

APPLICATIONS OF INTRAVENOUS IMMUNOGLOBULIN

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Summary

Intravenous immunoglobulin (IV Ig) preparations allow large amounts of IgG to be administered rapidly and painlessly. Currently, there are a number of IV IgG preparations available which differ in their manufacturing methods. However, all the licensed preparations are associated with a low incidence of adverse reactions on administration. They are used mainly for IgG replacement therapy in patients suffering from primary hypogammaglobulinaemia and other patients with antibody deficiency suffering from recurrent infections. A few patients with secondary hypogammaglobulinaemia and recurrent infections also benefit from IV IgG therapy, particularly patients with haematological malignancies. IV IgG in high dosage (> 100 g per patient) is also useful for non-immunodeficient conditions such as idiopathic thrombocytopenic purpura but widespread use in this condition is limited by the relatively short duration of IV IgG action in autoimmune disease, and by the cost of high dose IV IgG therapy.

Keywords: Intravenous immunoglobulin, hypogammaglobulinaemia, antibody deficiency, thrombocytopenia.

INTRODUCTION

The use of antibody - containing preparations from animals for passive immunisation dates back to the end of the 19th century and developments in immunoglobulin therapy for the prevention and treatment of human infections have paralleled the development of knowledge about mechanisms of immunity to infection for more than 40 years.¹ More recently, the importance of immunoglobulin preparations in the treatment of autoimmune disorders such as Idiopathic Thrombocytopenic Purpura (ITP) has been demonstrated² and has led to the application of intravenous immunoglobulin (IV Ig) therapy in autoimmune disease.

The history of the clinical use of immunoglobulin preparations provides a useful basis for an understanding of applications of intravenous immunoglobulin therapy. In the 1920s and 1930s, the purification of pneumococcal polysaccharides was followed by the development of methods for purifying anti-polysaccharide antibodies from animal sera. During the 1930s much work was done on the use of animal antibody in treating pneumococcal infection, foreshadowing IV IgG treatment of patients with primary hypogammaglobulinaemia who suffer from recurrent infections caused by encapsulated gram positive organisms. In addition, during this period, the problems of immediate reactions to intravenously administered preparations, and of allergic reactions to

animal immunoglobulins were first recognised.¹

The main advance in developing safe immunoglobulin preparations came during the Second World War when Cohn and co-workers developed methods for large scale extraction of gammaglobulins (now called immunoglobulins) based upon cold ethanol fractionation from human plasma,³ and many of the clinical uses for human immunoglobulins became established. Immunoglobulin preparations (also called antibody concentrates) consisting mainly of IgG were produced but it was soon recognised that intravenous injection of these preparations produced serious and immediate adverse reactions,⁴ especially in children who were ill with infection. Attempts to eliminate this serious problem failed, and such human immunoglobulin preparations were restricted to intramuscular administration. Until the 1970s, this restriction was an important limiting factor in the application of immunoglobulin therapy to human disease, since it limited the amount of antibody that could be administered.

In the last two decades, special methods were developed for further treatment of the IgG molecule after cold ethanol fractionation in an attempt to render it safe for intravenous use (Table 1).⁵ Early methods depended on chemical treatment of the molecule with proteolytic enzymes such as plasmin or pepsin, as it was thought that adverse reactions to intravenously administered IgG were due to

TABLE 1
IV IgG PREPARATIONS: SOME METHODS OF MANUFACTURE

Method*	Characteristics of IV IgG preparation	Manufacturer (Trade name)	Comment
Pepsin treatment	70–80% fragments. Fc region removed. Short half life. Not opsonically active.		No longer in general usage.
Plasmin treatment	50–60% fragments. Fc region removed. Short half life. Not opsonically active.		No longer in general usage.
Reduction by dithiothreitol and alkylation with iodoacetamide	>80% monomeric. Fc region intact but altered. Opsonically active. Half life slightly reduced.	Cutter Labs (Gamimmune)	No longer available
Beta-propiolactone treatment	85% monomeric IgG. Fc region intact but altered. Half life slightly reduced.	Biotest (Intraglobin)	
Incubation at pH4 and pepsin in low concentrations	>80% monomeric Fc region intact. Opsonically active.	Swiss Red Cross (Sando- globulin) Scottish National Blood Trans Service (SNBTS IV IgG)	Marketed by Sandoz
pH4 incubation	>80% monomeric. Fc region intact. Opsonically active.	Cutter Labs (Gamirune-N)	
Further purification by chromatography	More than 80% monomeric. Very low IgA content. Possible hepatitis risk.	Gammagard (Baxter/Hyland)	

*These forms of treatment are preceded by cold ethanol fractionation.

complement activation by the Fc regions of aggregated IgG molecules.⁵ As a result, there were many different attempts to produce modifications of the Fc region that did not lead to a reduced half life, as it was found that antibody preparations modified by enzyme treatment were heavily fragmented, and the enzymic removal of the Fc end of the IgG molecule reduced the half life of the modified antibody *in vivo*. Methods were thus developed for chemical modification of the IgG molecule which included (1) sulphonation of the IgG molecule and (2) reduction and alkylation, both methods resulting in destruction of the disulphide linkages within the IgG molecule and a slightly shortened half-life. Beta-propiolactone treatment was also used for modifying the IgG molecule but this also resulted in a slightly shortened half-life.

The breakthrough in IV IgG therapy came with the discovery that incubation of immunoglobulin preparations at pH4 with (or without) traces of pepsin could result in IV IgG preparation which had a normal half-life *in vivo* and which had an extremely low rate of adverse reactions.⁶ The need for pepsin is controversial and one currently available preparation with a pH4 incubation step is manufactured without the pepsin step. Although it is not clear how incubation at pH4 affects the IgG molecule, it appears to be identical to the "native" IgG molecule after pH4 treatment and fulfils the criteria for an ideal IgG preparation for intravenous use (Table 2).^{5,7}

As a result of these developments, there are a number of IV IgG preparations available throughout the world. Table 1 lists the trade names and manufacturers of some the

commonly available preparations, but availability depends on licensing regulations in each country.

ADVANTAGES OF IV IgG THERAPY

Most of the studies comparing IV IgG therapy with intramuscular (IM) administration of IgG have been performed on patients with forms of primary hypogammaglobulinaemia and in whom life-long IgG replacement therapy is required. Intramuscular (IM) IgG administration was painful and usually took place weekly. Frequently, IM administration was only partially successful in reducing respiratory tract infections to which patients were prone, and some of these patients eventually developed severe bronchiectasis. IV IgG therapy in this group of patients is associated with the absence of pain, high serum IgG levels and a reduction in the infection rate, compared with IM IgG (Table 3). It was advantageous in terms of antibiotic usage, days lost from school or work and days in which a pyrexia could be recorded.^{9,10}

The main disadvantages of IV IgG therapy are the cost of such treatment and the need for medical or nursing supervision during administration. Currently IV IgG costs about £15/g in the UK and treatment costs for IV IgG over a year for the average adult patient with primary hypogammaglobulinaemia is 52000 – £3000 in comparison with costs for IM IgG of approximately £750. There is an additional medical or nursing cost since the usual dose of IV IgG (200 mg/kg) needs to be administered over a 1 – 2 hour period. However, carefully selected patients with primary hypogammaglobulinaemia have been taught to administer IV IgG to themselves at home safely and such home administration allows the patients to avoid loss of time from work or school.^{**} For ITP therapy, the cost of IV IgG is approximately 52000 per course, but IV IgG costs for this indication should be compared with the cost of inpatient care, or surgery (in the case of bleeding patients with ITP) as these are equally high.

IV IgG PREPARATIONS AVAILABLE

In addition to different methods of modifying the IgG molecule after cold ethanol fractionation, there are four different categories of IV IgG preparations available.

1. IV IgG made from plasma from unselected blood donors which contains the full spectrum of antibodies present in the normal donor population.
2. IV IgG made from selected plasma donations that are enriched with certain antibody specificities. Examples of these "specific" IV IgG preparations are anti-cytomegalovirus (anti-CMV), anti-tetanus, anti-group-B streptococci and anti-pseudomonas IV IgG. These preparations are similar to various specific antibody preparations for intramuscular use, but have undergone the same manufacturing steps as IV IgG described above. Other than for anti-CMV (for IV use), they are generally available only on an experimental basis for selected patients, and are currently undergoing clinical trials in various research centres.²
3. Animal antibody preparations that can be given intravenously are rarely used now, but formerly included tetanus antitoxin of equine origin, anti-snake venom of equine origin and anti-lymphocyte globulin of equine or rabbit origin.
4. Monoclonal antibody preparations that are administered intravenously are usually of rodent origin. They may be used for diagnostic purposes e.g. imaging of tumours or for therapeutic reasons e.g. anti-OKT3 for reversal of renal transplant rejection. Many future developments will probably occur in this area and some potential applications are listed in Table 4. However, the main problems with these preparations at present is the formation of antibodies against the foreign molecule, leading to immune complex formation, and rapid clearance of the administered antibody. Attempts are being made to overcome these problems by either the development of human hybridomas, or the use of genetic engineering to produce "humanised" IgG molecules, or by modifications to their structure (Table 5).^{1,3}

APPLICATIONS OF IV IgG THERAPY

Treatment of infection in patients with primary immunodeficiency

Patients with recurrent infections due to primary hypogammaglobulinaemia (e.g. X-linked agammaglobulinaemia, common variable immunodeficiency, IgG subclass deficiency) benefit from IV IgG therapy with a reduction in bacterial infections and delay or postponement in the progression of structural lung damage. Similarly, patients with combined immunodeficiencies such as Severe Combined Immunodeficiency or the Wiskott-Aldrich Syndrome benefit from IV IgG therapy (Table

TABLE 2
CHARACTERISTICS OF AN IDEAL INTRAVENOUS IgG PREPARATION

No immunoglobulin aggregates

No fragmentation of the IgG molecule

As unmodified as possible

No prekallikrein activator, kallikrein or other contaminating proteases

Normal IgG subclass distribution

Normal complement binding activity

Opsonically active

Normal half life *in vitro*

Tolerated by normal and hypogammaglobulinaemic subjects at infusion rates of at least 0.1 g/kg/hour

Modified from WHO³ and Yap & McClelland⁵

TABLE 3
ADVANTAGES AND DISADVANTAGES OF INTRAVENOUS IMMUNOGLOBULIN COMPARED WITH INTRAMUSCULAR IMMUNOGLOBULIN

	IM	IV
Absorption	4-7 days	Immediate
Proteolysis at injection site	Present	Absent
Mercury exposure	Yes*	No
Adverse reactions	Rare	Rare
Volume limitations	Yes	No
Pain and local tissue injury	Yes	No
Injection frequency	Weekly	3-4 weekly
Achievability of high serum IgG levels	No	Yes
Use in patients with coagulation disorders	No	Yes
Duration**	Seconds	1-2 hours
Venous access	Not necessary	Necessary
Cost**	Low	High
Efficacy**	Moderate	Good

* depends on preparation – some intramuscular immunoglobulin preparations do not have mercury containing compounds as preservative.

** for patients receiving IgG replacement therapy for primary hypogammaglobulinaemia.

TABLE 4
SOME POTENTIAL APPLICATIONS OF MONOCLONAL ANTIBODY PREPARATIONS

Treatment of Infection:

Viruses: Hepatitis B
HIV

Bacterial: Pseudomonas aeruginosa.
Endotoxaemia due to Gram negative infection.
Haemophilus influenzae type B.

Protozoa: Pneumocystis carinii

Therapy of malignancy: chemically conjugated monoclonal antibody preparations.

Delivery of anti-tumour agents (radionuclides, toxins, drugs) to tumour sites.

Interference with growth or differentiation.

Activation of components of the immune system.

Therapy of Transplant Rejection and Graft versus Host **Disease**

Kidney transplantation

Bone marrow transplantation

Graft versus host disease

Therapy of Idiopathic Thrombocytopenic **Purpura**

Haemolytic Disease of the Newborn

Vaccination

Various applications of monoclonal anti-idiotypic antibody preparations as vaccines.

Summarised from Yap & Williams^{1 3}

TABLE 5
METHODS OF MODIFYING
MONOCLONAL ANTIBODIES

Antibody heteroconjugates
Bispecific antibodies

Single chain molecules
IgM-like antibodies
Antibodies with enhanced affinity
Chimaeric antibodies
Site directed mutagenesis of human
monoclonal antibodies
Drug antibody conjugate
Toxin antibody conjugate
Lymphokine antibody conjugate
Radionuclide antibody conjugate
Enzyme antibody conjugate

Modified from Yap & Williams^{1 3}

TABLE 6
PRIMARY IMMUNODEFICIENCIES IN
WHICH IV IgG MAY BE BENEFICIAL

Primary antibody deficiency:

X-linked hypogammaglobulinaemia
Common variable immunodeficiency
IgG subclass deficiency
Transient hypogammaglobulinaemia
of infancy (rarely)
Antibody deficiency with normal
immunoglobulin levels (very rare)

Combined immune deficiencies:

Severe combined immune deficiency
Wiskott-Aldrich syndrome
Ataxia-teleangiectasia
X-linked lymphoproliferative syndrome

6). The exact dosage and frequency of IV IgG treatment varies, but the objective of IV IgG therapy in this group of patients should be to attain a "trough" serum IgG concentration at or near the lower end of the normal range.

Our practice has been to treat patients with a dose of 200 mg/kg initially every three weeks and to increase the interval between infusions to 4 – 5 weeks if this still allows trough levels to be maintained at about 5 g/l.¹⁴ Patients with severe bronchiectasis or loss of IgG through the gut may need higher doses (400 mg/kg) given as frequently as even fortnightly. If recurrent infections despite IV IgG therapy are a problem, high dose antibiotics should be considered before increasing the dose of IgG, as high dose antibiotic regimes are less expensive and do not require admission to hospital.

More recently, the possibility of home therapy of IV IgG in patients with primary hypogammaglobulinaemia has been evaluated.¹ The selection of well-motivated patients and a detailed course of instruction for the patient is essential. Patients should be equipped for emergency self-administration of adrenaline and instructed on how to cope with adverse reactions. The co-operation and support of the patient's own home physician is essential. As a result of the development of home therapy, it has been suggested that an infusion regime of 100 mg/kg per week may be more effective at reducing infections. However, little controlled or comparative data exists between the different IgG replacement therapy regimes and, at the present time, it would seem sensible to use lower dose regimes such as 200 mg/kg every 3 – 4 weeks.⁴

One rare form of primary immunodeficiency occurs in patients who suffer from recurrent bacterial infections *inspite* of normal or raised serum immunoglobulin levels.⁵ Specific antibody deficiency with normal immunoglobulin levels is characterised by an inability to synthesise specific antibodies against certain organisms or when challenged by certain vaccines. Although difficult to diagnose, it is clear that these rare patients benefit from IV IgG therapy.

Treatment of infections in patients with secondary immunodeficiency.

Many forms of secondary immunodeficiency exist and the role of IV IgG therapy in patients with secondary immune deficiencies is controversial.⁶ Different indications have been suggested (Table 7) but in considering whether a patient is suitable for IV IgG therapy it is

important to decide whether the patient suffers from bacterial infections suggestive of antibody deficiency. Typically, the patient will suffer from recurrent upper respiratory tract infections or otitis media due to encapsulated organisms such as *Haemophilus influenzae* or *Strep. pneumoniae*. Thus patients with haematological malignancies that are accompanied by reduced serum immunoglobulin levels such as chronic lymphatic leukaemia or multiple myeloma may benefit from IV IgG, particularly during the initial stages of chemotherapy when infections are most common.

Infection with the Human Immunodeficiency Virus (HIV) is generally considered to be characterised by a severe cellular immunodeficiency, particularly in the latter stages of infection when a severe depletion of T4 (helper) lymphocytes occurs. Patients with HIV infection may also have *in vitro* and *in vivo* evidence suggestive of an antibody deficiency. For example, children with HIV infection acquired vertically from an HIV antibody positive mother or acquired in infancy may suffer from recurrent infections due to encapsulated organisms despite being hypergammaglobulinaemic. Such children benefit from IV IgG therapy at doses similar to patients with primary hypogammaglobulinaemia^{7,18} and it is possible that such therapy may delay the progression from the early symptomatic state to the development of AIDS, since a reduction in HIV core antigen levels was observed in some HIV infected children treated with IV IgG.¹⁸ In addition, although adult HIV infected patients with recurrent bacterial infections are uncommon, some of these patients appear to benefit from

TABLE 7
SECONDARY IMMUNODEFICIENCIES
IN WHICH INTRAVENOUS IgG
MAY BE BENEFICIAL

Haematological malignancies e.g. CLL, multiple myeloma.

Immunocompromised states e.g. following major surgery, trauma or chemotherapy.

Severe thermal injury.

After bone marrow transplantation.

Premature birth.

HIV infection, particularly in children.

Summarised from Yap¹⁶

IV IgG therapy at doses used for patients with primary hypogammaglobulinaemia.⁹

In addition to the above groups of patients, some patients may also have a transient deficiency of antibody. An increased incidence of severe pneumococcal infections after Bone Marrow Transplantation (BMT) in children has been reported, and some groups administer IV IgG for six months after BMT. However, IV IgG therapy is not required for conditions in which reduced serum immunoglobulin levels is not associated with recurrent infections suggestive of antibody deficiency e.g. protein losing enteropathies, the nephrotic syndrome, patients with severe thermal injury and after intensive plasmapheresis. It is likely that in conditions where IgG losses are occurring, the ability of plasma cells to synthesize specific antibodies in response to the infecting organism is still intact.

IV IgG therapy in non-immunodeficient patients

IV IgG therapy has been used for the treatment of numerous non-immunodeficient disorders (Table 8). It has been used successfully to treat Idiopathic Thrombocytopenic Purpura (ITP) and raised platelet counts occur in most patients after treatment.² However, the effect tends to be short-lived, and very large doses of IV IgG (0.4 g/kg each day for five consecutive days) are required, making the treatment very expensive – typically, for the average adult, doses as high as 120 g (costing 61800) are required. A sensible and less expensive approach is to treat the patient with a dose of 0.4 g/kg for two or three consecutive days and only continue IV IgG therapy if thrombocytopenia persists.

IV IgG therapy may also be effective in some other rare conditions in which there are specific anti-platelet antibodies, such as Post-Transfusion Purpura (PTP).² In this condition, although repeated courses of IV IgG may be required, there may be a permanent disappearance of the thrombocytopenia. Unlike the case with ITP. Unfortunately, the mechanism by which IV IgG raises the platelet counts in ITP or PTP is unknown. It has been suggested that the high dose of IgG administered causes Fc receptor blockade of the reticuloendothelial system. However, an increased clearance of immune complexes and a reduction of anti-platelet antibody levels have also been demonstrated after IV IgG therapy. Which, if any, of these mechanisms of action is important remains unclear.²¹

IV IgG therapy has also been evaluated in a number of other autoimmune conditions such as autoimmune haemolytic anaemia²² and

variable benefits have been demonstrated (Table 8). In contrast, no clear cut benefit has been shown in administering IV IgG to patients with systemic lupus erythematosus, or with rheumatoid arthritis. Because of the expense of IV IgG therapy and the great difficulty of performing satisfactory clinical trials, it is likely that the use of IV IgG in autoimmune disorders will remain limited to a few life-threatening conditions only.

Uses of specific IV IgG preparations

Various specific IV IgG preparations are currently undergoing evaluation. Anti-CMV IV IgG has been extensively evaluated in patients undergoing organ and bone marrow transplantation where severe life-threatening CMV disease may occur after the transplant. Typically, the most severely affected are CMV seronegative patients receiving a bone marrow transplant from a CMV seropositive donor. Although results are conflicting, anti-CMV IV IgG has appeared to be beneficial in some trials in the USA and in one trial in Europe.²³ It should be noted that anti-CMV IV IgG is not always necessary. We have found that if CMV seronegative patients receiving a CMV seropositive marrow transplant also receive blood products seronegative for CMV, then the rate of CMV infection is very low. Where CMV infection has occurred after BMT, it is also possible to treat the patient with anti-CMV IV IgG after diagnosis of CMV. Unfortunately, the actual degree of benefit is not easy to assess, due to the difficulty in performing well-controlled clinical trials.

A number of studies are currently being

**TABLE 8
NON-IMMUNODEFICIENT DISORDERS
IN WHICH INTRAVENOUS
IMMUNOGLOBULIN PREPARATIONS
HAVE BEEN EVALUATED**

Idiopathic thrombocytopenic purpura
Post-transfusion purpura
Autoimmune thrombocytopenia
Autoimmune neutropaenia
Autoimmune haemolytic anaemia
Kawasaki's disease
Myasthenia gravis
Guillaine-Barre syndrome
Polymyositis
Inflammatory bowel disease

carried out to evaluate the role of **anti-endotoxin IgG** preparations in patients suffering from septicaemia and shock due to Gram-negative infections – an earlier study using antiserum against endotoxin had shown a reduction in **mortality**.²⁴ These trials so far have produced conflicting data and the use of anti-endotoxin preparations are limited to patients entered into specific clinical trials. One general problem with using antibody preparations against Gram-negative infections is that they should ideally be administered early in the infection, when bacterial numbers and free endotoxin levels are low. Unfortunately, isolation and identification of Gram-negative organisms in septic patients is usually a late event and so specific antiendotoxin therapy may be relatively ineffective. It is likely that research over the next few years will define the role of antiendotoxin therapy and of specific anti-bacterial **immunoglobulin** preparations in the management of patients with septic shock. In particular, the availability of **monoclonal** anti-endotoxin antibody preparations may allow a more precise delineation of the importance of endotoxin neutralisation in the treatment of Gram-negative septic shock.

Table 9 describes the various infections for which specific IV **IgG** preparations are being evaluated. However, other than in echovirus infection in patients with X-linked **agammaglobulinaemia**, the precise role of such specific antibody preparations in the clinical management of patients remains unclear.

SAFETY OF IV IgG

Adverse reactions

Early experimental IV **IgG** preparations were associated with severe adverse reactions such

as chills, nausea, abdominal pain, flushing and headache in some patients. Janeway (1970) graphically described a severe adverse reaction that he himself suffered.' However, current licensed IV **IgG** preparations are well tolerated in high doses and adverse reactions, when they do occur, are usually minor. This low rate of adverse reactions is exemplified in a study of 37 patients with primary **hypogammaglobulinemia** receiving 1235 IV **IgG** infusions. Only 5 moderately severe adverse reactions in 4 patients occurred and all of these were directly related to the infusion rate at the first IV **IgG** infusion. Mild adverse reactions (mild pyrexia and mild rigors) also occurred in 3% of infusions and were noted particularly in initial infusions.²⁵

It is therefore important that the **manufacturers'** instructions, with respect to the infusion rate of IV **IgG** are closely followed, especially in patients with primary immunodeficiency commencing IV **IgG** therapy. Such patients have also been reported to have an increased incidence of chills and mild pyrexia following initial intravenous infusions of IV **IgG** compared with non-immunodeficient patients, especially if they have a co-existent infection," and it is important to treat these infections with antibiotics prior to commencing IV **IgG** therapy if possible.

If adverse reactions persist they can be prevented, or abolished by decreasing the rate of infusion, or by pretreatment with aspirin or an anti-histamine. Very rarely, anaphylactoid or anaphylactic reactions have been reported in patients with primary immunodeficiency who also have anti-IgA antibodies. Such patients are usually totally deficient in serum **IgA**, and should be treated with one of the IV **IgG** preparations that have a very low **IgA**

TABLE 9
INFECTIONS IN WHICH SPECIFIC ANTIBODY PREPARATIONS FOR INTRAVENOUS USE ARE CURRENTLY BEING EVALUATED

Viral Infections	Bacterial Infections
Cytomegalovirus	Group B Streptococci
Echovirus	<i>Pseudomonas aeruginosa</i>
Epstein-Barr Virus	Gram-negative bacteria
Respiratory Syncytical Virus	Patients suffering from endotoxaemia
Herpes Simplex Virus	
Vaticella – Zoster Virus	
Rotavirus	

Summarised from Stiehm¹².

content. Occasionally, when large doses are given rapidly for the treatment of ITP, there are anecdotal reports of patients suffering severe headaches. Although the mechanisms for these headaches is not clear, they can be prevented by administering the IV IgG more slowly.

Transmission of viral infections by IV IgG

One of the concerns regarding the safety of IV IgG therapy relates to the transmission of non-A, non-B Hepatitis (NANBH). In contrast to the various reports for IV IgG, IM IgG preparations have been shown not to transmit viral infections. However, it is not known exactly why intramuscular immunoglobulin preparations are free of this hazard. One possibility is that the freeze drying of the ethanolic antibody concentrate at the end of cold ethanol fractionation for the preparation of IM IgG might be virucidal.²⁶ This explanation has been used to explain why three IV IgG preparations which include one of the above virucidal steps in the manufacturing procedure, are free from the risk of NANBH transmission. However, two recent reports described NANBH transmission in licensed preparations which had a pH4/pepsin step in their preparation.^{27,28}

The transmission of NANBH to some, but not all recipients has also been observed in the majority of reports as summarised by Williams et al.²⁸ As there were no major differences in the doses of IV IgG given to patients, and as it seems unlikely that there should be unequal distribution of virus between different vials of the same homogenous batch of an IV IgG preparation, host factors may be critical in determining the outcome of exposure to virus. These factors may include previous exposure to the causative agent(s), differing cellular immunity in the exposed patient, and antibody levels against the NANBH agent present in the IV IgG batch. Alternatively, the putative NANBH virus may have been at limiting dilution.

The production of an infectious IV IgG batch could have been due to a failure of good pharmaceutical manufacturing practice (GMP) and a GMP failure was suspected as being the cause of a previous incident of NANBH transmission in the USA. Alternatively there could have been the presence of an abnormally high virus load in the starting plasma which exceeded the virus inactivation capacity of the manufacturing process. The recent introduction of a test for Hepatitis C, a recently identified putative causative virus for NANBH, may assist in avoiding this problem. Knowledge relating to the Hepatitis C

virus may also assist in the development of methods for removing or inactivating this virus. Nonetheless because of the significant though low hazard of NANBH transmission with existing IV IgG preparations, IV IgG therapy should be limited to patients in whom benefit is likely, and only licensed preparations should be used.

CONCLUSIONS

The development of safe and effective IV IgG preparations have undoubtedly transformed the lives of many patients with primary immunodeficiency. These patients no longer receive painful frequent injections and the frequency of respiratory infections suffered is decreased, thus delaying or abolishing the progression to severe bronchiectasis. For patients with ITP, the availability of IV IgG for life-threatening bleeding and its use prior to major surgery has helped management greatly. New applications for IV IgG therapy are being identified but the cost of this treatment remains an obstacle to its widespread use. However, in the next decade, it is likely that new "specific" IV IgG and monoclonal antibody preparations will be evaluated in various conditions thus fulfilling the prophecy made in 1913 by Paul Ehrlich that "we would have . . . an ideal medicament, which in the manner of magic bullets, seek out the enemy."

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