donors had been pooled. The spectrum and quality of antibodies were comparable to antibodies in the plasma of the starting material. Fc-mediated functions were preserved. Antibodies were enriched approximately 10- to 20-fold in the 15% to 18% solutions as compared with plasma. Transmission of viral diseases was a major concern because hepatitis B transmission did occur when the starting material was contaminated.^{41–44} If the single donations of plasma were free of hepatitis B surface antigen and if appropriate fractionation methodology was used, however, the final product was proven to be safe with respect to the transmission of hepatitis B. Serum Ig for intramuscular use also had great disadvantages. The intramuscular injection was painful, maximum serum levels were not reached before 24 hours and could take several days, and in vivo recovery was usually less than 50%.^{45,46} At higher dosages, the preservative containing mercury caused increased concern.^{47,48} These products could not be given intravenously because of adverse reactions. These reactions, mainly in children, caused chills and fever but also could be severe and lead to shock and even fatal reactions.⁴⁹ Adverse effects occurred in 15% to 25% or more of applications and were mainly attributed to aggregates in the product. Researchers soon recognized that reactions were more frequent

in agammaglobulinemic patients compared with patients with normal gammaglobulin serum levels, who received these products with the aim of preventing recurrent or severe infections.

Studies in patients with antibody deficiency demonstrated a reduction of acute and chronic infections by intravenous Ig (IVIg).^{50–52} Early studies in patients with common variable immunodeficiency showed a significant reduction in infection rate as compared with before IVIg treatment.⁵³ The superiority of IVIg to intramuscular Ig was proven by direct comparison.^{54,55} Ig products that could be applied intravenously were clearly desirable, and serum Ig had to be further treated to be tolerated via the IV route.

Different Intravenous Immunoglobulin Products

Several different methods have been tried to arrive at safe and efficacious preparations. Because aggregates were thought to be the main cause of adverse effects, proteolytic treatment was the first choice. Ample evidence from previous times when animal sera treated with pepsin or trypsin were used indicated that this treatment reduced reactivity. The first IVIg product from human plasma prepared by pepsin treatment, manufactured by Behringwerke in Germany, has been in clinical use since the 1960s. This product contains mainly Fab2 fragments, has no Fc-mediated activity, and has a half-life of 24 hours or less in the circulation. It was principally well tolerated, although it still has some adverse effects in immunodeficient patients. With its short half-life, however, it is clearly unsuitable for the treatment of patients with antibody-deficiency syndromes.

Other subsequently developed IVIg products that could be considered for treatment of patients with primary immunodeficiency diseases were chemically and enzymatically modified preparations. Several IVIgG preparations were created in which the Ig was basically unmodified. Different methods were used to arrive at products that were safe when given intravenously and showed wide variation with respect to functional integrity (**Table 1**).^{56–62}

In 1979, a workshop entitled “Ig: Characteristics and Uses of Intravenous Preparations” was organized by J.S. Finlayson and Barbara Alving and sponsored by the Bureau of Biologics, the US Food and Drug Administration, and the National Heart, Lung and Blood Institute. The purpose of the workshop was (according to the preface by the editors) to review the international use of IVIg preparations in the treatment of immunodeficient and immunosuppressed patients, explore potential clinical uses for such preparations, discuss the nature of adverse reactions to these products, and define, insofar as possible, the ideal characteristics of IVIg.⁶³ The specialties of the more than 200 attending investigators ranged from basic science to manufacturing to clinical medicine.

The consensus at the 1979 meeting was that IVIg products were indicated for the provision of antibodies to prevent certain infectious diseases and for the treatment of patients with antibody deficiency, primary immunodeficiencies with agammaglobulinemia and hypogammaglobulinemia, other forms of PID (eg, severe combined immunodeficiency, combined immunodeficiency), and secondary antibody deficiency.⁶⁴ At the meeting, individual clinical investigators reported their experience regarding treatment with the different enzymatically, chemically modified or intact Ig products. In most cases, the number of patients in the individual groups was between 10 and 20, and there was agreement that the IV route of Ig treatment was advantageous to intramuscular therapy.⁶⁵ The adverse reactions observed and reported by the different investigators were virtually identical and are described later in the article.^{49,66–98} The conclusion was that IVIg was a promising new option in the treatment of patients

Table 1 Intravenous immunoglobulin preparations		
Enzymatically treated		
Procedure	Manufacturer	Country
Pepsin	Behringwerke	Germany
	Nikon Seiyaku	Japan
	Kaketsuken	Japan
Plasmin	Hyland	USA
	Michigan	USA
	Green Cross	Japan
	Merieux	France
Chemically treated		
Procedure	Manufacturer	Country
β – propiolactone	Biotest	Germany
PH4 + treated pepsin	SRC, Sandoz	Switzerland
Reduced, alkylated	Cutter	USA
Unmodified		
Procedure	Manufacturer	Country
Si O ₂ QAE sephadex	Condie	USA
Ethanol DEAE sephadex stabilized with albumin	KABI	Switzerland
DEAE sephadex	Winnipeg	USA
PEG/HES	Armour	USA
PEG, Plasmin Treatment	Green Cross	Japan
Salting out, PEG, isoelectric precipitation	Immuno	Austria
Cohn II + III + PEG 4000	Continental	Canada
Ethanol, pH4	Scottish National Blood Transfusion Service	Great Britain

with humoral immunodeficiency: impaired antibody production. Adverse events often were seen, but they were manageable. The causes of those adverse events were not completely understood.

At the meeting in 1979, a single presentation from Japan⁶⁹ on 5406 cases of IVIg treatment for numerous diseases in the specialties of pediatrics, medicine, surgery, and neurosurgery with 82% effectiveness gave one of the early examples of an empiric approach indicating that there might be a much greater scope of treatment with IVIg than generally accepted at the time. Researchers soon realized that treatment with IgG, the only component of most IVIg products, is necessary and sufficient for the prevention of infection and the prophylaxis of acute exacerbations of lung disease (pneumonia) and sinusitis,^{50–52,70} even in patients in whom all isotypes of Ig were absent (the agammaglobulinemics). Researchers recognized that antibody quality, especially functions mediated by the Fc portion of the antibody, were important.

The question of antibody diversity was raised on several occasions before and a long time after this workshop in 1979. One of the questions raised was whether it was necessary to provide the starting material of individual products from the geographic area where the patients are.⁷¹ The current view, which is the result of a long-lasting debate, has been that as long as the number of donations is 15,000 to 60,000 per plasma pool for production, the antibody diversity in the product can

be considered adequate.⁷² Selective antibodies are tested lot-wise to show that anti-toxic, antiviral, and antibacterial qualities are preserved. Extended testing of current preparations proves that products have only traces of aggregates, contain 90% or more monomeric IgG, are free of vasoactive contaminants, and have proven Fab- and Fc-mediated antibody functions.^{66–68}

Fab and Fc Properties

The specific antibody activity, the function of antigen binding, resides in the Fab part of the Ig, and secondary functions of the Ig are carried by the Fc portion of the molecule. The Fc portion determines its isotype (eg, class and subclass). It interacts with receptors on phagocytic cells (eg, neutrophil granulocytes and macrophages) to facilitate engulfment of antibody-coated cells and pathogens. The Fc portion initiates activation of the complement cascade via the classic activation pathway by binding C1q (an early complement component). It is responsible for the active passage of Ig from mother to fetus through the placenta and determines the half-life of Ig in the circulation. The Fab and Fc regions of the Ig are connected by the hinge region of the molecule. The hinge region is flexible; its function is important for avidity, and it is the most sensitive portion of Ig with respect to chemical and enzyme treatment.

Specific antibody activities are crucial for antigen recognition. Fab fragments are sufficient for toxin neutralization. Antiviral activity depends on recognition through Fab but is much more potent by the intact antibody molecule. The elimination of bacteria requires the Fab and the Fc moiety of the Ig.

Immunomodulatory Activity

Early observations by Barandun in the 1960s noted that in a patient who had primary immunodeficiency disease and hemolytic anemia, signs and symptoms of hemolysis decreased and Coomb's test results normalized when treated with IVIg. Parallel to those observations, a child who had idiopathic thrombocytopenic purpura (ITP) and chicken pox was treated with IVIg, and platelet counts normalized. Subsequent to those observations, other patients with thrombocytopenia were successfully given IVIg.⁷³ Imbach and colleagues⁷⁴ followed up on these anecdotes and started clinical studies in children with acute and chronic ITP. The dose was 400 mg/kg for 5 days, and almost all patients showed a dramatic response with fast normalization of platelet counts.

After the report by Imbach⁷⁴ on the effect of IVIg in ITP, numerous studies confirmed these results,^{75–82} and other studies have been conducted to investigate the effect of IVIg in different organ-specific and systemic autoimmune diseases.^{83–95} These studies included—but were not limited to—investigations in the following areas: hematology (numerous), dermatology (eg, bullous pemphigoid), endocrinology (eg, thyroid disease, diabetes), and neurology (eg, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, intractable childhood epilepsy, myasthenia gravis). The effect of IVIg treatment in autoimmune diseases clearly depended on the Fc portion of the Ig. Although chemically modified IVIg with its Fc function mainly preserved was effective in ITP, pepsin-treated Ig, which contained only the Fab2 part of the Ig molecule, had only minimal effect.^{96,97}

Although the mechanism of action of IVIg in different autoimmune diseases was not clear, the following hypotheses have been suggested to explain the results observed:

1. Ig binds activated complement components, solubilizes immune complexes, and inhibits their binding to target cells. Basta and coworkers⁹⁸ protected guinea pigs by Ig in the complement-mediated Forssman shock and emphasized that the binding of activated complement components could be the crucial mechanism

- of the effect of IVIg in hematologic autoimmune diseases.^{99,100} This hypothesis became the basis of a later controlled study that demonstrated the effect of IVIg in dermatomyositis.^{101,102}
2. Another hypothesis centered around the inhibition of the binding of antibody-coated target cells to Fc receptors on phagocytic cells: Fc receptor blockade.^{75,103} Based on this hypothesis, an Ig product with anti RHO(D) specificity was later licensed for the treatment of ITP.^{104–106} An experimental study with an anti-Fc receptor monoclonal antibody proved the principle but has not been followed up as a routine mode of treatment.^{107,108}
 3. The immunomodulatory effect of IVIg was described and thought to be crucial in the down-modulation of the production of autoantibodies by B cells.¹⁰⁹ The importance of anti-idiotypic antibodies has been emphasized.¹¹⁰ Anti-idiotypic antibodies are present in IVIg and antibodies to $\alpha\beta$ T-cell receptors,¹¹¹ major histocompatibility complex class I,¹¹² CD45 (Fas),^{113,114} and other self-determinants¹¹⁵ and were thought to be the effective principle in the treatment of other autoimmune diseases (eg, myasthenia gravis, Guillain-Barré syndrome, systemic lupus erythematosus, nephritis).^{110,116} In addition to their specificities, anti-idiotypic antibodies are leading to Ig dimerization and the functional importance of the dimers in Fc receptor ligation, and signaling has been demonstrated.¹¹⁰
 4. Several studies indicated that IVIg has an immunomodulatory effect, not only on B cells but also on T cells. It down-modulates not only B-cell activation but also T- and B-cell interaction and is inhibitory in mixed lymphocyte reaction and mitogen and interleukin-2-induced proliferation of mononuclear cells.¹¹⁷ IVIg products were shown to contain antibodies against different cytokines, and these antibodies were thought to be important for the immunomodulatory effect.¹¹⁸ Based on the down-regulation of the immune response, IVIg has been studied in bone marrow and solid organ transplantation.^{119–123}

Modulation of Inflammation by Immunoglobulin

Certain pathophysiologic events (eg, Kawasaki disease, vasculitis) are characterized by systemic, excessive inflammation. Cells and mechanisms of the innate and adaptive immunity are operational in this process. Phagocytes, B cells, and T cells are central in mounting inflammatory host response to gram-negative and -positive bacteria and their products, such as lipopolysaccharide and superantigens.^{124–128} A deregulated release of inflammatory cytokines results in life-threatening pathology with fever and organ damage and may lead to shock and fatality. The release of inflammatory cytokines and their activity can be regulated at different levels: gene expression, translation, release, receptor expression, and neutralization of cytokine activity by antibody or soluble cytokine-binding inhibitors. IVIg has been shown to regulate the burst of inflammatory cytokines at the level of cytokine receptor interaction with antibodies against cytokines and the induction of receptor antagonists.^{118,129–133}

The effects of monomeric polymeric IgG and immune complexes on Fc receptors have been studied in several laboratories.^{75,134–136} Clinical evidence that IVIg treatment is safe and effective in a deregulated inflammatory disease has been provided by large, controlled clinical studies of children who have Kawasaki disease, which is a disease with prolonged fever, rash, erythema of palms and soles, and mucosal inflammation with involvement of the oral pharynx and conjunctiva.¹³⁷ The underlying pathology is characterized by vasculitis that involves medium and large arteries. Up to 25% of children who have this syndrome and received aspirin as the standard treatment developed coronary artery lesions with severe sequelae. High-dose IVIg (400 mg/kg on 5 consecutive days or 2 g/kg in one infusion) impressively stopped

the inflammatory symptoms and significantly reduced the prevalence of coronary artery abnormalities to less than 5% when given early in the disease.^{138,139} Clinical trials were double-blind, randomized controlled studies that compared the then-standard treatment of Kawasaki disease with aspirin to aspirin plus IVIg.

Expanding the Scope of Accepted Indications in 1990

The accepted modes of action of IgG, namely provision of antibodies,^{140–146} inhibition of Fc receptor binding (on phagocytes), down-modulation of inflammation, and down-modulation of antibody production^{147–149} (immune response), were the basis of the consensus in 1990.¹⁴⁰ According to the consensus of 1990, IVIg was indicated for the prevention and treatment of the following disorders:

- Primary immunodeficiencies
- Pediatric aids
- Bone marrow transplantation
- Chronic lymphocytic leukemia with hypogammaglobulinemia
- Idiopathic thrombocytopenic purpura
- Kawasaki syndrome
- Chronic inflammatory demyelinating polyneuropathies
- Guillain-Barré syndrome

Although a trial to prevent infections in premature infants was one of the first randomized trials with intramuscular Ig,¹⁵⁰ the question whether treatment with Ig is beneficial in this vulnerable group of patients is still undecided.

At the 1990 consensus meeting, large clinical trials to answer the question of efficacy of Ig in premature infants and neonates were thought to be important. A large multicenter controlled trial¹⁵¹ could not provide clear results for efficacy, and smaller clinical studies later came to similar conclusions.^{152,153}

Adverse events observed in the course of high-dose treatment were of increasing concern, as was the transmission of blood-borne pathogens at that time because of the theoretic threat of possible HIV transmission by IVIg, which fortunately did not happen. Transmission of blood-borne pathogens did occur, however, in the 1990s, when hepatitis C was transmitted in clinical trials and with treatment with IVIg of patients who had PID (see the later section on adverse events). The recently developed test kits based on hepatitis C antigen produced by a recombinant technology opened the way to eliminating donations from hepatitis C antibody–positive plasma donors. Industry, in cooperation with the health authorities, reacted in a fast and proper way. By the end of the decade, all licensed products could be considered free of contaminating viral agents.

In the 1990s, off-label use of IVIg started to widen for numerous autoimmune and inflammatory indications in the treatment of neurologic diseases.^{154–156} The dose was usually 2 g/kg either in five applications of 400 mg/kg each or in two applications of 1 g/kg each. In the course of expanding high-dose treatment, rare but severe adverse events were noticed, and it became evident that although rare, they might occur in patients who had PID and were on regular replacement therapy.

Although during the course of almost two decades [1990–2008] changes in labeled indications for IVIg treatment were minimal, more diseases have been treated off-label.

CONSENSUS STATEMENTS, 1999–2001 (EXPERT MEETINGS, NATIONAL INSTITUTES OF HEALTH, FOOD AND DRUG ADMINISTRATION, AND PUBLISHED REPORTS)

The results started to come in from studies initiated to analyze the effect of IVIg in the different areas of autoimmune disease.^{157,158} Studies of IVIg treatment in 53 different

diseases from the areas of hematology, infectious disease, neurology, obstetrics, rheumatology, endocrinology,^{92–94} and other specialties were investigated. The first studies, even when based on meta-analysis of several clinical trials, were not large enough to give clear support for additional indications, even when the results did look promising. These studies opened the way for further trials, which, almost a decade later, arrived at several indications supported by grade I evidence. Based on these results, IVIg became a generally accepted standard way of treatment by the end of the twentieth century in numerous neurologic diseases such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. By 2003–2004, approximately 60% to 65% of IVIg had already been used for patients with neurologic disease.^{72,159}

In 2006, a document was prepared by a committee of the American Academy of Allergy, Asthma and Immunology on the use of IVIg in human disease.⁷² This consensus gave a factual review of labeled indications “as licensed by the FDA” and off-label indications based on (practically all) publications available. A summary of FDA-approved indications for licensed products follows:¹⁶⁰

PID or primary humoral immunodeficiency
 B-cell chronic lymphocytic leukemia (hypogammaglobulinemia)
 HIV infection (pediatric)
 Kawasaki disease
 Idiopathic thrombocytopenia
 Bone marrow transplantation

Off-label indications increased significantly at that point. More than 80% of the IVIg is used off-label, supported by definitely beneficial and probably beneficial indications based on category Ia–IIb evidence. From the 2006 consensus about the use of IVIg in human diseases, the main off-label uses based on category Ia–IIb evidence are summarized in **Table 2**.⁷²

The concerns and risks center around adverse events (mainly the rare and serious), or around supply and economic considerations. The concern regarding the

Definitely Beneficial	Grade	Probably Beneficial	Grade
Grave's ophthalmopathy	Ib	Dermatomyositis and polymyositis	IIa
ITP	Ia	Autoimmune uveitis	IIa
Guillain-Barré syndrome	Ia	Lambert-Eaton myasthenic syndrome	Ib
Chronic demyelinating polyneuropathy	Ia	IGM antimyelin paraprotein associated neuropathy	Ib
Multifocal motor neuropathy	Ia	Myasthenia gravis	Ib–IIa
—	—	Stiff-man syndrome	Ib
—	—	Neonatal sepsis	Ia
—	—	Rotaviral enterocolitis	Ib
—	—	Toxic epidermal necrolysis and Stevens Johnson's syndrome	IIa

These and additional IVIg products are available in Europe.

Data from Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525–53.

transmission of blood-borne pathogens still exists as a theoretic scenario without any practical relevance.

Dosage

Numerous publications have dealt with the question of optimal dose as replacement for patients with primary immunodeficiency disease.^{72,161–169} After a loading dose, 400 mg/kg/mo is the generally accepted standard treatment. Diminished pulmonary function is the major cause of morbidity and mortality in patients with antibody deficiency syndrome, and it is clear that early diagnosis and prompt initiation of IVIg treatment significantly reduce these complications. Two large studies analyzed the question of dose in patients in whom IVIg treatment was started when impairment of pulmonary function was already present. In the trial by Roifman and colleagues,¹⁶⁷ doses of 200 mg/kg/mo and 600 mg/kg/mo were compared in a cross-over study. This study and the trials conducted by Bernatowska and colleagues,¹⁷⁰ proved that in patients on high-dose treatment, pulmonary function improved. This improvement did not take place at the lower dose level, which could be attributed to the additional anti-inflammatory effect of IVIg, which requires treatment at higher dose.

The determination of whether standard doses (eg, 400 mg/kg/mo) are preferable or whether trough levels should guide IVIg treatment is still undecided. A previous study demonstrated that trough IgG levels of 500 mg/dL in patients were beneficial,^{52,167,171} and a recent study indicated that the rate of infection can be further reduced with a trough level of 900 mg/dL.¹⁷² This finding might be important for long-term prognosis.¹⁶⁸ Certain conditions in patients who have PID must be treated with a higher dose. Patients with impairment of pulmonary function at presentation might need a total of 600 mg/kg/mo in one or two doses, and a few patients with chronic echo virus, meningoencephalitis, a previously fatal disease, may improve and then be maintained on 1 g/kg per dose, which has to be given repeatedly.^{173–176}

Doses of IVIg required for immunomodulation are much higher. Up to 2 g/kg are recommended and may have to be repeated.¹³⁸ This usually applies to clinical situations in which IVIg is given for true immunomodulation and for the treatment of systemic inflammatory conditions (eg, Kawasaki disease).

ADVERSE EVENTS

Inflammatory Reactions

Reactions during the course of, or immediately after, Ig treatment already were observed when Ig was given intramuscularly and have continued to be of concern with IVIg therapy. These reactions were anaphylactoid in nature.^{177–183} The following list details adverse reactions to IVIg:

- Fever
- Chest tightness
- Chills
- Dyspnea
- Facial flush
- Wheezing
- Tachycardia
- Urticaria
- Palpitation
- Rash
- Lowering of blood pressure
- Anxiety

Shock
Nervousness
Lumbar pain
Headache
Abdominal pain
Nausea
Vomiting

Several investigators gave prophylactic steroids, antihistamines, or anti-inflammatory agents to avoid reactions or reduce severity.^{178,184} In many cases, adverse reactions could be avoided just by lowering the rate of infusion. The fact that patients with the most pronounced impairment of antibody production had the highest likelihood of adverse reaction made a true anaphylactic reaction most unlikely.¹⁷⁷ The question of whether these reactions were caused by formation of immune complexes^{100,180,181} to anticomplementary activity or some other properties of aggregates was a subject of discussion.^{185,186} The fact that patients with severe adverse reactions often did not show a drop in complement levels in serum and changes in serum complement levels were not associated with adverse events indicated that other properties of Ig aggregates in addition to complement activation may be operational. IgG aggregates in IVIg products may trigger the release of pharmacologically active mediators by ligation of Fc receptors from macrophages and leucocytes.^{187–189} Substances such as prostaglandins, platelet-activating factor, and cytokines (eg, tumor necrosis factor- α , interleukin-6) have been described to cause reactions such as fever, bronchospasm, and changes in blood pressure, which are characteristic adverse events of IVIg treatment. Another possibility for the release of mediators is that in patients with infections, the antibodies infused react with circulating microbial antigens to form immune complexes, which again trigger the release of the respective mediators. Vasoactive contaminants (eg, enzymes such as prekallikrein activator) that were present in earlier products could have contributed to reactions through the generation of bradykinin.^{190,191}

The question of whether the frequency and severity of anaphylactoid reactions could be related to some extent to individual products, their mode of production, and their preparation is still pending. To give definite answers, controlled trials specifically designed for comparison of different products are needed, because results of such trials are scarce.¹⁷²

Because IVIg was infused in large quantities, it was essential that it be free of isoagglutinins and nonagglutinating antibodies against red cells. Hemolytic reactions have been described in rare instances.

Transmission of Infectious Agents

Fortunately, because of HIV partitioning during plasma fractionation, Ig products did not transmit HIV at any time, even in the early 1980s, when the infectious agent was as yet unknown and testing for antibodies or the virus was not possible. Hepatitis C virus transmission did occur, however, with different IVIg products in the late 1980s to mid-1990s.¹⁹² In most of the products involved, ion exchange chromatography was used in purification, but one of the products was prepared by the pH4 pepsin treatment.¹⁹³

Soon after cases of viral contamination were reported, additional steps and controls in the course of IVIg manufacturing were implemented. The industry responded with donor screening, donor testing, inventory management, plasma pooling, and testing. Quality control measures of viral partitioning during fractionation were introduced, and

additional viral inactivation steps were performed. Licensed products currently are considered safe with respect to transmission of viral agents, especially HIV and hepatitis viruses.¹⁹⁴ Unknown agents are only of theoretic risk.

Thromboembolic Events

With broad application of IVIg, especially high-dose therapy, previously rare complications have been observed and described more frequently.¹⁹⁵ Most of the patients in whom thromboembolic events occurred in the course of mainly high-dose IVIg treatment were patients with neurologic diseases or polymorbid patients. Numerous medical conditions have been recognized as risk factors (eg, hypertension, cardiovascular disease, diabetes, kidney disease).^{196–198} Thromboembolic complications also were observed in a few patients with primary immunodeficiency who had been treated with a regular dose. Because antibody deficiency syndromes have moved from the pediatric to the adult population and treatment with IVIg of elderly patients who have PID is not a rarity anymore, underlying morbidity (pulmonary, cardiac, renal) must be taken into consideration in IVIg treatment of patients who have PID.

The mechanisms of action for thromboembolic complications are not well understood. Dalakas suggested that increased serum viscosity plays a crucial role.¹⁹⁷ Antiphospholipid antibodies in IVIg also were mentioned as of possible importance. Wolberg and colleagues detected coagulation factor XI as a contaminant in IVIg products and showed that IVIg samples that contained factor XI shortened clotting time in factor XI-deficient plasma.^{183,199}

Rapid infusions, which have been suggested because of the inconvenience of the regular lengthy infusion time for patients who had to receive large amounts of IVIg, seemed to be more prone to causing thromboembolic complications. The rate of adverse events after rapid infusion was higher than reported in usual standard rates of application. Some reports still favor rapid infusion, mainly because of lower cost.^{200,201}

Renal Complications

Renal complications in the course of IVIg treatment have been described since the mid-1980s. Usually, but not exclusively, they occur with high-dose treatment. These reactions, although infrequent, resulted in severe morbidity; more than one third of the patients required dialysis, and fatalities have been reported.^{198,202,203} The mechanisms explaining these adverse effects included sucrose or maltose in the product, because renal lesions caused by sucrose have been known since the 1940s. Risk factors were similar to those observed in thromboembolic disease, especially old age (> 60), diabetes, and prior renal disease.^{204,205}

ADVERSE EVENTS CAUSED BY IMMUNOGLOBULIN A

Severe (transfusion) reactions have been described in patients with gastrointestinal disease who were IgA deficient. After these observations, reactions to IVIg—usually anaphylactoid—were contributed to IgA²⁰⁶ in the product and IgA antibodies in the patient.^{207–209} In two patients, true anaphylactic reactions were reported; they had IgE antibodies against IgA.²¹⁰ During the decades of discussion about anaphylactic/anaphylactoid reactions to IgA, cases in which IgE antibodies could be identified as the reason for the reaction have been rare. Most patients with anaphylactoid reactions to IVIg are unable to produce antibodies of any class or specificity, and numerous patients who had IgA antibodies did not show reaction to IVIg products containing IgA.

CURRENT STATUS AND ONGOING DEVELOPMENTS

IVIg treatment is the most commonly applied mode of Ig replacement therapy for patients with antibody deficiency syndromes and the only mode of Ig treatment for all other indications. Intravenous immunoglobulin products available in the United States can be seen in [Table 3](#).

Home treatment with immunoglobulin for subcutaneous application

Already at the beginning of Ig treatment in the early 1950s, Janeway preferred the subcutaneous application of Ig. In 1979, Berger and colleagues described Ig replacement therapy by slow subcutaneous infusion using small, battery-operated pumps and found that the “subcutaneous infusions were tolerated remarkably well with minimal local reaction and no evidence of adverse systemic effects.” Later, subcutaneously applicable Ig preparations without mercury-containing preservatives were made available for clinical studies. During these trials, it became evident that Ig given subcutaneously is well tolerated.^{211,212} The most common side effects are local reactions lasting 12 to 24 hours after infusion. Systemic reactions seem to occur less frequently. The dose is usually 100 mg/kg/wk but might be modified slightly according to the situation of the patient. Several papers reported that this way of treatment also makes IgA-deficient individuals tolerant to IgA, so they do not show anaphylactoid reactions even if treated intravenously afterwards.²⁰⁸ Several licensed products for subcutaneous application are available in the United States and Europe. This mode of Ig replacement opens the way for home treatment. Some patients have a clear preference for IV therapy once or twice a month, whereas others prefer the subcutaneous way of treatment. These latter patients can choose the time at their own convenience and regard the independence gained by this procedure as a major improvement in their quality of life.

Monoclonal antibodies

In the mid-1970s, the epoch-making discovery by Jerne, Köhler, and Milstein (Nobel Prize for Medicine or Physiology, 1984) opened the way for the production of

Table 3 IVIg products currently available in the United States		
Manufacturer	Name of Product	Indications
Talecris Gamunex2	Immune globulin intravenous (human), 10% caprylate/chromatography purified	PID; ITP
Baxter	Gammagard liquid immune globulin intravenous (human) 10%(KIOVIG)	PID associated with defects in humoral immunity
Baxter	Gammagard/S/D immune globulin intravenous (human)	PID, ITP, CLL, Kawasaki syndrome
ZLB Behring	Carimune NF nanofiltered immune globulin intravenous (human)	Immunodeficiency, ITP
Grifols	Flebogamma 5% immune globulin intravenous (human)	PID
Octapharma	Octagam immune globulin intravenous (human) 5%	PID

Data from Sorensen R. Expert opinion regarding clinical and other outcome considerations in the formulary review of immune globulin. *J Manag Care Pharm* 2007;13(3):278–83.

monoclonal antibodies in virtually unlimited quantities. The hope that these antibodies would be used extensively in the prevention and treatment of infectious disease was widely expressed. Over several decades we learned that monoclonal antibodies with a single specificity recognizing a single epitope on the target antigen cannot substitute for polyclonal antibodies in prophylaxis and treatment of infectious disease. The task of humanization to arrive at products that are not recognized as antigens in the recipient became challenging. Monoclonal antibodies are widely used in the treatment of cancer and thromboembolic disease; however, their use in infectious disease is limited and they still have no place in Ig replacement therapy for antibody-deficient patients.

Increasing understanding in the expression of Fc receptors, ligand binding, and signaling led to new hypotheses to explain the numerous immunomodulating properties of IVIg.^{213,214} Most hematopoietic cells, including phagocytes, express high-affinity Fc receptors that transduce positive signals and low affinity Fc receptors, which down-modulate cell activation to keep the balance. B cells only express the inhibitory Fc receptor. This FcR has been shown to regulate positive signals coming from the B-cell antigen receptor, which could explain the true immunosuppressive effect observed in the clinic where IVIg had a long-term effect in patients with autoimmune diseases because of autoantibodies. One is tempted to speculate that this could have been the mechanism in one of the first observations by Barandun³⁰ while treating a patient who had antibody deficiency and hemolytic anemia. The patient turned Coombs-negative during Ig treatment.

Recently, Ravetch provided experimental evidence that the suppression of inflammation is mediated by sialylation of a defined position in the Ig structure.^{215–217} He suggested that a product containing the Fc part of the IgG with the proper sialylation might be 30-fold more effective than an IVIg product and could be produced by recombinant technology. Limited experimental evidence indicates that such a preparation could be developed into a clinical product, but history teaches that the time course of developments in this area from the first experimental evidence to successful treatment might span decades. The following list details the chronologic events leading up to the currently available treatment.

1890

Serum of rabbits immunized with tetanus toxin protected normal animals against tetanus

1901

Von Behring won the first Nobel Prize in Physiology or Medicine “for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths”

1890–1910

Curative (animal sera) prepared and applied against diseases caused by toxins, bacterial disease, allergic disease and cancer

1907

Convalescent sera in the prevention of measles

1910–1930

Human (convalescent) sera preferred to animal sera in prevention and treatment
Initiation of pepsin treatment of animal sera for reduced reactogenicity

1933–1938

Prevention of measles with gammaglobulin (placenta)

1940

Cold ethanol fractionation

- 1949 until vaccination
 - Prevention and treatment of poliomyelitis, measles, mumps, pertussis, and hepatitis A by Ig
- 1952
 - Treatment of PID with Ig
- 1960
 - Pepsin-treated IVIg
- 1970
 - Other chemically, enzymatically modified and unmodified (treated) IVIg products
- 1979
 - Consensus meeting on IVIg indicated for procurement of antibodies
 - IVIg has to be safe with unimpaired function
- 1984
 - César Milstein, with Georges Köhler and Niels K. Jerne, received the Nobel Prize for Physiology or Medicine for “theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies”
- 1990
 - Consensus meeting on IVIg indicated for the provision of antibodies and immunomodulation.
 - Interference with Fc receptor binding (targets of autoantibodies) ITP
 - Anti-inflammatory effect: Kawasaki disease
 - Immunosuppression
 - Guillain-Barré syndrome
 - Chronic inflammatory demyelinating polyneuropathy
- 1995–2001
 - Consensus meeting
 - Basically identical indications to 1990
 - Extensive off-label use
- Present
 - FDA licensed indications
 - Basically similar to Consensus 1995–2001
 - Numerous further indications for off-label use based on clinical studies with clear (CL1-2) evidence

SUMMARY

Soon after the first report by von Behring on toxin neutralization by serum proteins, clinical scientists took the opportunity to apply this principle to a wide range of infectious diseases. After important discoveries in the field of biochemistry, it became clear that antibodies are in the gammaglobulin fraction of serum, that serum can be fractionated to obtain gammaglobulins, and that some patients' serum lacks gammaglobulins. The principle: the provision of antibodies with Ig for intramuscular use and later IVIg to prevent and treat infection, especially in patients with agammaglobulinemia (ie, antibody deficiency, PID), was the governing principle for IVIg use until the 1980s, as can be seen in the consensus of 1979. The possibility of modulation of inflammation, immunomodulation, and immunosuppression with Ig first emerged in the early 1960s and has expanded since the 1980s. The consensus of 1990 demonstrated examples of clinical use based on immunomodulation. In the last 20 years, the off-label use of Ig exploded mainly for inflammatory and hematologic, neurologic, medical, and dermatologic autoimmune diseases, often based on solid clinical

evidence. The dose is generally 400 mg/kg/mo for the provision of antibodies, up to 2 g in single or multiple doses for immunomodulation.

Concerns regarding adverse effects changed during the decades of experience. The early problems of inflammatory reactions are manageable; viral transmission has been eliminated by prompt and effective action. Serious adverse events, such as thromboembolic and renal complications, are rare; however, when they appear, especially in polymorbid patients, they are worrisome. Old and new practical developments move toward home treatment for patients who prefer this mode of therapy. The question of shortage of Ig in the course of extended use and high costs urge us to critically assess available evidence for application of this precious material in treatment. New scientific developments help us to understand the immunomodulatory function of Ig on the cellular and molecular level and may open the way for a different Ig product for immunomodulation. More than 100 years after initiation of antibody treatment and more than 50 years after treatment of patients with PID became state-of-the-art, the provision of antibodies/treatment with Ig (IV or subcutaneous) to patients who have PID remains the life-saving, classic, and first indication for IVIg, and all Ig products currently available are licensed for it.

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REFERENCES

1. von Behring EA, Kitasato S. Über das zustandekommen der diphtherie-immunität und der tetanus-immunität bei tieren. *Dtsch Med Wochenschr* 1890;16: 1113–4.
2. Ehrlich P. Experimentelle untersuchungen über immunität. I. Über Ricin. II. Über Abrin. *Dtsch Med Wochenschr* 1891;17:976–9, 1218–9.
3. Wolff-Eisner A. Handbuch der serumtherapie und experimentellen therapie: ein handbuch für klinik und praxis. München: J.F. Lehmanns Verlag; 1910.
4. Verhandlungen der Berliner Medizinischen Gesellschaft 1894.
5. Calmette A. Die gifte, die gifttiere und die serumtherapie gegen die tierischen gifte. Paris: Masson; 1907.
6. Flexner S. Experimental cerebro-spinal meningitis in monkeys. *J Exp Med* 1907;9: 142–67.
7. Flexner S. Concerning a serum therapy for experimental infections with *Diplococcus intracellularis*. *J Exp Med* 1907;9:168–85.
8. Eibl MM, Wedgwood RJ. Intravenous immunoglobulin: a review. *Immunodef Rev* 1989;1(Suppl):1–42.
9. Cenci F. Alcune esperienze di sieroimmunizzazione e sieroterapie nel norbillo. *Rivista di Clinica e Pediatria* 1907;5:1017–25.
10. McKhann CF, Chu FT. Use of placental extract in prevention and modification of measles. *Am J Dis Child* 1933;45:475–9.
11. Gibson RB. The concentration of antitoxin for therapeutic use. *J Biol Chem* 1906; 1:161–70.
12. Karelitz S. Prophylaxis against measles with the globulin fraction of immune adult serum. *Am J Dis Child* 1938;55:768–75.
13. Tiselius A, Kabat EA. Electrophoresis of immune serum. *Science* 1938;87:416–7.
14. Cohn EJ. Blood proteins and their therapeutic value. *Science* 1945;101:51–6.

15. Cohn EJ, Luetscher JA Jr, Oncley JL, et al. Preparation and properties of serum and plasma proteins. *J Am Chem Soc* 1940;62:3396–400.
16. Cohn EJ. The history of plasma fractionation. In: Merler E, editor. *Advances in military medicine*, vol. 1. Boston: Little, Brown and Company; 1948. p. 364–443.
17. Janeway CA. The development of clinical uses of immunoglobulins: a review. In: *Immunoglobulins*. Washington, DC: National Academy of Science; 1970. p. 3–14.
18. Stokes J, Maris EP, Gellis SS. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XI. The use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prophylaxis and treatment of measles. *J Clin Invest* 1944;23:531–40.
19. Stokes J, Neefe JR. The prevention and attenuation of infectious hepatitis by gamma globulin. *JAMA* 1945;127:144–5.
20. Nation NS, Pierce NF, Adler SJ, et al. Tetanus; the use of human hyperimmune globulin in treatment. *Calif Med* 1963;98:305–7.
21. Pollack W, Gorman JG, Freda VJ, et al. Results of clinical trials of RhoGAM in women. *Transfusion* 1968;8(3):151–3.
22. Zuckermann AJ. Prophylaxis of hepatitis type B: immunoglobulins and vaccines. *Clin Gastroenterol* 1980;9(1):65–83.
23. Goebel U, Schwamborn D, Moeller B, et al. Intravenous hyperimmunoglobulin to prevent varicella-zoster infection. *Pediatr Infect Dis* 1987;6(23):224.
24. Welliver RC. Respiratory syncytial virus immunoglobulin and monoclonal antibodies in the prevention and treatment of respiratory syncytial virus infection. *Semin Perinatol* 1998;22(1):87–95.
25. Storch GA. Humanized monoclonal antibody for prevention of respiratory syncytial virus infection. *Pediatrics* 1998;102:648–51.
26. Centers for Diseases Control and Prevention (CDC). Recommendations of the Immunization Practices Advisory Committee (ACIP) Varicella-Zoster Immune Globulin for the prevention of chickenpox. *Morbidity and Mortality Weekly Report (MMWR)* 1984;33(7):84–90, 95–100.
27. Bruton OC. Agammaglobulinemia. *Pediatrics* 1952;9:722–7.
28. Good RA, Varco RL. A clinical and experimental study of agammaglobulinemia. *Lancet* 1955;75(6):245–71.
29. Gitlin D, Janeway DC. Agammaglobulinemia: congenital, acquired and transient forms. *Prog Hematol* 1956;1:318–29.
30. Barandun S. Die gammaglobulin-therapie: chemische, immunologische und klinische grundlagen. *Bibl Haematol* 1964;17:1–138.
31. Stiehm ER. Immunodeficiency disorders: general considerations. In: Stiehm ER, Fulginiti VA, editors. *Immunologic disorders in infants and children*. Philadelphia: WB Saunders; 1973. p. 145–67.
32. Hitzig WH, Muntener U. Conventional immunoglobulin therapy. In: Gerdsmas D, editor. *Immunodeficiency in man and animals*. Sunderland (MA): Sinauer Associates; 1975. p. 339–42.
33. Domz CA, Dickson DR. The agammaglobulinemics: relation and implications. *Am J Med* 1957;23:917–27.
34. Janeway CA, Rosen FS. The gamma globulins. IV. Therapeutic uses of gamma globulin. *N Engl J Med* 1966;275:826–31.
35. Report of a WHO Scientific Group. The use of human immunoglobulin. *Technical Report Series* 1966;327.
36. Fudenberg HH, Good RA, Goodman HC, et al. Primary immunodeficiencies: report of a World Health Organization committee. *Pediatrics* 1971;47:927–46.

37. Cooper MD, Faulk WP, Fudenberg HH, et al. Classification of primary immunodeficiencies. *N Engl J Med* 1973;288:966–7.
38. Report of a WHO Scientific Group. Immunodeficiency: technical report series. Document no. 630. Geneva (Switzerland): World Health Organization; 1978. p. 3–80.
39. Abernathy RS, Strem EL, Good KA. Chronic asthma in childhood: double-blind controlled study of treatment with gamma-globulin. *Pediatrics* 1958;21(6): 980–93.
40. MRC Working Party on Hypogammaglobulinaemia. Hypogammaglobulinaemia in the United Kingdom. London: Her Majesty's Stationery Office; 1971.
41. Tabor E, Gerety RJ. Transmission of hepatitis B by immuno serum globulin. *Lancet* 1979;2(8155):1293.
42. John TJ, Ninan GT, Rajagopalan HS, et al. Epidemic hepatitis B caused by commercial human immunoglobulin. *Lancet* 1979;1(8125):1074.
43. da Silva LC, Sette H, Antonacio F, et al. Commercial gammaglobulin (CGG) as a possible vehicle of transmission of HbsAG in familial clustering. *Rev Inst Med Trop Sao Paulo* 1977;19:352–4.
44. Petrilli FL, Crovari P, De Flora S. Hepatitis B in subjects treated with a drug containing immunoglobulins. *J Infect Dis* 1977;135:252–8.
45. Morell A, Schnoz M, Barandun S. Build-up and maintenance of IgG serum concentrations with intravenous immunoglobulin in patients with primary humoral immunodeficiency. *Vox Sang* 1982;43:212–9.
46. Smith GN, Griffiths B, Mollison D, et al. Uptake of IgG after intramuscular and subcutaneous injection. *Lancet* 1972;1(7762):1208–12.
47. Haeney MR, Carter GF, Yeoman WB, et al. Long-term parenteral exposure to mercury in patients with hypogammaglobulinemia. *BMJ* 1979;2:12–4.
48. Matheson DS, Clarkson TW, Gelfand EW. Mercury toxicity (acrodynia) induced by long-term injection of gammaglobulin. *J Pediatr* 1980;97:153–5.
49. Barandun S, Kistler P, Jeunet F, et al. Intravenous administration of human gammaglobulin. *Vox Sang* 1962;7:157–74.
50. Ammann AJ, Ashman RF, Buckley RH, et al. Use of intravenous gamma-globulin in antibody immunodeficiency: results of a multicenter controlled trial. *Clin Immunol Immunopathol* 1982;22:60–7.
51. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine (Baltimore)* 1985;64:145–56.
52. Quartier P, Debre M, De Blic J, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;134:589–96.
53. Cunningham-Rundles C, Siegal FP, Smithwick EM, et al. Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. *Ann Intern Med* 1984;101:435–9.
54. Nolte MT, Pirofsky B, Gerritz GA, et al. Intravenous immunoglobulin therapy for antibody deficiency. *Clin Exp Immunol* 1979;36:237–43.
55. Roifman CM, Lederman HM, Lavi S, et al. Benefit of intravenous IgG replacement in hypogammaglobulinemic patients with chronic sinopulmonary disease. *Am J Med* 1985;79:171–4.
56. Skvaril F, Probst M, Steinbuch A, et al. Distribution of IgG subclasses in commercial and some experimental γ -globulin preparations. *Vox Sang* 1977; 32:335–8.
57. Römer J, Morgenthaler JJ, Scherz R, et al. Characterization of various immunoglobulin preparations for intravenous application. I. Protein composition and antibody content. *Vox Sang* 1982;42:62–73.

58. Morell A, Schürch B, Ryser D, et al. In vivo behaviour of gamma globulin preparations. *Vox Sang* 1980;38:272–83.
59. Ochs HD. Intravenous immunoglobulin therapy of patients with primary immunodeficiency syndromes: efficacy and safety of a new immune globulin preparation. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 9–14.
60. Pirofsky B, Anderson CJ, Bardana EJ. Therapeutic and detrimental effects of intravenous immunoglobulin therapy. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 15–22.
61. Barandun S, Morell A, Skvaril F. Clinical experiences with immunoglobulin for intravenous use. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 31–5.
62. Mondorf AW, Duswald KH. Intravenous immunoglobulin in high-risk patients: efficacy and tolerance of long-term administration. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 37–40.
63. Alving BM, Finlayson JS. Preface. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 9–14.
64. Overview of potential uses for immunoglobulin preparations, possible etiologies of adverse reactions and ideal characteristics of intravenous preparations. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*, proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 229–33.
65. Eibl M. Treatment of defects of humoral immunity. *Birth Defects Orig Artic Ser* 1983;19(3):193–200.
66. Kjellman H. Adverse reactions to human immune serum globulin in Sweden (1969–1978). In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 143–50.
67. Hanson LA, Björkander J, Ljunggren C, et al. Problems with use of immunoglobulins in treatment of immunodeficiency patients. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 150–9.
68. Cassidy JT, Stein LD, Reynolds RT. Intravenous immune globulin: five-year clinical experience with efficacy and adverse reactions in immunodeficiency. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 161–6.

69. Funakoshi S, Suyama T, Naito R. Use of Intravenous immunoglobulin in Japan. In: Alving BM, Finlayson JS, editors. Immunglobulins: characteristics and uses of intravenous preparations. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 219–25.
70. 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(6):1001–4.
71. Brunko P. Community requirements relating to drugs derived from human blood and plasma. *Ann Pharm Fr* 1994;52(2):89–98.
72. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525–53.
73. Barandun S, Isliker H. Development of immunoglobulin preparations for intravenous use. *Vox Sang* 1986;51:157–60.
74. Imbach P, d'Apuzzo V, Hirt A. High-dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1(8232):1228–31.
75. Fehr J, Hofmann V, Kappeler U. Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med* 1982;306:1254–8.
76. Mori PG, Mancuso G, del Principe D, et al. Chronic idiopathic thrombocytopenia treated with immunoglobulin. *Arch Dis Child* 1983;58:851–5.
77. Carroll RR, Noyes WD, Rosse WH, et al. Intravenous immunoglobulin administration in the treatment of severe chronic immune thrombocytopenic purpura. *Am J Med* 1984;76(Suppl 3a):181–6.
78. Warrier I, Lusher JM. Intravenous gammaglobulin treatment for chronic idiopathic thrombocytopenic purpura in children. *Am J Med* 1984;76:193–8.
79. Warrier LA, Lusher JM. Intravenous gammaglobulin (Gamimune) for treatment of chronic idiopathic thrombocytopenic purpura (ITP): a two-year follow-up. *Am J Hematol* 1986;23:323–8.
80. Bussel J. Intravenous immune serum globulin in immune thrombocytopenia: clinical results and biochemical evaluation. *Vox Sang* 1985;49(Suppl 1):44–50.
81. Vos JJ, van Aken WG, Engelfriet CP, et al. Intravenous gammaglobulin therapy in idiopathic thrombocytopenic purpura. *Vox Sang* 1985;49:92–100.
82. Abe T, Matsuda J, Kawasugi K, et al. Clinical effect of intravenous immunoglobulin on chronic idiopathic thrombocytopenic purpura. *Blut* 1983;47(2):69–75.
83. Becton DL, Kinney TR, Chaffee S, et al. High-dose intravenous immunoglobulin for severe platelet alloimmunization. *Pediatrics* 1984;74:1120–3.
84. Hanada T, Saito K, Nagasawa T, et al. Intravenous gammaglobulin therapy for thrombocytopenic neonates of mothers with systemic lupus erythematosus. *Eur J Haematol* 1987;38:400–4.
85. Derycke M, Dreyfus M, Ropert JC, et al. Intravenous immunoglobulin for neonatal isoimmune thrombocytopenia. *Arch Dis Child* 1985;60:667–9.
86. Berlin G, Selbing A, Ryden G. Rhesus haemolytic disease treated with high-dose intravenous immunoglobulin. [letter]. *Lancet* 1985;1(8438):1153.
87. Drachman DB, Adams RN, Josifek LF, et al. Functional activities of autoantibodies to acetylcholine receptors and the clinical severity of myasthenia gravis. *N Engl J Med* 1982;307:769–75.

88. Morel E, Eymard B, Vernet-der-Garabedian B, et al. Neonatal myasthenia gravis: a new clinical and immunologic appraisal on 30 cases. *Neurology* 1988;38:138–42.
89. Ruhr G, Kusterer K, Schille M, et al. Treatment of Crohn's disease and ulcerative colitis with 7S-immunoglobulin. [letter]. *Lancet* 1987;1:170.
90. Pococco M, de Campo C, Cantoni L, et al. Effect high dose intravenous IgG in newly diagnosed diabetic children. *Helv Paediatr Acta* 1987;42:289–95.
91. Silverstein J, Maclaren N, Riley W, et al. Immunosuppression with azathioprine and prednisone in recent-onset-dependent diabetes mellitus. *N Engl J Med* 1988;319:599–604.
92. Antonelli A, Navarranne A, Palla R, et al. Pretibial myxedema and high-dose intravenous immunoglobulin treatment. *Thyroid* 1994;4(4):399–408.
93. Baschieri L, Antonelli A, Nardi S, et al. Intravenous immunoglobulin versus corticosteroid in treatment of Gráves ophthalmopathy. *Thyroid* 1997;7(4):579–85.
94. Kahaly G, Pitz S, Müller-Forell W, et al. Randomized trial of intravenous immunoglobulin versus prednisolone in Gráves ophthalmopathy. *Clin Exp Immunol* 1996;106(2):197–202.
95. Czernik A, Bystryń JC. Improvement of intravenous immunoglobulin therapy for bullous pemphigoid by adding immunosuppressive agents: marked improvement in depletion of circulating autoantibodies. *Arch Dermatol* 2008;144(5):658–61.
96. Tovo PA, Miniero R, Fiandino G, et al. Fc-depleted vs intact intravenous immunoglobulin in chronic ITP. *J Pediatr* 1984;105(4):676–7.
97. Burdach SE, Evers KG, Geursen RG. Treatment of acute idiopathic thrombocytopenic purpura of childhood with intravenous immunoglobulin G: comparative efficacy of 7S and 5S preparations. *J Pediatr* 1986;109(5):770–5.
98. Basta M, Langlois PF, Marques M, et al. High-dose intravenous immunoglobulin modifies complement-mediated in vivo clearance. *Blood* 1989;74(1):326–33.
99. Frank MM, Basta M, Fries LF. The effects of intravenous immune globulin on complement-dependent immune damage of cells and tissues. *Clin Immunol Immunopathol* 1992;62(1 Pt 2):S82–6.
100. Lin RY, Racis SP. In vivo reduction of circulating C1q binding immune complexes by intravenous gammaglobulin administration. *Int Arch Allergy Appl Immunol* 1986;79:286–90.
101. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329(27):1993–2000.
102. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. *J Clin Invest* 1994;94(5):1729–35.
103. Bussel JB. Fc receptor blockade and immune thrombocytopenic purpura. *Semin Hematol* 2000;37(3):261–6.
104. Bussel JB, Graziano JN, Kimberly RP, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: analysis of efficacy, toxicity, and mechanism of effect. *Blood* 1991;77(9):1884–93.
105. Becker T, Kuenzlen E, Salama A, et al. Treatment of childhood idiopathic thrombocytopenic purpura with Rhesus antibodies (anti-D). *Eur J Pediatr* 1986;45:166–9.
106. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute immune thrombocytopenic purpura. *Lancet* 1994;344(8924):703–7.

107. Clarkson SB, Kimberly RP, Valinsky JE, et al. Blockade of clearance of immune complexes by an anti-Fc gamma receptor monoclonal antibody. *J Exp Med* 1986;164(2):474–89.
108. Clarkson SB, Bussel JB, Kimberly RP, et al. Treatment of refractory immune thrombocytopenic purpura with an anti-Fc gamma-receptor antibody. *N Engl J Med* 1986;314(19):1236–9.
109. Andemariam B, Bussel J. New therapies for immune thrombocytopenic purpura. *Curr Opin Hematol* 2007;14:427–31.
110. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001;345(10):747–55.
111. Marchalonis JJ, Kaymaz H, Dedeoglu F, et al. Human autoantibodies reactive with synthetic autoantigens from T-cell receptor beta chain. *Proc Natl Acad Sci U S A* 1992;89:3325–9.
112. Kaveri S, Vassilev T, Hurez V. Antibodies to a conserved region of HLA class I molecules, capable of modulation CD8 T cell-mediated function, are present in pooled normal immunoglobulin for therapeutic use. *J Clin Invest* 1996;97:865–9.
113. Prasad NK, Papoff G, Zeuner A, et al. Therapeutic preparations of normal polyclonal IgG (IVIg) induce apoptosis in human lymphocytes and monocytes: a novel mechanism of action of IVIg involving the Fas apoptotic pathway. *J Immunol* 1998;161:3781–90.
114. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490–3.
115. Dwyer DS, Bradley RJ, Urquhart CK, et al. Naturally occurring anti-idiotypic antibodies in myasthenia gravis patients. *Nature* 1983;301:611–4.
116. Negi VS, Elluru S, Siberil S, et al. Intravenous immunoglobulin: an update on the clinical use and mechanism of action. *J Clin Immunol* 2007;27(3):233–45.
117. Andersson J, Skansén-Saphir U, Sparrelid E, et al. Intravenous immune globulin affects cytokine production in T lymphocytes and monocytes/macrophages. *Clin Exp Immunol* 1996;104(Suppl 1):10–20.
118. Okitsu-Negishi S, Furusawa S, Kawa Y, et al. Suppressive effect of intravenous immunoglobulins on the activity of interleukin-1. *Immunol Res* 1994;13(1):49–55.
119. Sullivan KM, Kopecky KJ, Jocom J. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990;323(11):705–12.
120. Winston DJ, Ho WG, Rasmussen LE, et al. Use of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2001;28:187–96.
121. Jordan SC, Vo A, Bunnapradist S, et al. Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation* 2003;76:631–6.
122. Cordonnier C, Chevret S, Legrand M, 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.
123. Glotz D, Antoine C, Julia P, et al. Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). *Am J Transplant* 2002;2:758–60.

124. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003;348(2):138–50.
125. Munoz C, Carlet J, Fitting C, et al. Dysregulation on in vitro cytokine production by monocytes during sepsis. *J Clin Invest* 1991;88:1747–54.
126. Ertel W, Kremer JP, Kenney J, et al. Downregulation of proinflammatory cytokine release in whole blood from septic patients. *Blood* 1995;85(5):1341–7.
127. Faulkner L, Cooper A, Fantino C, et al. The mechanism of superantigen-mediated toxic shock: not a simple Th1 cytokine storm. *J Immunol* 2005;175(10):6870–7.
128. Sriskandan S, Altmann DM. The immunology of sepsis. *J Pathol* 2008;214:211–23.
129. Aukrust P, Froland SS, Liabakk NB, et al. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. *Blood* 1994;84(7):2136–43.
130. Wolf HM, Hauber I, Gulle H, et al. Anti-inflammatory properties of human serum IgA: induction of IL-1 receptor antagonist and Fc alpha R (CD89)-mediated down-regulation of tumour necrosis factor-alpha (TNF-alpha) and IL-6 in human monocytes. *Clin Exp Immunol* 1996;105(3):537–43.
131. Abe Y, Horiuchi A, Miyake M, et al. Anti-cytokine nature of natural human immunoglobulin: one possible mechanism of the clinical effect of intravenous immunoglobulin therapy. *Immunol Rev* 1994;139:5–19.
132. Arend WP, Leung DY. IgG induction of IL-1 receptor antagonist production by human monocytes. *Immunol Rev* 1994;139:71–8.
133. Dinarello CA. Is there a role for interleukin-1 blockade in intravenous immunoglobulin therapy? *Immunol Rev* 1994;139:173–88.
134. Jungi TW, Eiholzer J, Lerch PG, et al. The capacity of various types of immunoglobulin for intravenous use to interact with FC receptors of human monocytes and macrophages. *Blut* 1986;53(4):321–32.
135. Kimberly RP, Salmon JE, Bussel JB, et al. Modulation of mononuclear phagocyte function by intravenous gamma-globulin. *J Immunol* 1984;132:745–50.
136. Mannhalter JW, Ahmad R, Wolf HM, et al. Effect of polymeric IgG on human monocyte functions. *Int Arch Allergy Appl Immunol* 1987;82(2):159–67.
137. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315(6):341–7.
138. Newburger JW, Takahashi M, Beiser AS. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633–9.
139. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007;356(7):663–75.
140. NIH consensus conference. Intravenous immunoglobulin: prevention and treatment of disease. *JAMA* 1990;264(24):3189–93.
141. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. *N Engl J Med* 1991;325(2):73–80.
142. Spector SA, Gelber RD, McGrath N, et al. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. Pediatric AIDS Clinical Trials Group. *N Engl J Med* 1994;331(18):1181–7.

143. Mofenson LM, Moye J Jr, Korelitz J, et al. 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(6):477–84.
144. Griffiths H, Brennan V, Lea J, et al. Crossover study of immunoglobulin replacement therapy in patients with low-grade B-cell tumors. *Blood* 1989;73(2):366–8.
145. [No authors listed] Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomised, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. *N Engl J Med* 1988;319(14):902–7.
146. Chapel HM, Lee M, Hargreaves R, et al. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. *Lancet* 1994;343(8905):1059–63.
147. van Doorn PA, Brand A, Strengers PF, et al. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled study. *Neurology* 1990;40(2):209–12.
148. Vermeulen M, van Doorn PA, Brand A. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 1993;56(1):36–9.
149. van der Meché FG, Schmitz PI. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. Dutch Guillain-Barré Study Group. *N Engl J Med* 1992;326(17):1123–9.
150. Sweet LK, Howell J, McMurray LG, et al. The use of normal serum gamma globulin antibodies (human) concentrated (immune serum globulin) in the treatment of premature infants. *J Pediatr* 1946;28:571–3.
151. Fanaroff AA, Korones SB, Wright LL, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research. *N Engl J Med* 1994;330:1107–13.
152. Sandberg K, Fasth A, Berger A, et al. Preterm infants with low immunoglobulin G levels have increased risk of neonatal sepsis but do not benefit from prophylactic immunoglobulin G. *J Pediatr* 2000;137:623–8.
153. Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database Syst Rev* 2004;CD001239.
154. van der Meché FG, van Doorn PA. The current place of high-dose immunoglobulins in the treatment of neuromuscular disorders. *Muscle Nerve* 1997;20(2):136–47.
155. Dalakas MC. Controlled studies with high-dose intravenous immunoglobulin in the treatment of dermatomyositis, inclusion body myositis, and polymyositis. *Neurology* 1998;51(6 Suppl 5):S37–45.
156. Gold R, Stangel M, Dalakas MC. Drug insight: the use of intravenous immunoglobulin in neurology: therapeutic considerations and practical issues. *Nat Clin Pract Neurol* 2007;3(1):36–44.
157. Ratko TA, Burnett DA, Foulke GE, et al. Recommendations for off-label use of intravenously administered immunoglobulin preparations. University Hospital Consortium Expert Panel for Off-Label Use of Polyvalent Intravenously Administered Immunoglobulin Preparations. *JAMA* 1995;273(23):1865–70.

158. Sacher RA, Ivig Advisory Panel. Intravenous immunoglobulin consensus statement. *J Allergy Clin Immunol* 2001;108(4 Suppl):S139–46.
159. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. *Transfusion* 2006;46(5):741–53.
160. Sorensen R. Expert opinion regarding clinical and other outcome considerations in the formulary review of immune globulin. *J Manag Care Pharm* 2007;13(3):278–83.
161. Ochs HD, Fischer SH, Wedgwood RJ, et al. Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. *Am J Med* 1984;76(3A):78–82.
162. Roifman CM, Gelfand EW. Replacement therapy with high dose intravenous gamma-globulin improves chronic sinopulmonary disease in patients with hypogammaglobulinemia. *Pediatr Infect Dis J* 1988;7(5 Suppl):S92–6.
163. Gelfand EW, Reid B, Roifman CM. Intravenous immune serum globulin replacement in hypogammaglobulinemia: a comparison of high- versus low-dose therapy. *Monogr Allergy* 1988;23:177–86.
164. Van T, Sussman G, Pruzanski W. Impact of intravenous infusion of low and high doses of gamma globulins (IVIg) on phagocytic functions in adults with primary humoral immunodeficiency. *Inflammation* 1994;18(4):419–26.
165. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973–93. *Arch Dis Child* 1996;74(6):527–30.
166. Liese JG, Wintergerst U, Tympner KD, et al. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992;146:335–9.
167. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;1(8541):1075–7.
168. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effects 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.
169. Buckley RH. Long term use of intravenous immune globulin in patients with primary immunodeficiency diseases: inadequacy of current dosage practices and approaches to the problem. *J Clin Immunol* 1982;2(Suppl):S15–21.
170. Bernatowska E, Madalinski K, Janowicz W, et al. Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. *Clin Immunol Immunopathol* 1987;43:153–62.
171. de Gracia J, Vendrell M, Alvarez A, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol* 2004;47:745–53.
172. Roifman CM, Schroeder H, Berger M, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: a randomized double-blind trial. *Int Immunopharmacol* 2003;3(9):1325–33.
173. Dwyer JM, Erlandsson K. Intraventricular gamma-globulin for the management of enterovirus encephalitis. *Pediatr Infect Dis J* 1988;7:530–3.
174. Mease PJ, Ochs HD, Wedgwood RJ. Successful treatment of echovirus meningoencephalitis and myositis-fasciitis with intravenous immune globulin therapy

- in patient with X-linked agammaglobulinemia. *N Engl J Med* 1981;304:1278–81.
175. Mease PJ, Ochs HD, Corey L, et al. Echovirus encephalitis/myositis in X-linked agammaglobulinemia. *N Engl J Med* 1985;313:758.
 176. Quartier P, Foray S, Casanova JL, et al. 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.
 177. Part 3. Adverse reactions to immunoglobulins: methods used to produce “safe” immunoglobulin preparations. In: Alving BM, Finlayson JS, editors. *Immunoglobulins: characteristics and uses of intravenous preparations*. Proceedings of a workshop, DHHS Publication no. (FDA)-80-9005. Washington DC: US Department of Health and Human Services; 1979. p. 137–225.
 178. Pirofsky B. Intravenous immune globulin therapy in hypogammaglobulinemia: a review. *Am J Med* 1984;76(Suppl 3a):53–60.
 179. Gislason D, Hanson LA, Kjellman H, et al. Intravenous gamma-globulin infusions in patients with hypogammaglobulinemia. *Vox Sang* 1978;34:143–8.
 180. Cunningham-Rundles C, Day NK, Wahn V, et al. Reactions to intravenous gammaglobulin infusions and immune complex formation. In: Nydegger UE, editor. *Immunochemotherapy: a guide to immunoglobulin prophylaxis and therapy*. London, New York: Academic Press; 1981. p. 447–50.
 181. Barandun S, Morell A. Adverse reactions to immunoglobulin preparations. In: Nydegger UE, editor. *Immunochemotherapy: a guide to immunoglobulin prophylaxis and therapy*. London, New York: Academic Press; 1981. p. 223–7.
 182. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003;17:241–51.
 183. Wolberg AS, Kon RH, Monroe DM, et al. Coagulation factor XI is a contaminant on intravenous immunoglobulin preparations. *Am J Hematol* 2000;65(1):30–4.
 184. Lederman HM, Roifman CM, Lavi S. Corticosteroids for prevention of adverse reactions to intravenous immune serum globulin infusions in hypogammaglobulinemic patients. *Am J Med* 1986;81:443–6.
 185. Aronson DL, Finlayson JS. Historical and future therapeutic plasma derivatives (epilogue). *Semin Thromb Hemost* 1980;VI:121–39.
 186. Eibl M. Treatment of defects of humoral immunity. In: Wedgwood RJ, Rosen FS, Paul NW, editors. *Primary immunodeficiency diseases*. Birth defects. New York: Alan R. Liss; 1983. p. 193–200.
 187. Goodwin JS, Webb DR. Regulation of the immune response by prostaglandins. *Clin Immunol Immunopathol* 1980;15:106–22.
 188. Passwell JH, Dayer JM, Merler E. Increased prostaglandin production by human monocytes after membrane receptor activation. *J Immunol* 1979;123:115–20.
 189. Camussi G, Aglietta M, Coda R, et al. Release of platelet activating factor (PAF) and histamine. II. The cellular origin of human PAF: monocytes, polymorphonuclear neutrophils and basophils. *Immunol* 1981;42:191–9.
 190. Eibl MM. PKA contamination of immunoglobulin G. [letter]. *N Engl J Med* 1985;313:581.
 191. Alving BM, Hojima Y, Pisano JJ, et al. Hypotension associated with prekallikrein activator (Hageman-factor fragments) in plasma protein fraction. *N Engl J Med* 1978;299(2):66–70.
 192. Rosenfeld EA, Shulman ST, Corydon KE, et al. Comparative safety and efficacy of two immune globulin products in Kawasaki disease. *J Pediatr* 1995;126:1000–3.

193. Schiff RI. Transmission of viral infections through intravenous immune globulin. *N Engl J Med* 1994;331:1649–50.
194. Eibl MM. Intravenous immunoglobulins in neurological disorders: safety issues. *Neurol Sci* 2003;24:S222–6.
195. Miller JLC, Petteway SR Jr, Lee DC. Ensuring the pathogen safety of intravenous immunoglobulin and other human plasma-derived therapeutic proteins. *J Allergy Clin Immunol* 2001;108(4):91–4.
196. Klaesson S, Ringdén O, Ljungman P, et al. Does high-dose intravenous immune globulin treatment after bone marrow transplantation increase mortality in veno-occlusive disease of the liver? *Transplantation* 1995;60(11):1225–30.
197. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994;44(2):223–6.
198. Grillo JA, Gorson KC, Ropper AH, et al. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. *Neurology* 2001;57:1699–701.
199. Stangel M, Müller M, Marx P. Adverse events during treatment with high-dose intravenous immunoglobulins for neurological disorders. *Eur Neurol* 1998;40:173–4.
200. Alving BM, Tankersley DL, Mason BL, et al. Contact-activated factors: contaminants of immunoglobulins preparations with coagulant and vasoactive properties. *J Lab Clin Med* 1980;96(2):334–46.
201. Orbach H, Katz U, Sherer Y, et al. Intravenous immunoglobulins: adverse effects and safe administration. *Clin Rev Allergy Immunol* 2005;29(3):173–84.
202. Kallenberg CG. A 10% ready-to-use intravenous human immunoglobulin offers potential economic advantages over a lyophilized product in the treatment of primary immunodeficiency. *Clin Exp Immunol* 2007;150(3):437–41.
203. Brannagan TH III, Nagle KJ, Lange DJ, et al. Complications of intravenous immune globulin treatment in neurologic disease. *Neurology* 1996;47:674–7.
204. Gaines A, Varricchio F, Kapit R, et al. Renal insufficiency and failure associated with globulin intravenous therapy. *MMWR Morb Mortal Weekly Rep* 1999;48:518–21.
205. Stewart RR, Winney RJ, Cash JD. Renal toxicity of intravenous immunoglobulin. *Vox Sang* 1993;65(3):244.
206. Orbach H, Tishler M, Shoenfeld Y. Intravenous immunoglobulin and the kidney: a two-edged sword. *Semin Arthritis Rheum* 2004;34(3):593–601.
207. Cunningham-Rundles C, Zhou Z, Mankarous S, et al. Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with anti-IgA antibodies. *J Clin Immunol* 1993;13(4):272–8.
208. Salama A, Schwind P, Schönhage K, et al. Rapid detection of antibodies to immunoglobulin A molecules by using the particle gel immunoassay. *Vox Sang* 2002;81(1):84–5.
209. Horn J, Thon V, Bartonkova D, et al. Anti-IgA antibodies in common variable immunodeficiency (CVID): diagnostic workup and therapeutic strategy. *Clin Immunol* 2007;122:156–62.
210. Salama A, Temmesfeld B, Hippenstiel S, et al. A new strategy for the prevention of IgA anaphylactic transfusion reactions. *Transfusion* 2004;44(4):509–11.
211. 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(9):560–4.

212. Chapel HM, Spickett GP, Ericson D, et al. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol* 2000;20(2):94–100.
213. Wade N. Hybridomas: the making of a revolution. *Science* 1982;215(4536):1073–5.
214. Baudino L, Nimmerjahn F, Azeredo da Silveira S, et al. Differential contribution of three activation IgG Fc receptors (FcγRI, FcγRIII, and FcγRIV) to IgG2a- and IgG2B-induced autoimmune hemolytic anemia in mice. *J Immunol* 2008;180(3):1948–53.
215. Nimmerjahn F, Ravetch JV. Fc-receptors as regulators of immunity. *Adv Immunol* 2007;96:179–204.
216. Anthony RM, Nimmerjahn F, Ashline DJ, et al. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science* 2008;320(5874):373–6.
217. Nimmerjahn F, Ravetch JV. The antiinflammatory activity of IgG: the intravenous IgG paradox. *J Exp Med* 2007;204(1):11–5.