

# Intravenous gammaglobulin: pharmacology, clinical uses and mechanisms of action

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Intravenous gammaglobulin (IVIG) is currently one of the major expenditures at many hospital pharmacies, especially in tertiary care centers. Its use was once the exclusive province of immunologists caring for patients with rare disorders of humoral and cellular immunity. However, the development of preparations of IgG that could be infused in very large quantities led to the discovery that IVIG can have an immunomodulating effect on the immune system. IVIG is being used to treat an ever increasing list of autoimmune and inflammatory diseases, though few controlled trials are available to prove the efficacy of such therapy. In addition, infectious diseases such as CMV that can not be treated effectively with low doses of gammaglobulin are being treated with some success with very high doses. Thus, IVIG is being used to treat and prevent infections in patients undergoing chemotherapy and bone marrow transplantation.

The usefulness of IVIG in the treatment of primary immunodeficiency diseases is unquestioned, and studies have established the ability of high doses of IVIG to ameliorate ITP and Kawasaki Disease. The efficacy of gammaglobulin in other conditions is suggested but unproven. The clinician is faced with several publications each month that report the use of IVIG in yet another clinical condition. The decision of how and when to use this very expensive and scarce product is difficult, but should be based on an understanding of the mechanisms of action of IgG, the limitations of therapy, and an assessment of the literature related to the use of IVIG in various disease states.

## History of therapy with gammaglobulin

Well before the discovery of immunoglobulins, scientists were aware of the protective role of substances in the serum of individuals who had survived an infectious episode. They discovered that these substances, or “antitoxins”, could be produced in horses and other large animals by injecting them with the toxic material. The ability of these antitoxins, or antibodies, to passively protect patients from tetanus and diphtheria was demonstrated by von Behring & Kitasato in 1890 and by Paul Erlich in 1897 (1). These antibodies proved to be effective against infection, but the use of animal serum was limited by immediate anaphylactoid reactions and serum sickness. Human serum was shown by Enders in the 1930s to be effective to prevent measles, but the techniques used to concentrate the globulin fraction often resulted in bacterial contamination and adverse reactions. The modern use of gammaglobulin preparations began in the 1940s when John Cohn was commissioned by the Navy to devise a method to prepare stable plasma fractions for use as volume expanders. His method, which utilized precipitation in ethanol at low temperatures, efficiently produced albumin fractions that were free of bacterial products and were effective as a volume expander, but Cohn envisioned greater uses for the method. Supported by grants from the Rockefeller Foundation, Cohn and his colleague Oncley, refined the ethanol fractionation process to enable the isolation of other plasma products (2, 3). The fraction that precipitated at an ethanol concentration of 25%, pH 6.8 and  $-5^{\circ}\text{C}$ , known as Cohn fraction II, was shown by Enders to contain the majority of anti-measles activity (1). Gammaglobulin concentrates made by the

Cohn-Oncley process or a modification by Kistler & Nitschmann (4) are the starting material for all of the immune serum globulin and intravenous gammaglobulin preparations in use today.

The first gammaglobulin product, a 16% IgG solution of Cohn fraction II (immune serum globulin, ISG), given intramuscularly in small amounts, proved useful for prophylaxis against measles, tetanus, and diphtheria; however, when larger amounts were given intravenously to children with measles they developed hyperpyrexia, convulsions, restlessness, chills, and vasomotor collapse. Doses as low as 3 cc led to severe reactions when given intravenously to children with infections. Thus, this product was suitable only for intramuscular administration, which severely limited the amount that could be administered. This was not a problem when the only use was prevention of specific infectious diseases since small amounts would suffice. The recognition of agammaglobulinemia in 1952 by Bruton (5) and the recognition of the benefits of ISG in these immune deficient patients necessitated the development of products that could be safely administered intravenously in large quantities.

The mechanisms responsible for causing the adverse reactions that occurred when ISG was given intravenously were studied in the early 1950s by Barandun & Isliker and their colleagues at the Swiss Red Cross. They found that ISG could be administered slowly in dilute solutions to normal volunteers, but that hypogammaglobulinemic patients or patients with infections frequently experienced anaphylactoid or phlogistic reactions (6). They infused a large number of normal controls and antibody deficient patients and found that only the patients with antibody deficiency reacted. They discovered that if the infusion was interrupted when the reaction occurred, it could be resumed when the symptoms waned and completed without further adverse reaction. Reactions were also more frequent when patients were first treated with gammaglobulin; subsequent infusions were often tolerated without difficulty. The study of these patients led to the recognition of both exogenous and endogenous causes of the adverse reactions. Among the exogenous causes were thought to be antigen-antibody complexes that formed when the antibody in the ISG reacted with the infectious organisms or their products. Endogenous causes were due to aggregates of IgG that developed during the manufacturing process. Such aggregates were able to spontaneously fix complement which then stimulated the release of mediators that led to the anaphylactoid reactions. The anti-complementary effects of the ISG could be reduced by ultracentrifugation or by digestion of the Fc portion of the IgG with enzymes such as pepsin. Centrifugation was not practical for commercial production

and the aggregates re-formed on storage. Enzyme digestion destroyed the ability of the IgG to fix complement after combining with antibody, prevented interaction with the Fc receptors on phagocytes, and shortened the half-life. During the course of their investigations they discovered that treatment of the ISG at pH 4 in the presence of trace amounts of pepsin reduced the spontaneous anti-complementary effect without damaging the normal activity of the molecule. Most importantly, large quantities of the resulting preparation, later marketed under the name of Sandoglobulin® could be rapidly infused into immunodeficient patients without causing serious side-effects. Subsequently, many other techniques were successfully employed by other pharmaceutical companies to produce IgG preparations with normal activity and low incidence of adverse reactions.

The most recent chapter in the history of the use of gammaglobulin began in 1981 with the observation that several patients with hypogammaglobulinemia and thrombocytopenia had an increase in their platelet count following infusions of intravenous gammaglobulin (7). This was followed by other isolated reports of resolution of thrombocytopenia and hemolytic anemia following infusions of large quantities of gammaglobulin, leading to speculation that the IgG could have a suppressive or modulating effect on autoimmune reactions. In recent years IVIG has been used to treat a wide range of inflammatory or autoimmune diseases as diverse as Kawasaki disease, idiopathic thrombocytopenic purpura (ITP), polyneuritis, myasthenia gravis, and inflammatory bowel disease. The efficacy of gammaglobulin and the possible mechanisms of action are currently the subjects of intense investigation.

## **Pharmacology of IgG**

### **Function of IgG**

Immunoglobulins constitute one of the most important components of specific immunity. Although IgM is important in the first response to infection, IgG comprises more than 80% of the total antibody pool and is crucial for long-term immunity. IgG antibodies have activity against viruses, bacteria, protozoa and microbial toxins. With a molecular weight of 150 KD, IgG is capable of diffusing out of the blood vessels where it distributes to most of the extravascular space. At times of inflammation IgG can be found on mucosal surfaces and in cerebral spinal fluid. IgG also crosses the placenta, beginning in the second trimester, and by term provides the newborn infant with serum concentrations equivalent to, or slightly more than, that of the mother.

The structure of IgG has been well described. It is composed of four covalently linked chains, two

heavy chains of approximately 50 KD each and two 25 KD light chains. The amino end of each chain is highly variable and the carboxy end is relatively constant. The amino terminal ends of all four chains form the antigen-binding region, the  $F(ab')_2$  portion; the carboxy end of the two heavy chains, the Fc portion, has functions that are critical to the activity of the molecule. The Fc portion of IgG binds to specific Fc receptors on macrophages, polymorphonuclear cells (polys), and NK cells. This binding provides a link, known as opsonization, to attach antigen to the macrophage for phagocytosis. The Fc portion also activates complement, which can attach to cells or microorganisms and provide another link to macrophages through complement receptors, or directly lyse susceptible cells. IgG also provides regulatory functions, blocking IgE binding to mast cells, inhibiting further antibody production through feed-back inhibition on B cells, and regulating T cells through antibody to T cell receptors and other membrane receptors.

IgG is composed of four subclasses, IgG1, IgG2, IgG3, and IgG4, that differ in the structure of the constant region of the heavy chain. They are located on chromosome 14 in that order, and switching is thought to be under T cell control. IgG1 is found in the greatest concentration, comprising more than 60% of the total IgG. It fixes complement and binds tightly to Fc receptors. Many of the antibodies to bacterial and viral proteins are found in this subclass. IgG2 antibodies constitute about 30% of the total and contain most of the antibodies to bacterial polysaccharides. However, in the absence of IgG2, IgG1 subclass antibodies will be formed against carbohydrate antigens. IgG3 antibodies are important for the neutralization of viruses; this subclass constitutes about 6% of the total and has the shortest half-life because it contains an extra segment that renders it more susceptible to proteolytic enzymes in the plasma. IgG4 is found in only trace amounts, often below the limits of detection of methods such as radial immunodiffusion, but is thought to have unique properties. Only IgG4 binds to mast cells and may either activate the cells or block binding of IgE.

The  $F(ab')_2$  end of the molecule has a conformation that allows it to tightly associate with a specific antigen. When large quantities of a single antibody are produced, their specific conformation can be recognized as new or "foreign" and the body can respond by producing an antibody to part of the antigen-binding site. These antibodies, known as anti-idiotypic antibodies because they bind to a unique site or idiotope on an antibody, are very important in regulation of both B and T cell function. An antibody against another antibody could bind to the antibody on the surface of a B cell and either stimulate or inhibit further antibody forma-

tion. Similarly, the antibody could bind to a T cell receptor and regulate its activity. Another generation of anti-idiotypic-antibodies can form against the first generation, and yet another can form against the second, and so on. This idiotypic network is thought to be critical to regulation of immunity and may be important to many of the actions of IVIG.

### Metabolism

The metabolism of IgG was described and extensively reviewed by Waldmann & Strober in 1969 (8), and little has been added to our understanding since that time. Most of our knowledge is derived from studies conducted using trace amount of Cohn fraction II or chromatography-purified IgG radiolabeled with  $^{125}\text{I}$  and injected intravenously into "normal" subjects and patients with immune deficiency or malignancy. These small amounts of IgG were well tolerated and did not alter the intrinsic concentration of IgG. Those studies indicated that the metabolism of IgG followed multicompartmental first order kinetics. Thus, after infusion of labeled IgG there is an initial period of redistribution to extravascular body compartments, which can require several days, followed by an elimination phase. If the log of the IgG concentration is graphed against time, the resulting graph is linear and the slope of the elimination phase is proportional to the half-life. One of the caveats of first order kinetics is that the elimination is independent of the concentration. It was somewhat surprising, therefore, when it was discovered that the half-life of IgG in normal individuals was approximately 18 to 21 days, but that in hypogammaglobulinemic patients it could be 35 days or longer, and in patients with hypergammaglobulinemia it could be as short as 11 days (9). This becomes of importance when considering treatment of patients with agammaglobulinemia, for if the half-life becomes shorter as the patient is treated and the concentration is increased, then ever increasing doses would be necessary.

Many factors are involved in the measurement of the elimination of IgG and specific antibody during therapy with IVIG (10). Although the early studies were conducted using radiolabeled IgG, the risks and difficulties of using radioisotopes made it necessary to use other techniques. Most recent studies have measured the decline in the concentration of IgG or specific antibody after an infusion of IVIG (11-14). Because large quantities of IgG are infused, the serum concentration is greatly increased, and if the rate of elimination is dependent on concentration it is possible that the half-life could be altered.

This technique is useful primarily in patients with no intrinsic synthesis of IgG; if the patient does produce IgG the serum concentration is increased

Table 1. Intravenous gammaglobulin preparations available in the United States

| Brand name       | Method of preparation                   | pH   | Osmolality (mOsm) | IgA content $\mu\text{g/mL}^*$ | Additives                                               | Form        | Supply (gm)         | Conc. (%)  | Manufacturer              |
|------------------|-----------------------------------------|------|-------------------|--------------------------------|---------------------------------------------------------|-------------|---------------------|------------|---------------------------|
| Gamimune®-N      | pH 4.25                                 | 4.25 | 335               | 270                            | 10% maltose                                             | Liquid      | 0.5, 2.5, 5.0, 12.5 | 5          | Miles Biological          |
| Gamimune®-N, 10% | pH 4.25                                 | 4.25 | 375               | NA                             | 0.2 M glycine                                           | Liquid      | 5, 10, 20           | 10         | Miles Biological          |
| Gammagard®       | DEAE-Sephadex Polyethylene glycol (PEG) | 6.8  | 630               | <2                             | 2% glucose<br>0.2% PEG<br>0.3 M glycine<br>0.3% albumin | Lyophilized | 0.5, 2.5, 5.0, 10.0 | 5<br>10§   | Baxter/Hyland             |
| Gammar® I.V.     | Low ionic strength                      | 7.0  | 333               | 20‡                            | 5% sucrose<br>2.5% albumin                              | Lyophilized | 1.0, 2.5, 5.0, bulk | 5          | Armour                    |
| Iveegam®         | low pH, PEG, immobilized trypsin        | 6.8  | 375               | ≤2‡                            | 5% glucose<br>0.5% PEG                                  | Lyophilized | 0.5, 1.0, 2.5, 5.0  | 5          | Immuno-US                 |
| Polygam™         | DEAE-Sephadex PEG                       | 6.8  | 630               | <2                             | same as Gammagard®                                      | Lyophilized | 2.5, 5.0, 10.0      | 5          | Hyland American Red Cross |
| Sandoglobulin®   | low pH, trace Pepsin                    | 6.6  | 375 (6%)          | 720                            | 10% sucrose (6%)                                        | Lyophilized | 1.0, 3.0, 6.0       | 3, 6, 12§§ | Sandoz                    |
| Venoglobulin®-I  | DEAE-Sephadex, PEG                      | 6.8  | 225               | 20–24‡                         | 2% D-mannitol<br>1% albumin<br><0.6% PEG                | Lyophilized | 0.5, 2.5, 5.0, 10.0 | 2.5, 5     | Alpha Therapeutics        |
| Venoglobulin®-S  | DEAE-Sephadex, PEG Detergent            | 5.2  | 302               | 10–27‡                         | 5% D-sorbitol<br>≤0.2% albumin<br>≤0.6% PEG             | Liquid      | 2.5, 5.0, 10.0      | 5          | Alpha Therapeutics        |

\* Concentrations approximate; there is a great deal of lot-to-lot variability

‡ Data provided by the manufacturer

§ Use of higher concentration supported in reference [1622]

§§ Use of higher concentration supported in reference [1391]

and the half-life appears to be falsely prolonged (10). Measurement of specific antibody can be more accurate, especially if an antibody that is not likely to be consumed, such as anti-tetanus antibody, is used for the evaluation. Other antibodies, such as those to *H. influenza* or the pneumococci, may be rapidly consumed during an infection, resulting in a half-life which appears to be falsely short (14). Alteration of the IgG molecule can also result in inaccurate measurement of the half-life. Radiolabeling IgG can damage the molecule, and it is possible that some of the early studies were inaccurate because the damaged molecules were eliminated more rapidly than were normal intact molecules. Many of the processes used to modify Cohn fraction II to make it acceptable for intravenous use cleaved or partially cleaved the molecule or altered the Fc portion. These altered molecules, especially fragments of IgG, are rapidly eliminated and in most cases resulted in a shortened half-life. However, it is possible for a large proportion of the molecules to be eliminated in the first few hours or days and then for the remaining molecules to be eliminated in a more normal fashion. This could give the appearance of a normal half-life even though most of the IgG was rapidly eliminated. Even though the slopes of the elimination curves would be similar, the area under the

curve of the rapidly eliminated IgG would be much less; thus, measurement of the area under the curve (AUC), with calculation of elimination rather than half-life, is a better measure of the metabolism (10).

Most studies in patients with hypogammaglobulinemia confirmed the early studies that indicated that the half-life was the same or longer than that seen in normals (11–14). There was not a demonstrable alteration in the half-life as the serum concentration was increased (10, 13) even though some reports suggested that the half-life was shortened (15). Perhaps this should not be too surprising since the studies reported by Waldmann & Strober suggested that the half-life did not shorten significantly until the concentration of IgG approached 2000 or 3000 mg/dl (9). Others have suggested that the half-life of IgG actually becomes longer following therapy (16), perhaps due to clearance of infection and saturation of Fc receptors. In the absence of infection, elimination of specific antibody is similar to that for total IgG (17); however, specific antibody may be eliminated rapidly, as during infection with CMV (18) or pneumococcus (14). The half-life of the IgG subclasses IgG1, 2, and 4 are all similar to that for total IgG, but IgG3 has a shorter half-life (9), though some studies suggest that there are two populations of IgG3 molecules, one with a short and the other

with a half-life similar to the other subclasses (17). Finally, the half-life of IgG may be different in other conditions. Not surprisingly, the half-life is decreased in burn patients (19). In most studies in neonates, the half-life is similar to that of older children and adults (20).

#### IVIG Preparations

As was discussed in the introduction, all of the available IVIG preparations begin with an IgG concentrate produced by the Cohn fractionation technique (2, 3) or the modification by Kistler & Nitschmann (4). This process effectively removed most viruses and vasoactive amines, but upon storage the IgG tended to aggregate. For more than 30 years investigators have devised a variety of methods to prevent formation of aggregates which fix complement upon intravenous infusion. Many of these altered the IgG molecule, which prevented aggregation but also impaired the normal activity such as complement fixation and binding to Fc receptors. These are primarily of historic interest as none are currently available in the US. All of the currently licensed products are unmodified and have normal activity (Table 1). Unfortunately, there are few published reports of the characteristics of the newer IVIG preparations, Gamimune®-N, 10%, Gammagard® I.V., Venoglobulin®-I, Venoglobulin®-S or Iveegam®.

The characteristics of the first generation of IVIG preparations are reviewed by Römer et al. (21, 22) and by Morell & Skvaril (23). None of the products that utilized modification of the IgG molecule by enzymes such as pepsin or papain, or by reduction and alkylation, sulfonation, or  $\beta$ -propiolactone are currently in use in the US, and only Intraglobin®-F, prepared by treatment with  $\beta$ -propiolactone, is being used in Europe. The three major IVIG preparations used in the US, Sandoglobulin®, Gamimune®-N 5%, and Gammagard®, have been compared in several recent publications (24–26). The main differences noted was a lower concentration of aggregates in the Gamimune®-N and a higher IgG4 content in the Sandoglobulin®. Another very important point is the very low concentration of IgA in Gammagard® and Polygam™ (27). Iveegam® also has a low content of IgA. One unusual preparation, not yet available in the US, is known as Pentaglobin (Biotest Pharma, GmbH) and contains significant quantities of IgA and IgM which may provide benefit when the gammaglobulin is used to treat bacterial infections, especially in the presence of endotoxin (28). Pentaglobin has increased opsonic activity compared to a traditional preparation that exclusively contains IgG (29), probably due to its increased quantity of IgM.

Several different approaches have been used to make IVIG preparations that are well tolerated. Gamimune®-N 5% and 10% are treated at pH 4.25 and maintained at that low pH to prevent reaggregation. Sandoglobulin®, on the other hand, is treated at low pH in the presence of trace amounts of pepsin which prevents reaggregation when the IgG is brought back to physiologic pH but does not cleave the molecule. Gammagard®, and Venoglobulin® prepared by ion exchange chromatography with additives such as polyethylene glycol (PEG) to help precipitate aggregates. Iveegam® is prepared by treatment with insolubilized trypsin and then purified by PEG precipitation. Gammagard® IV is not modified but is stabilized by addition of sucrose and albumin to prevent reaggregation. Three of the preparations, Gamimune®-N 5%, Gamimune®-N 10%, and Venoglobulin®-S, are maintained in the liquid form, whereas the others are stored as a lyophilized powder that is reconstituted at the time of use. The liquid preparations are convenient to use and tend to have fewer aggregates so that in general they are very well tolerated by the majority of patients. A minor disadvantage is that liquids have a shorter storage life and can not be reconstituted at various concentrations. The choice of liquid or lyophilized powder is mostly one of individual preference as both are well received by patients.

The first modified immune serum globulin prepared by reduction and alkylation caused a very high incidence of side effects until maltose was added (30). Since then every IVIG preparation has contained either a sugar or amino acid such as glycine. The choice is more one of avoiding patent infringement than it is of one being significantly better than another. The glycine used in Gamimune®-N 10% helps maintain the pH and also results in a lower osmolality than most of the others that utilize sugars.

Although every lot of IVIG must be shown to contain antibody to a few antigens such as measles and tetanus toxoid, there is no standardization or requirement for more extensive testing. Nonetheless, studies have confirmed that all of the available preparations contain good titers to a wide variety of microorganisms (31–34). There is concern, however, that as high-risk populations are eliminated from the donor pool, the titers of some antibodies, such as anti-CMV will decline. Although several investigators have noted a decline in titers, there is as yet no formal publication of such results. Part of the reason that there is no requirement for standardization is that the proper assays are not universally agreed upon, and the results may differ significantly depending upon which assay is used. For example, the titers of anti-CMV antibodies differed between several IVIG preparations and different lots of the same preparation, but there was little correlation

between the results of an ELISA and neutralization assay (35). Different preparations may differ in their ability to opsonize bacteria, despite similar titers by immunologic assays, though the intact IVIG preparations all opsonized very well (36, 37).

Preparations of gammaglobulin must be free of vasoactive amines such as prekallikrein activator (PKA), proteases, and pyrogens (38) and should have low titers of isoagglutinins. However, in addition to traces of albumin and IgA, IVIG preparations may contain HLA class I and class II antigens (39, 40) or microaggregates of idiotype-anti-idiotypic dimers (41). It is not known what effect these might have, but they could be important with regard to the immunomodulating effects of IVIG.

#### Dosage and administration

*Determination of dose* – The dose of IVIG that is required obviously depends on the disease that is treated and can range from as little as 100 mg/kg/month for patients with antibody deficiency to more than 5 g/kg for patients with hemolytic anemia. The optimal dose has never been studied in a systematic way for any disease, but rather has been derived from anecdotal experience and a few small studies. This is best exemplified in the treatment of antibody deficiency. When Bruton described the first patient with X-linked agammaglobulinemia in 1952 (5) he began treating the patient with intramuscular gammaglobulin. He consulted Rosen and Janeway who, based on the study of subsequent patients with hypogammaglobulinemia, determined that the incidence of infections was greatly reduced if the serum concentration of IgG was over 200 mg/dl (42). A dose of 100 mg/kg per month, given in weekly divided doses, achieved that level in most patients. A large, but uncontrolled, study by the British Medical Research Council that began in 1956 determined that there was a slight but statistically insignificant benefit of 50 mg/kg/week compared to 25 mg/kg/week (43). The doses used in these early investigations were limited by the amount that could be injected intramuscularly, and serious studies of dose requirements did not begin until intravenous forms of gammaglobulin became available.

Patients treated with 150 mg/kg of IVIG given once monthly had significantly fewer infections than those treated with 20 ml (3.3 gm) of intramuscular gammaglobulin (44). The IM dose is equivalent to 47 mg/kg for a 70 kg adult, and the rate of infection decreased from a mean of 0.295 infections per month to 0.103. However, a prospective study of 19 patients treated with 400 mg/kg/month of IVIG compared to 16 patients treated with 100 mg/kg/month failed to show any objective benefit of the higher dose, though most of the patients said that

they felt better while receiving the higher dose (45). Several subsequent studies provided evidence that higher doses were more beneficial, but few were well controlled and none were blind. Cunningham-Rundles et al. compared the incidence of infection in 21 patients treated with 300 mg/kg/month of IVIG compared with each patients' historical control period when they had received 100 mg/kg of IM gammaglobulin (46). Though there was a substantial reduction in the incidence of infection and use of antibiotics, it is difficult to compare the two periods since the data were collected retrospectively during the period of IM therapy. Gelfand et al. conducted a cross-over study comparing 200 mg/kg with 600 mg/kg, and although there was not a significant difference in the incidence of infection between the two periods, there was a decrease in the incidence whenever the serum IgG concentration was over 500 mg/dl (47, 48). The study design did not include a washout period or a pre-load to reach steady state within a short period of time. Thus, the patients had not reached steady state during the period that data were collected. The study by Cunningham-Rundles (46) suggested that the incidence of infection was lower during the second six months of the study, presumably because it takes several months to reach steady state and to clear chronic infection. Finally, in another prospective cross-over study comparing 150 mg/kg to 500 mg/kg of IVIG there was significant reduction in the incidence and severity of infections during the period the patients received the higher dose (49). In addition, even the low dose was more effective when compared to the previous year when patients had received plasma.

Although none of the studies are conclusive, most have shown a significant benefit when immunodeficient patients are treated with doses of 300 mg/kg/month or more. The levels of specific antibody may be rapidly consumed during an acute infection and are quite low during treatment with the "standard" doses of 100 mg/kg/month (12, 14, 18). Thus, most investigators now recommend doses of at least 200 to 400 mg/kg/month. The dose must be individualized as some patients will improve with higher doses or shorter intervals. The serum level of IgG is less important than the clinical response, but should be at least 500 mg/dl over baseline; in patients with substantial intrinsic synthesis of IgG but poor production of specific antibody, it must be remembered that the baseline serum concentration should not be considered since it is not effective. The decision as to increase dose or decrease the dosing interval is based on convenience and cost, but in general if the patient is experiencing increased difficulty during the end of the dosing interval it is more effective to decrease the interval rather than to increase the dose. One final consideration when de-

termining the dose used is to know the size vials that are available and to "round-off" to the nearest whole vial. The dose is never a precise number, and a few milligrams taken from a 2.5 gram vial results in unacceptable waste of a scarce resource and an unnecessary and avoidable expense to the patient.

The dose of IVIG necessary for the treatment of the autoimmune diseases is much higher than that required for antibody replacement. The reason such high doses are required is not known, but may be due either to the need for massive amounts of IgG to paralyze the Fc receptors or because only a very small proportion of the antibodies are relevant to the specific situation. The selection of dose in these disorders will be considered when each disorder is discussed.

**Administration** – The first gammaglobulin preparations caused severe reactions when infused intravenously and thus were injected intramuscularly. This was painful, limited the dose that could be given, delayed absorption, and was difficult in patients with small muscle mass or thrombocytopenia. Plasma therapy was used as a substitute for several years, but transmission of hepatitis was frequent and discouraged its use. Several investigators (50, 51) gave the intramuscular preparation by slow subcutaneous infusion to avoid side effects and to allow higher doses to be given. Patients could infuse themselves at home each night so that very high doses could be given over the course of a month. One advantage of this technique is that the less expensive ISG preparation can be used instead of IVIG, though there is concern that at high doses the amount of mercury-containing preservative could be toxic (52).

The recommended rates of infusion of IVIG are based in large part on the original observations made when ISG or the early preparations of IVIG were infused intravenously (53). Caution was certainly justified, as the first generation of IVIG preparations were associated with a high incidence of side effects, particularly in patients with antibody deficiency (54). Initial rates were 0.01 ml/kg/min which, using a 5% solution of IgG, is equivalent to 0.5 mg/kg/min. The rate is then increased stepwise to a maximum of 0.08 ml/kg/min which is equivalent to 4 mg/kg/min. The currently available IVIG preparations are much better tolerated, and most patients without immune deficiency and the majority of patients with antibody deficiency can tolerate much higher rates, particularly with 10% or 12% solutions. In a study using Sandoglobulin® reconstituted to 6%, 9%, or 12%, 13 of 16 patients were able to tolerate rates up to 15 mg/kg/min (55). At that rate infusions of 400 mg/kg could be completed in 15 to 20 minutes. Gammagard® can be reconstituted to 10% and also can be infused rapidly with very few

side effects (56). These patients were selected on the basis of having tolerated standard rates of infusion without adverse effects, and no patient should be infused at rapid rates until they have a proven safety record. That is particularly important in immunodeficient patients since the incidence of adverse reactions is much higher during the first few treatments.

Home therapy with IVIG has been proposed and studied by several investigators (57–62). Factors to consider when deciding to use home therapy are convenience, cost, and safety. Home infusions are convenient and patient acceptability has been high in all of the studies. There is less time missed from work or school and less stress of travel and going to the doctor's office or infusion center. The cost may be less (59) than infusion in the hospital, but that is not always the case. The cost depends on whether the patients infuse themselves or if a visiting nurse is necessary to establish vascular access or supervise the entire infusion. The cost of IVIG varies greatly, and as many home therapy programs charge more than do hospital pharmacies, the cost savings may not be as high. The safety issue is an important one, especially for patients with immune deficiency. In each of the published studies the patients selected to be infused at home had been infused for several months under medical supervision and had a proven record of having tolerated the IVIG without adverse reactions. However, even in those patients severe adverse reactions requiring epinephrine, diphenhydramine,  $\beta$ -agonists, and corticosteroids have occurred at times of infections. Thus, care must be taken at all times. It is not acceptable for immune deficient patients to receive their first infusion therapy at home, even if a nurse is present. It is also important that the physician prescribing and supervising the infusions be familiar with the use of IVIG and the treatment of adverse effects. Emergency medications must be available and someone other than the patient must be present and trained in their use. Home therapy may be appropriate for some patients who have tolerated IVIG without difficulty, provided that the proper precautions are taken. The decision to begin home therapy must consider these issues as well as the decreased supervision and observation that results from fewer physician visits. In some situations, especially where the patient tends to ignore or deny symptoms of illness, the benefits of close medical attention may outweigh the convenience of home therapy.

### Limitations of the use of IVIG

Treatment of immunodeficient patients with gammaglobulin has been extraordinarily successful in reducing the incidence and severity of acute in-

Table 2. Clinical uses of IVIG

|                                                   |
|---------------------------------------------------|
| Clearly indicated and approved                    |
| Primary Immunodeficiency                          |
| Immune Prophylaxis (e.g. Varicella)               |
| Kawasaki Disease                                  |
| Idiopathic Thrombocytopenic Purpura               |
| Supported by controlled clinical trials           |
| Immunodeficiency 2° to HIV Infection              |
| Bone Marrow Transplantation                       |
| Specific Infections in Neonates                   |
| Group B <i>Streptococcus</i>                      |
| Neurologic Diseases                               |
| Multiple Sclerosis                                |
| Guillain-Barré Syndrome                           |
| Chronic Inflammatory Demyelinating Polyneuropathy |
| Hemophilia 2° to Anti-Factor VIII                 |
| Experimental                                      |
| Secondary immune deficiency                       |
| Burns                                             |
| Surgery/trauma                                    |
| Chemotherapy                                      |
| Hematologic disorders                             |
| Neutropenia                                       |
| Hemolytic anemia                                  |
| Red cell aplasia                                  |
| Neurologic diseases                               |
| Intractable seizures                              |
| Inflammatory myopathy                             |
| Myasthenia gravis                                 |
| Collagen-vascular disease                         |
| Systemic lupus erythematosus                      |
| Systemic vasculitis                               |
| Rheumatoid arthritis                              |
| Inflammatory bowel disease                        |
| Anticardiolipin/recurrent abortions               |
| Miscellaneous inflammatory disorders              |
| Asthma                                            |
| Diabetes mellitus                                 |
| Bullous pemphigoid                                |
| Birdshot retinopathy                              |

fections. Antibody replacement is less successful in eliminating chronic infections, especially after severe tissue damage has occurred. Intravenously administered gammaglobulin does not replace defects of mucosal immunity, though there is some evidence that antibody may penetrate onto mucosal surfaces such as in sinuses (63). The concentration of IgG may be higher in the CSF, lungs, or GI tract at times of acute inflammation that opens tight junctions and allows transudation of serum proteins. Since this is not as efficient as active secretion, higher intravenous doses may be more beneficial when treating infection in these difficult areas. When a normal individual encounters a pathogen, specific B cells are activated and very large quantities of antibody are produced that are directed against that organism. Standard IVIG contains a wide variety of antibodies, but since it is derived from plasma of healthy adults, the amount of any one specific antibody is low. When an immunodeficient patient becomes infected

the antibody directed against that specific pathogen is utilized very rapidly. Therapy of an infection requires much higher doses of IVIG than are used for prophylaxis, or may necessitate use of a hyper-immune gammaglobulin preparation or monoclonal antibody directed against the pathogen. An important limitation is that replacement of antibody can not compensate for defects in cellular immunity. Patients with T cell defects often have disorders of antibody production due to lack of T cell help, so therapy with IVIG is necessary. It does not, however, prevent most opportunistic infections.

### Clinical uses of intravenous gammaglobulin

Currently, IVIG is being used for a myriad of indications, including antibody deficiency (both primary and secondary) treatment of specific infections, treatment of autoimmune diseases and other inflammatory conditions (Table 2). For some of these diseases the use of IVIG is unequivocal, in others although there are good controlled trials, the role of IVIG is not yet proven and its use should be reserved for situations where other modes of therapy have failed, and in many other conditions there are only anecdotal observations and the use of IVIG should be considered experimental.

#### Treatment of antibody deficiency

The initial, and indeed the primary use of gammaglobulin, is to provide specific antibodies against infectious organisms. This includes replacement therapy in patients who are immunodeficient and unable to make antibodies, such as those with primary antibody deficiency, or those who can not due to immaturity, lack of exposure, or other illnesses that temporarily impair humoral immunity. Whereas the use of IVIG to treat patients with severe primary disorders of immunity is well established, the benefit of therapy in partial antibody deficiency or secondary immunodeficiency has not been adequately determined.

#### Primary disorders of humoral immunity

*Hypo- and agammaglobulinemia* – Treatment of primary disorders of humoral immunity was the first indication for gammaglobulin. Shortly after Bruton reported the first patient with what is now known as X-linked agammaglobulinemia (5), other patients with similar defects in antibody production were identified and treated (42). When the British Medical Research Council initiated a study of the treatment of hypogammaglobulinemia in 1956, only four years after the first description of the disease, they decided that it would be unethical to include a pla-

cebo control (43). Thus, there has never been a controlled study of the use of ISG or IVIG in humoral immunodeficiency diseases. However, many anecdotal and retrospective studies have firmly entrenched the use of IgG in the treatment of patients with defective production of antibody. In Europe, therapy with intravenous gammaglobulin began in the early 1960s and rapidly became the standard of care (64). In the US the first trial of IVIG began in the mid 1970s with a reduced and alkylated product later licensed in 1981 and marketed as Gamimune® (54). The original material caused an unacceptably high incidence of side effects until 10% maltose was added (30). This new IVIG preparation allowed treatment with higher doses of IgG and proved more effective and better tolerated than the previously used intramuscular preparation (44, 54). A series of clinical trials confirmed the effectiveness of Gamimune® (65, 66), a  $\beta$ -propiolactone-modified product (Intraglobin®, Biotest Serum Institute) (12, 13), an unmodified IVIG preparation that was an early version of the product now marketed by Immuno AG under the name Iveegam® (67), and another unmodified product developed by the Swiss Red Cross and marketed by Sandoz as Sandoglobulin® (46). In the mid 1980s Gamimune was replaced by an unmodified, pH 4.25 product Gamimune®-N (14) which was better tolerated and had normal Fc activity. The European experience was summarized in 1986 (68). Robertson & Hosking reported the use of a product similar to Sandoglobulin® in 54 patients in Australia (69). Clinical studies performed in the late 1980s continue to support the benefits of intravenous gammaglobulin compared with intramuscular (49, 70, 71), high dose therapy compared with low dose (48, 49), and native or unmodified gammaglobulin compared with IVIG in which the Fc portion is chemically altered (72).

Although therapy with gammaglobulin has never been compared to placebo, few would question the necessity of treating patients with severe disorders of humoral immunity, including X-linked agammaglobulinemia, common variable immune deficiency (CVID), and X-linked hyper IgM syndrome. Treatment of patients with transient hypogammaglobulinemia of infancy is generally considered to be unnecessary unless there is a significant inability to produce specific antibody (73, 74). Selective IgA deficiency is generally considered to be a contraindication to the use of gammaglobulin therapy. Most patients produce antibodies normally and replacement with IVIG can not correct the absence of antibody at the mucosal surface. In addition, patients with complete absence of IgA are at risk of developing anaphylactic reactions to IgA that is present in nearly all IVIG and ISG preparations. There are, however, some patients with IgA deficiency as-

sociated with IgG subclass deficiency in whom there is a defect in antibody production. These patients often suffer from recurrent infections and there is evidence that therapy with IVIG may reduce the incidence of infections (75), though the benefits must be weighed against the risk of serious or even life-threatening anaphylactic reactions. The use of IVIG in IgG subclass deficiency will be discussed in a later section.

*Combined immune deficiency* – Although there are no controlled studies, replacement therapy with IVIG is indicated in any disease in which there is a defect in antibody production. Thus, in severe combined immune deficiency where the primary abnormality is absent T cell function, with concomitant defect in antibody production, patients should be treated with gammaglobulin. In most T cell defects, including most patients with complete Di George syndrome, there is poor antibody production due to lack of T cell help. Therapy with IVIG is also indicated in diseases such as the Wiskott-Aldrich syndrome (76–78), hyper-IgE syndrome (79), and ataxia telangiectasia (80, 81) in which immunoglobulin concentrations are normal, but there is a significant defect in the ability to produce specific antibody. Gammaglobulin replacement may also be of benefit in the accelerated phase of Chediak-Higashi syndrome (82) or in patients with X-linked lymphoproliferative syndrome (83, 84). Replacement of antibody prevents many bacterial and viral infections but does not correct the underlying defect or decrease the incidence of malignancy; it can be life-saving, however, while awaiting definitive therapy.

*IgA and IgG subclass deficiency* – There are 4 subclasses of IgG that differ in their structure and physiochemical properties. A series of investigations pioneered in Sweden by Oxelius associated certain selective IgG subclass deficiencies with an increased incidence of infection, IgA deficiency, juvenile diabetes mellitus, and intractable seizures (85, 86). More specifically, IgG2 deficiency was associated with recurrent sinopulmonary disease and poor response to carbohydrate antigens, IgG2-IgG4 deficiency was associated with IgA deficiency and ataxia telangiectasia, and IgG3 deficiency with recurrent viral infections and bronchitis in adults. Deficiency of one or more IgG subclasses may also be associated with other primary immunodeficiency disorders (87), (88).

It is clear that IgG2 subclass deficiency in particular is associated with frequent infections and immunologic dysfunction (89–91). Many patients with IgG2 deficiency fail to respond to polysaccharide antigens such as *Hemophilus influenzae* or *Strepto-*

*coccus pneumoniae*. Some of these patients also had other subclass defects or abnormalities of IgA or IgM. Others have reported a similar association (92–94). However, despite the association of IgG2 subclass deficiency and poor responses to polysaccharide antigens, it appears that the increased incidence of infections is associated with the poor antibody response, not the absence of any subclass of IgG (95). Thus, although the presence of IgG subclass deficiency may be a marker of immune dysregulation and therefore increase the likelihood that there will be a defect in antibody production, it is only the ability to produce specific antibody that is relevant (96). Measurement of IgG subclasses often adds little to the evaluation other than as a research tool.

Gammaglobulin treatment of patients with poor antibody responses, whether associated with IgG subclass deficiency or not, can decrease the incidence of infection and be beneficial in those patients with intractable infections that do not respond to treatment with antibiotics (97). IgG subclass deficiency and poor antibody response may be associated with IgA deficiency (75, 98). Some of these patients may develop IgG or IgE antibodies to IgA if infused with IVIG that contains IgA. If clinically indicated, IgA deficient patients can be treated with IVIG preparations such as Gammagard® that are very low in IgA (75, 99); however, patients that are completely IgA deficient are always at risk of developing anaphylactic reactions and must be infused with caution and in a situation where emergency care is available.

*Neonates* – Newborn infants and especially premature infants are highly susceptible to overwhelming bacterial and viral infections (100). There are a number of reasons for this susceptibility, including antibody deficiency (101–103), complement deficiency and neutrophil dysfunction (104), decreased monocyte and neutrophil chemotaxis (105), impaired T cell function and cytokine production (106), and decreased fibronectin levels (107). *Escherichia coli* and group B *Streptococcus* are the predominant bacterial pathogens for the newborn infant in the US, though other organisms may be predominant in local areas (108). With this seemingly overwhelming number of defects, is it rational to believe that the addition of antibody could have a significant impact on host defense? Data from experimental models of sepsis and preliminary data from human trials suggested that it might (109–111). In the newborn rat model of group B *Streptococcal* infection, antibody plus penicillin was more effective than penicillin alone (112). The addition of monoclonal antibody against group B *Streptococcus* or 750 to 1000 mg/kg of IVIG, either alone or in combination with fibronectin, greatly improved survival in the same model

(109). The use of antibody appeared to prevent the neutropenia and depletion of marrow stores that occurred in the infected animals.

Treatment of neonates with intramuscular gammaglobulin began as early as 1960, but in a series of studies little or no benefit was observed (110). When a high-risk population of Apache Indian infants was treated with three doses of 80 mg of ISG there was a significant decrease in the incidence of *Hemophilus influenzae* infections (113). Intravenous immunoglobulin infusions were begun in the 1970s in an open controlled study by the Perinatology Division at the University of Berne (114, 115). Infected infants given antibiotics plus 0.5 to 1 gm of IVIG daily for 6 days had a significantly lower incidence of infection and mortality rate compared to infants given antibiotics alone. The obstetric personnel were so convinced of the efficacy of IVIG that the trial had to be terminated and all infected infants were treated. There were no late sequelae of the IVIG therapy with regard to development or immunologic maturation. They later attempted a prophylactic approach by infusing IVIG into high-risk pregnant women late in gestation using either a low dose of 12 gm or high dose of 24 gm/day for 5 days (115). Significant increases in IgG levels and specific antibody in the cord blood were seen only with the high dose regimen and if the infusion were given after 32 weeks gestation. No infections occurred in 7 infants born of mothers in the high-dose group whereas 6 of 16 control infants and 3 of 9 low-dose infants developed infections requiring antibiotics. The same group evaluated the transplacental passage of IgG in seven women with chorioamnionitis at risk of preterm delivery (116). They infused the women with 24 gm/day for 5 days. Following delivery they were able to measure normal subclass distribution of IgG in the cord blood and an increase in specific antibody to group B *Streptococci*. None of the infants showed signs of sepsis. Several subsequent studies demonstrated the safety of the infusions (117, 118) and the ability to increase the titers of specific antibody in the neonate (119).

The results of several small, controlled, but unblinded studies conducted in the late 1980s provided evidence of the ability of IVIG to prevent sepsis in neonates (100, 110). Chirico et al. (120) in Pavia, Italy, stratified 133 infants into those <1500 gm and those >1500 gm receiving intensive care and assisted ventilation. Approximately half of each group received IVIG at a dose 0.5 gm/kg/week for 4 weeks. There was no apparent effect of IVIG in the infants >1500 gm, but in the infants <1500 gm the incidence of infection was reduced from 77% to 51% and the incidence of septicemia was reduced from 20% to 5%. Although these differences were statistically significant, the high rate of infection

made it difficult to compare their experience to that of most US hospitals. In another study in Italy (121), although the mortality from sepsis decreased from 12.5% to 7.5%, the results were not statistically significant. Haque et al. in Saudi Arabia reported similar results (122). They treated 50 infants with a single dose of 120 mg/kg of Intraglobin®, a second group with two doses on days 1 and 8, and the third group was not treated. The incidence of infection in the control group was 16% whereas in the two treated groups the incidence was only 4%. Two infants in the control group died, but there was no mortality among the treated infants. The same group also studied the ability of an IgM-enriched IVIG preparation to treat septic infants (123). Two groups of 30 infants were randomized to antibiotics alone or antibiotics plus 5 ml/kg/day for four days of Pentaglobin®. The mortality rate in the control group was 20% but was only 3.3% in the infants treated with immunoglobulin. These studies confirmed the utility of IVIG in centers where the morbidity and mortality from infection are very high, but it was not clear whether similar benefits would be seen in neonatal units where the rates of infection are low.

Many of the studies in the US have shown marginal benefit of treating premature infants; this may be due to inadequate titers of antibody toward many of the pathogens responsible for infections in the neonatal population (124). Clapp et al. (125) administered IVIG to maintain a serum IgG concentration of 700 mg/dl to 115 premature infants weighing 600 to 2000 grams in a double-blind, placebo-controlled study. An additional 85 infants were not treated at parental request. There were 7 episodes of sepsis in the placebo group and 9 episodes in the group that was untreated. No infant receiving IVIG became infected. All infants who became infected had serum IgG concentrations below 400 mg/dl.

Another placebo-controlled study of 240 infants was reported by Bussel in 1990 (126). The infants weighed < 1300 gm and were randomly assigned to receive five infusions of either 1 gm of IVIG or placebo; the first four infusions were given on the first four days of life and the fifth was given on day 15. Preliminary analysis of the first 126 patients indicated that sepsis had occurred in 9 of 61 patients given IVIG and in 16 of 65 given placebo. That difference was no longer present by 70 days.

In contrast, a double-blind, placebo-controlled study of 170 infants showed no benefit (127). The infants were randomized to receive 750 mg/kg of IVIG or placebo within 72 h of admission and every 14 days until discharge. There were five systemic infections in each group and there was no effect on the incidence of necrotizing enterocolitis, local infections, length of hospitalization or need for oxygen. No differences were observed when the in-

fants were stratified into weight categories of < 1000 gm, 1000 to 1500 gm, or > 1500 gm.

A large multicenter double-blind, placebo-controlled prophylactic study was recently reported by Baker et al. (128). Five hundred eighty-eight infants weighing 500 to 1750 gm at birth were stratified as to birth weight and then randomized to receive either several doses of 500 mg/kg of IVIG or placebo. There was a significant decrease in the risk of a first nosocomial infection in the infants receiving IVIG, with a relative risk of 0.7. There was also a decrease in the mean number of hospital days in the treated infants from 68 to 62 days, but the difference was not significant except for the infected infants in whom the mean number of hospital days decreased from 101 days to 80 days.

The ability of IVIG to treat infants with early sepsis was studied in a multicenter study involving 753 neonates (129). The infants were randomized to receive 500 mg/kg of a selected IVIG or albumin. Thirty-one infants were septic, with group B *Streptococcus* and *E. coli* being the most frequently isolated organisms. During the first seven days, 5 of 17 albumin-treated, but none of the 14 IVIG-treated, infants died, but by 56 days of age there was no difference in mortality. All of the deaths in the placebo-treated infants occurred within the first week; two IVIG-treated infants died of infection and respiratory complications at 9 and 16 days of age. The lots of Sandoglobulin® used for this study were selected to have good opsonic activity for group B streptococci types Ia, II, and III, but did not have opsonic activity against *E. coli* with K1 antigen. In a smaller study of 22 infants with clinical signs of sepsis, eleven received 750 mg/kg of IVIG and eleven received placebo (130). All infants survived, but recovery of neutrophil counts and arterial oxygen tension was more rapid in the treated infants.

Fischer et al. have intensively evaluated the role of specific antibody in the treatment of neonatal infections (131, 132). Standard IVIG preparations contained varying amounts of antibody to group B streptococci and the opsonizing capacity was often very low. They prepared a hyperimmune IVIG from donors who had been immunized with group B streptococcus and demonstrated improved efficacy *in vitro* and *in vivo* in a rat model of sepsis. Clinical trials are currently underway comparing standard IVIG with the hyperimmune preparations.

In a study of septic, neutropenic premature neonates, granulocyte transfusions were more beneficial than infusions of IVIG (133). All 21 of the infants given neutrophil transfusions survived whereas only 9 infants survived of 14 who received 1000 mg/kg/day for the first three days of sepsis. The dose of IVIG was high enough to cause Fc receptor blockade, and, as it has been shown that high concentra-

tions of IgG can impair the antibacterial activity of antibiotics and increase mortality (134), perhaps the study should be repeated using lower doses or a combination of IVIG and neutrophil infusions.

Despite a great deal of effort on the part of many investigators, the role of IVIG in the prevention or treatment of neonatal sepsis is far from clear. Many of the studies suffer from serious design flaws, such as small size or non-blinding, or were improperly analyzed. Even the well conducted studies often failed to measure the levels of specific antibody to the relevant pathogens. Studies done in populations with a very high incidence of infection may not be generally applicable. However, even with all of these concerns, the overall conclusion from the studies is that the risk of death from infection is reduced when the infants are treated with IVIG. Future studies must address the problems of proper stratification of patients to determine which infants may benefit from IVIG, and the question of antibody concentrations to specific pathogens. Studies must determine to which organisms must antibody be present, what is an adequate titer and what is the proper assay to measure the antibody concentration, and what is the proper dose and schedule. Until more data are available, IVIG should not be used routinely to treat all neonates, but may be appropriate for the very low birthweight infant and as an adjunct to other modes of therapy for septic infants.

## Secondary defects of immunity

### *Transplantation*

*Bone marrow transplantation (BMT)* – The use of IVIG in bone marrow transplants (BMT) has been studied extensively, especially in relation to cytomegalovirus (CMV) infection. Patients undergoing BMT are severely immunosuppressed as a result of chemotherapy, irradiation, graft-versus-host disease (GVHD), and immunosuppressive agents used to treat GVHD (135). Infection is a common complication of BMT and often is an important factor in the overall mortality (136). Approximately 40% of patients develop interstitial pneumonia, with CMV the most common pathogen (137). Many different techniques are being employed to reduce the risk of infectious complications, including laminar flow isolation, use of CMV-negative blood products, hyper-fractionated irradiation to reduce the risk of interstitial pneumonia, use of hematopoietic growth factors such as GM-CSF to reduce the period of neutropenia, and aggressive use of antibacterial, anti-viral, and anti-fungal antibiotics (135, 138). Within this context the use of IVIG has been evaluated and appears to offer some benefit in reducing the incidence of infection and modulating GVHD, though the degree of improvement is not clear.

The early studies of IVIG were summarized by Sullivan in 1987 (139). He reviewed 12 studies, 5 of which were controlled. In those five studies, CMV infection developed in 30% of 172 patients who received IVIG and in 43% of 165 who did not. However, the incidence of interstitial pneumonia was 17% in those treated compared to 43% in those who were not. The impression of the investigators was that although the incidence of CMV infections was not significantly reduced, the severity and outcome were favorably influenced (140). This, and many of the other studies, used hyperimmune preparations so that the titer of anti-CMV antibody was much higher than that obtained using standard preparations of IVIG (141, 142). Subsequent studies indicated that it might not be necessary to use hyperimmune IVIG. In a study of 38 BMT patients treated with 1000 mg/kg of IVIG weekly for four months post-transplant, the overall incidence of CMV infections was similar to a control group of 37 patients not given IVIG (143, 144). However, symptomatic infection occurred less often, 21% compared to 46% in controls, as did interstitial pneumonia, 18% versus 46% in controls.

In a large multicenter study, 382 patients were given 500 gm/kg of IVIG weekly for 90 days then monthly for one year post-transplant (145). The effect of the IVIG depended on whether the patients were seronegative for CMV prior to transplant. Of the 61 seronegative patients, none developed interstitial pneumonitis. Of the 308 seropositive patients, 13% of the IVIG-treated patients and 22% of the untreated patients developed pneumonia. There was also a decreased risk of sepsis and local infection in the IVIG-treated patients, although the overall survival was not altered. Another observation was that 1 of the patients over 20 years of age, there was a decreased incidence and severity of GVHD in the treated patients, 34% in treated compared to 51% in controls. Despite the apparent benefit of IVIG following BMT, the mortality rate associated with interstitial pneumonia remains high. In a multicenter European study, 49 patients who had developed interstitial pneumonitis were evaluated (146). All had received Ganciclovir and IVIG in varying dose schedules. Only 31% survived, which is not significantly better than historical reports of 20% survival.

Casper et al. summarized the results of several studies of the use of IVIG in children following bone marrow transplantation (147). In a non-randomized study 29 patients received IVIG and 21 did not. Systemic infections developed in 24% of the treated patients and 67% of the controls and the overall survival was greater in the treated group. In a randomized pediatric trial, 31 patients received 500 mg/kg of IVIG weekly until Day 91 and 28 patients were

untreated and served as controls. There was a significantly lower incidence of patients who needed pressors, oxygen, and ventilatory support, and a lower incidence of fungal infections in the treated group; the mortality was less in the first 100 days but no difference was seen upon longer follow-up.

A randomized multicenter, non-blind study of the American Bone Marrow Transplant Group concluded that there was no benefit of treating with IVIG in the post BMT period (148). Eighty-two received weekly infusions of 500 mg/kg of IVIG and 88 were untreated controls. There was no difference in the incidence of clinical infection, bacteremia, or fungemia. Death from infection occurred in 4.9% of the treated group and 2.3% of the control group. The overall survival was higher in the control group, which was due to a higher incidence of veno-occlusive disease in patients receiving IVIG.

The dose of IVIG and the infusion schedule might significantly alter the outcome of therapy. Continuous infusions of IVIG resulted in higher serum levels of IgG and lower incidence of infection than did intermittent infusions (149). Most of the difference was due to bacterial and fungal infections, and the incidences of interstitial pneumonia and GVHD were not different between the two groups.

In nearly all of the studies IVIG has been used prophylactically, but it might have benefit in patients already infected. Emanuel et al. at the Memorial Sloan Kettering Cancer Center evaluated the effects of IVIG and ganciclovir in patients with CMV pneumonitis (150). Ten patients treated with ganciclovir plus high doses of IVIG, 500 mg/kg every other day for 10 doses followed by 500 mg/kg twice a week for 8 weeks, were compared to a historical control group of 11 patients treated with ganciclovir plus 400 mg/kg per day for 10 days of either hyperimmune CMV gammaglobulin or standard IVIG. All patients in the treatment group showed improvement and 70% survived, whereas none of the patients in the control group survived. The experience at the Fred Hutchinson Cancer Research Center in Seattle was similar (151). Twenty-five patients with culture and biopsy-proven CMV pneumonia following BMT were treated with ganciclovir plus cytomegalovirus immunoglobulin 400 mg/kg on Days 1, 2, and 7 and 200 mg/kg on Day 14. The survival rate was 52% (13 of 25 patients), which was significantly better than the historical control of 15% (13 of 89 patients) treated with other protocols, including 14 patients treated with IVIG alone. Three of the patients relapsed after the treatment period, and ultimately only 8 of the 25 patients survived. Another, somewhat unique study, utilized an IVIG preparation enriched for IgM and IgA (Pentaglobin®) (28). The IgM in the preparation has anti-endotoxin properties, and patients receiving Pentaglobin® were

significantly protected from dying from infection in the first 100 days post transplant. There were no deaths among 29 patients given Pentaglobin compared with 6 deaths from infection among the 34 control patients.

Several controlled studies concluded that the use of IVIG reduces the severity of CMV infections and interstitial pneumonia, but other studies have failed to show a difference. Patients have been treated with a variety of dosage schedules and other factors such as the age of the patients and other complications make comparison of the studies difficult. It is not clear if specific hyperimmune sera are needed (152), and IVIG preparations with high titers of antibody to CMV when measured by one assay such as ELISA might not have good neutralizing titers (35). Large, multicenter, blind controlled studies, with well-defined anti-CMV preparations and adequate stratification to ensure uniformity between groups, are needed to determine the proper use of IVIG in patients undergoing bone marrow transplantation.

*Solid organ transplants* – There have been few studies of the effects of IVIG in solid organ transplants. Although patients are treated with immunosuppressive drugs to prevent rejection, and thus might be expected to experience a variety of opportunistic infections, the major problem has been CMV infection (153). Schafers et al. (154) administered CMV hyperimmune globulin to 75 cardiac transplant recipients and reported a reduction in the incidence of primary CMV disease and decreased severity of reactivation disease, though the difference was not statistically significant. A similar study of patients receiving liver transplants indicated a reduced incidence of CMV infection (155). However, Dussaix & Wood (156) were not able to demonstrate a beneficial effect of prophylaxis in pediatric liver recipients, though the combination of prophylactic CMV hyperimmune globulin combined with ganciclovir reduced the severity of disease in seronegative pediatric patients. In a prospective non-blind trial of seronegative patients given livers from seropositive donors, the incidence of CMV disease was reduced from 75% in 20 historical controls to 16.7% in 18 patients given 500 mg/kg each week for six weeks (153). Further controlled studies are ongoing.

As would be expected, renal transplant recipients have been most extensively studied. In a multicenter, prospective, randomized trial, 59 CMV-negative recipients of kidneys from CMV-positive donors were randomized to receive either CMV immune globulin or no treatment (157). The incidence of CMV-associated disease was reduced from 60% to 21% in the treated patients and associated complications such as leukopenia and fungal and parasitic

superinfections were seen less commonly. That group subsequently reported a follow-up to the controlled study and an open-label study of the hyperimmune gammaglobulin with persistent benefit (158). In a randomized study utilizing standard IVIG preparations, the incidence of febrile episodes attributable to CMV was reduced from 63% to 26% and there was a significant reduction in the number of hospitalized days, which more than compensated for the cost of the IVIG (159). These results were confirmed in another prospective randomized study by the same group (160) and studies by Conti et al. (161) and Khawand et al. (162). In contrast, acyclovir plus low-dose IVIG of 300 mg/kg every two weeks did not alter the incidence of CMV infection or disease in seronegative patients given solid organ transplants from seropositive donors (163). It is possible that higher doses of standard IVIG or use of hyperimmune IVIG would have been more efficacious. If adequate doses were used, in nearly every study the severity of CMV-related disease was reduced, though the incidence of positive viral cultures was not altered. The use of IVIG in this setting appears to reduce the complications that result from transplantation and subsequent immunosuppression though further studies of the dose and schedule are urgently required.

**Burns and surgery** – Major trauma and surgery create severe stress on the body, leading to immunologic changes collectively referred to as the post-traumatic immunodeficiency syndrome (PTIDS) or postsurgery immunodeficiency syndrome (PSIDS). The effects of the trauma or surgery may be compounded by malnutrition or infection. In these syndromes there is a fall in immunoglobulins, the complement components C3, C4 and factor B, the number of circulating lymphocytes with decreases in the subpopulations CD3, CD4, CD8, and natural killer cells CD16; as the same time there is a rise in acute phase reactants, neopterin, and IL-2 receptors (164). The use of IVIG in these patients was considered both to replace specific antibodies and to modulate the inflammatory changes that occur post-trauma (165).

Open heart surgery causes profound immunologic suppression, perhaps as a result of the prolonged hypothermia, hemodilution, or anesthesia. Lozano et al. studied 40 patients undergoing bypass surgery randomized to receive 17.5 gm of pepsinated immunoglobulin given as 2.5 gm every 12 h, or no therapy (166). There were no infections in the treated group whereas 6 of 20 patients not given IVIG developed serious infections and 2 died. Not all trials have yielded beneficial results. Jesdinsky et al. (167) used a low dose, 10 g, of IVIG to treat 145 patients with fibrinopurulent peritonitis but found no clinical ben-

efit compared with a similar group of 143 patients not given IVIG. Duswald et al. administered a low dose, 2.5 g, of IVIG (Intraglobin®) prophylactically to 150 critically ill patients, but found no decrease in the incidence of wound infections, urinary tract infections, or pneumonia (168). Glinz et al. administered a much higher dose, 36 g given in three doses on Days 0, 5, and 12 after admission (169). One hundred and fifty patients were treated in a non-blind fashion and the only difference was a decrease in the incidence of radiographically-diagnosed pneumonia.

A large multicenter, double-blind study compared standard IVIG at 400 mg/kg to IVIG selected to be high in antibody to core-lipopolysaccharide to *E. coli* J5, and to placebo (170). A total of 352 patients were enrolled and 329 could be evaluated. The incidence of infection, especially pneumonia caused by gram-negative bacteria, was significantly reduced in the group receiving standard IVIG compared to placebo, but no effect was observed in the group receiving the hyperimmune IVIG. This study suggested that the use of IVIG could be helpful in preventing infections in a subset of patients who had undergone major surgical procedures. A recent study evaluated the effect of 15 g of IVIG given on the 1st and 5th postoperative day following surgery for gastrointestinal cancer (171). One hundred-fifty-nine patients considered to be at high risk for sepsis were randomly assigned to IVIG or no therapy. There was a significant reduction in the incidence of infection in the subgroup undergoing colon surgery and a trend was observed in the other surgical group; the study suggested a benefit from IVIG, but it was not statistically significant. Given the great heterogeneity of post-trauma complications, it is very important that large multicenter studies be performed to evaluate the role of IVIG in these patients.

Burns are a special form of trauma; not only is the body severely stressed, but the loss of integument provides a portal of entry for microorganisms, the damaged tissue provides a medium for them to grow, and the loss of a barrier results in significant losses of plasma proteins, particularly gammaglobulin. The losses of gammaglobulin correlated with the extent of the burn (172). A number of immunologic abnormalities have been reported, including increased production of IgG by isolated lymphocytes and variable ability to respond to tetanus toxoid (173). Even in specialized burn units infection may account for 70% of the deaths. The potential benefit of gammaglobulin and plasma in reducing infection and mortality was reported as early as 1962, well before preparations of IVIG were available (172, 174, 175). Shirani et al. attempted to determine the kinetics of infused IVIG in burn patients, but while they were able to demonstrate that infusions of 500

mg/kg twice a week could maintain normal serum IgG concentrations, their kinetic studies were difficult to interpret other than there was either rapid losses or distribution to extravascular spaces (176). Hansbrough et al. confirmed those findings and demonstrated that there was a post-burn defect in the opsonic capacity of serum, even if the IgG concentration was normal (19). The opsonic defect could be corrected by infusions of 500 mg/kg of Sandoglobulin®. Despite the theoretical utility of gammaglobulin and the early reports of benefit, all of which were before the development of burn units and antibiotics that are effective against gram-negative organisms such as *Pseudomonas*, recent controlled trials have been disappointing. Munster et al. randomly treated 20 patients with severe burns with either 500 mg/kg of IVIG for 7 days, or with albumin (177). There was a decreased incidence of positive blood cultures, but no change in mortality. In a prospective, randomized, double-blind study of 50 severely burned adults and children, there was no significant difference between treatment with IVIG at 500 mg/kg twice a week or placebo (178). Thus, despite early promise, the role of IVIG in burns has yet to be defined.

**Malignancy and chemotherapy** – Certain malignancies, particularly multiple myeloma, chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia are known to induce significant impairment in humoral immunity (179–181). In other malignancies, antibody deficiency may be induced by chemotherapy. Bacterial infections are a major cause of morbidity and mortality especially as more intense chemotherapy regimes are employed to eradicate the tumor. Intramuscular injections of gammaglobulin were given to patients with multiple myeloma in an attempt to reduce the incidence of infections (182). No difference was observed, probably because of the low amounts of IgG that could be injected and because of the hypercatabolism that occurs in patients with very high serum concentrations of IgG.

Intravenous gammaglobulin has been used in a variety of malignancies and following intensive chemotherapy as reviewed by Morell & Barandun (183). The use of IVIG reduced the incidence of pulmonary infections in a cross-over study of patients with myeloma. There was also a significant decrease in infections in patients undergoing chemotherapy for small cell carcinoma. Chronic lymphocytic leukemia is the best studied of the malignancies. Eighty-four patients were studied in a multicenter randomized controlled study (184). Patients were infused with 400 mg/kg every three weeks for a year. Patients receiving immunoglobulin had significantly fewer infections. There was no difference

in the incidence of non-bacterial infection and there was no difference in overall mortality. Besa summarized a number of studies of IVIG in CLL, noting the reduced incidence of infection as demonstrated in the collaborative study, but also beneficial effects on complications such as thrombocytopenia and hemolytic anemia that often accompany CLL (181). He also studied the effect of IVIG on leukemia activity and found that the use of IVIG resulted in a reduction of lymphocyte counts and adenopathy. The effect of IVIG was greatest early in the disease and although 78% had an initial response, in 39% the effect was only transient. Finally, even though IVIG reduced the incidence of infection, there was no influence on ultimate outcome, and Weeks et al. created a model to evaluate the effectiveness of gammaglobulin in CLL and concluded that it was not cost-effective compared to other forms of therapy (185). Thus, despite tacit approval for the use of IVIG in CLL, further studies are needed before such use should be considered routine.

**HIV infection** – The human T lymphotropic virus type III (HTLV-III) or human immunodeficiency virus is a retrovirus capable of binding to and destroying CD4+ T lymphocytes, resulting in the acquired immunodeficiency syndrome (AIDS). Infection is characterized by progressive decline in cellular immunity, but because T helper cells are destroyed, B cell function is severely affected (186). Most patients present with opportunistic infections such as *Pneumocystis pneumoniae* or *Candida albicans*, but many, particularly children, suffer from recurrent bacterial infections (187). Although immunoglobulin concentrations are usually elevated as a result of loss of T cell control and direct activation of B cells by HIV, hypogammaglobulinemia has been reported in children (188), and specific antibody formation is profoundly abnormal (189, 190). Thus, patients with HIV infection were considered to have defects similar to those seen in some patients with common variable immune deficiency.

Oleske et al. treated a small number of children with IVIG and found that the incidence of serious bacterial infections was reduced, though the ultimate mortality was not altered (191). Rubenstein et al. reported that patients treated with IVIG had an increase in the CD4/CD8 ratio and in lymphocyte transformation to phytohemagglutinin and pokeweed mitogen (192). Calvelli & Rubinstein (193) treated 14 children with an escalating dose of 50 to 300 mg/kg administered every 2 to 3 days and compared them with 27 patients not given IVIG. Only 3 febrile episodes and one septic episode occurred in the treated group compared to 26 febrile episodes and 18 episodes of sepsis in the control group. There was also a moderate improvement in CD4 counts

and in mitogen responsiveness in the treated group compared to the control which showed deterioration during the course of the study. In a small, uncontrolled study, Haque et al. (194) treated 8 HIV-infected children with 200 mg/kg/dose every 3 weeks for 12 to 26 months. After 12 months all had subjective improvement and fewer serious infections compared to the patients' own historical control period, but no control group was included. Therapy with IVIG was also useful to treat the thrombocytopenia that sometimes accompanies HIV infection (195, 196). Gupta et al. (197) demonstrated improvement in suppressor T cell function in patients infused with IVIG. Serum lactate dehydrogenase levels are elevated in patients with HIV infection and lymphoid interstitial pneumonia, irrespective of whether it is caused by *P. pneumoniae* (198). Treatment with IVIG was more effective in reducing LDH levels than was conventional therapy such as trimethoprim/sulfamethoxazole or pentamidine.

The National Institutes of Health sponsored a multicenter trial involving 376 patients at 28 centers. Patients were treated with 400 mg/kg of IVIG or a 0.1% albumin placebo every 28 days (199), (200, 201). They concluded that the administration of IVIG to patients with CD4 counts over  $0.20 \times 10^9/L$  prolonged the time patients were free of serious bacterial infections and decreased acute hospitalization. The greatest difference was seen in the reduction in the incidence of viral and minor bacterial infections (199).

#### Treatment of specific infections

**Cytomegalovirus** – Nearly all the studies of the use of IVIG to prevent or treat CMV infections have been in the transplant patients discussed in a previous section. IVIG in very high doses and in combination with ganciclovir may be effective for both prevention and treatment, but the results of studies are conflicting and well-controlled studies are necessary to determine if the specific anti-CMV antibody is capable of modifying the disease or if the use of IVIG ameliorates other infections and non-specifically reduces morbidity.

**ECHO virus meningoencephalitis** – Chronic, progressive, and often fatal infections with enteroviruses were described in patients with X-linked agammaglobulinemia more than 15 years ago (202) and the world's experience of 42 patients was summarized by McKinney et al. in 1987 (203). Infections often are characterized by signs and symptoms of acute central nervous system infection, with headache, seizures, weakness or coma, hearing loss, ataxia, and paresthesias. Virus can be isolated from spinal fluid for months to years and protein and cell

counts are persistently elevated. Many of the patients have a dermatomyositis-like syndrome with rash, fever, hepatitis, and myositis. The majority have been infected with the ECHO viruses, but in some patients coxsackievirus A or B has been isolated. Nearly all patients have had X-linked agammaglobulinemia, but a few girls, most lacking B lymphocytes and, thus, phenotypically resembling the X-linked disease, have been described. Nearly all patients were being treated with intramuscular or standard doses of intravenous gammaglobulin at the time of diagnosis. Thus, routine therapy with IVIG was not sufficient. Some patients have responded to intravenous therapy with very high doses, often 400 mg/kg/week or more (204, 205), but often patients relapse weeks or months later, especially if the dose of IVIG is reduced. Thus, permanent cure is unlikely. A number of patients who failed to improve with high doses of intravenous gammaglobulin have had reduction in viral titers and symptoms with instillation of IVIG directly into the cerebral spinal fluid through lumbar puncture (206) or via an Omaya reservoir directly into the lateral ventricle (207). Several different IVIG preparations have been used, but the use of preparations of low pH should be avoided. Initially IVIG is injected daily, but as the infection is controlled the frequency can be reduced to once a week and in some patients intermittent therapy every few months has been adequate to control the infection. In some patients, control can be achieved only with constant therapy with IVIG and  $\alpha$ -interferon (208), again emphasizing that the disease may never be eradicated with current therapy.

#### Other viral infections

**Adenovirus** – Adenovirus is a significant cause of morbidity and mortality in patients with primary immunodeficiency disorders and following bone marrow transplantation (147). One immunodeficient child lacking neutralizing antibody recovered after receiving intramuscular gammaglobulin (209). Adenovirus is frequently isolated from patients undergoing BMT, and in a small uncontrolled study 17 patients were treated with 1 to 2 g/kg/day for three days (147). Ten of the patients had either elimination of the virus or reduction in viral titer. In the 7 patients who did not respond, virus was present at autopsy in 4 of the 5 patients evaluated. Although no controlled studies have been done, IVIG should be considered for high risk patients as no specific therapy is available.

**Epstein-Barr virus (EBV)** – In normal individuals EBV causes a prolonged but self-limited infection manifest by fatigue and associated with hypergammaglobulinemia, lymphadenopathy, hepatospleno-

megaly and T cell activation. In patients with a genetic predisposition, EBV infection leads to the X-linked lymphoproliferative syndrome with either lymphoma or hypogammaglobulinemia (83). Intravenous gammaglobulin is recommended in those patients with hypogammaglobulinemia, but its use to counteract other manifestations such as lymphoproliferation has not been demonstrated (84).

Some patients complain of chronic fatigue that has been linked to chronic EBV infection; definition of the disease is difficult and the relationship to EBV or other viruses such as Herpes virus 6 has not yet been established (210–212). DuBois (213) reported improvement in 89.5% of 57 patients treated with intramuscular gammaglobulin in an uncontrolled study. No blinded, controlled studies have been done and the use of intravenous gammaglobulin has not been reported in any organized fashion.

*Respiratory syncytial virus and parainfluenza* – The popularity of IVIG for a variety of indications has again raised arguments for and against the use of gammaglobulin to prevent upper respiratory infections (214, 215). Although the data supporting the use of ISG or IVIG for common respiratory ailments is scanty, there have been attempts to evaluate the efficacy of antibody for specific viral respiratory infections. Intravenous gammaglobulin failed to eradicate para-influenza pneumonia in a child with severe combined immune deficiency (216). The use of IVIG to treat respiratory syncytial virus (RSV) infections has been studied both clinically and in animal models. Both parenteral and tracheal instillation of gammaglobulin in cotton rats decreased viral shedding and severity of illness (217, 218). Further, in uncontrolled studies in children, IVIG caused significant improvements in oxygenation and reduced shedding of virus (217). More recently, 23 high risk children with cardiopulmonary disease were treated with 500, 600, or 750 mg/kg per month of an IVIG preparation shown to have an RSV neutralizing antibody titer of 1:10,000. There were 12 RSV infections over a two year period; 11 were mild and one child receiving 500 mg/kg died of progressive RSV infection (219). Since this was only a phase I study it is not possible to assess efficacy, but the results justify initiating controlled studies in high risk patients.

*Gastrointestinal infections* – Most gastrointestinal infections are self-limiting, but in infants and immunocompromised patients organisms such as rotavirus and cryptosporidium can cause a chronic, debilitating illness (220, 221). IgA is the major immunoglobulin of the gastrointestinal tract, but orally administered IgG can survive passage through the gastrointestinal tract in an immunologically active form

(222, 223). Thus, oral administration is feasible in an effort to replace mucosal immunity. One child with immunodeficiency secondary to chemotherapy had prompt resolution of a prolonged cryptosporidial infection shortly after treatment with orally administered human serum globulin (224), and another immunodeficient child responded to feeding a hyper-immune bovine colostrum (225). However, administration of a bovine colostrum containing anti-cryptosporidia antibody failed to alter the course of cryptosporidial infection in two adults with HIV infection and another with hyper-IgM syndrome (226). Orally administered antibody may be beneficial in other enteropathic infections, such as toxigenic *E. coli* (227, 228), though these studies were conducted with immunoglobulin prepared from the colostrum of immunized cows, and no data are available regarding the efficacy of human IVIG in such infections.

The effects of orally administered gammaglobulin on rotavirus infection have been studied in animal models and clinically. Normal adults develop serum IgM, IgG, and IgA antibodies during rotavirus infection (229). As expected, IgA was the predominant antibody in the feces, but significant quantities of IgG and IgM could be detected. Interestingly, the highest quantity of IgA in the feces was found in patients with prolonged illness, suggesting that the antibody could not inhibit viral shedding.

Antibody administered to lambs prior to infection (230) or to newborn mice by immunization of the mother (231) was able to prevent symptoms when the animals were subsequently infected with rotavirus. Thus, antibody may be more important to prevent infection than to treat an established infection. In a double-blind, placebo-controlled clinical trial of oral gammaglobulin in low birth weight infants, 75 babies in a nursery where rotavirus was endemic were fed 4 ml of 16% ISG without thiomersal four times a day for one week (232). Twenty-five of the infants became infected; 14 had been fed gammaglobulin and 11 were in the placebo group. The duration of viral shedding did not differ between the groups but 4 of the placebo babies shed larger amounts of virus. Six of the 11 babies in the placebo group developed diarrhea that required a change to a low-lactose formula, whereas only one of 14 antibody fed infants had significant diarrhea.

Human IVIG does not contain high titers of anti-rotavirus antibody and hyperimmune preparations are not available. Ebina et al. utilized colostrum from cows that they immunized with human rotavirus (233). They fed 6 normal infants the immune colostrum and seven regular milk. One month later 6 of 7 infants given milk, but only 1 of 6 infants fed immune colostrum, developed diarrhea. The colostrum did not prevent viral shedding and did not

interfere with the natural immunologic response to the virus. Hilpert et al. also used a bovine milk immunoglobulin concentrate containing antibody to rotavirus to treat infants infected with rotavirus (234). They demonstrated a decrease in viral shedding and a decrease in the duration of diarrhea, but only in infants with the highest antibody titers in the stool.

An oral gammaglobulin preparation that contained 73% IgA was prepared from human serum and used in clinical trials to prevent necrotizing enterocolitis (NEC) (235, 236). Infants weighing between 800 and 2000 gm were enrolled if breast milk was not available. A total of 434 infants were randomized to receive either 600 mg of the oral Ig preparation per day in three or more doses, or formula only. Only 179 infants completed the study as many were withdrawn when breast milk became available. There were no cases of NEC in the 88 infants given the IgA-IgG preparation whereas there were 6 cases in the 91 control infants. The study was not blinded and many of the children were withdrawn, so that although the results are encouraging, they can not be considered conclusive.

**Bacterial infections and sepsis** – The use of gammaglobulin for prophylaxis of bacterial infections in immunodeficient patients is well documented, but its use for established infections is unclear. The use of IVIG in infected premature infants may decrease the mortality rate as was discussed in a previous section. In animal studies the administration of specific antibody to newborn rats infected with group B *streptococcus* significantly improved the clearance of bacteria from the blood and reduced the mortality rate (112). For an IVIG preparation to be effective, it must contain adequate titers of specific antibody and the antibody must retain opsonic activity. Not all IVIG preparations contain antibody of adequate activity, so that it may be necessary to use specific high-titered preparations if they are to be effective (237). Intravenous gammaglobulin contains antibodies to a large number of pathogens, such as K1 *E. coli* and *Klebsiella*, but thus far there have been no clinical trials evaluating efficacy against infection with these organisms.

In addition to the studies of group B streptococcal infections in infants, there have been numerous investigations of the effect of gammaglobulin on infections with *Pseudomonas*. *Pseudomonas aeruginosa* is a major cause of morbidity and mortality in burn patients, neutropenic patients, and in patients with cystic fibrosis. The use of IVIG in burn patients is discussed in another section. In an anecdotal study of two neutropenic cancer patients with *Pseudomonas aeruginosa* septicemia, there was temporally associated clinical benefit when IVIG was added to

granulocyte transfusions and antibiotics (238). The use of IVIG in patients with cystic fibrosis have been encouraging but not conclusive. A randomized, double-blind trial of IVIG at 100 mg/kg/day for 3 days in CF patients with acute pulmonary exacerbations demonstrated improvement in the pulmonary function tests, but the duration of hospitalization was not altered and there was no difference between the groups on follow-up 6 weeks later (239). A subsequent study using hyperimmune anti-*Pseudomonas* globulin showed persistent benefit (240). Ten patients with cystic fibrosis and colonization with antibiotic-resistant *Pseudomonas aeruginosa* were infused with 500 mg/kg of an IVIG preparation enriched 5-fold for antibody to *P. aeruginosa* lipopolysaccharide. Their clinical course during the admission, compared to each patient's historical control admission, was improved and the improvement persisted longer.

### Prophylaxis

The use of gammaglobulin to prevent or modify infections antedates the recognition of IgG. During the past 40 years hyperimmune sera have been recommended and used to prevent tetanus, Rh isoimmunization, and a number of viral infections including hepatitis A, hepatitis B, non-A, non-B hepatitis (hepatitis C), varicella zoster, rubella, rubella, and rabies (8, 241). In most instances the use of specific high-titered immune serum globulin (ISG) for intramuscular use is adequate. The volume used for prophylaxis is small and easily administered and the cost generally is less than if IVIG were used. However, under some circumstances the use of IVIG might be desirable. Hyperimmune gammaglobulin preparations such as tetanus immune globulin or varicella immune globulin are not readily available in small hospitals or pharmacies. Some patients might not be considered suitable candidates for intramuscular injections because of thrombocytopenia or shock that might delay absorption.

The proper dose of immune serum globulin has not been rigorously established in any of the diseases for which it is used, and the titers of specific antibodies are not determined or reported in individual lots of IVIG. Therefore, the optimal dose of IVIG to replace ISG is not known. Lee & Lederman (33) measured the titer of anti-tetanus antibody in several lots of IVIG from different manufacturers and determined that, depending on the titer of the specific lot, between 1.6 and 6 g of IVIG would be required to provide the minimum 500 IU of anti-tetanus antibody. Few other studies are available for other diseases; infusion of 4 to 6 ml/kg (200 to 300 mg/kg) resulted in anti-varicella titers equivalent to that attained with varicella-zoster immune globulin

(242). The amount of specific antibody to organisms other than tetanus might be relatively low in IVIG since the source plasma is obtained from normal healthy adults who may not have been exposed to viruses such as measles for many years. Even if the titers of some antibodies are low, an infusion of 200 to 400 mg/kg would be certain to provide an adequate amount of antibody to replace ISG in all disease states and could be used until more specific data are available.

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