

3.8 IMMUNOGLOBULIN PREPARATIONS

Introduction

Passive immunity can be provided by administration of human immunoglobulin.¹⁻³ The protection afforded is immediate, but is transient and lasts for only a few weeks, as the half-life of IgG, the major constituent, is between 3 and 4 weeks.

There are 2 types of immunoglobulin, normal and specific. It is important to recognise that separate immunoglobulin preparations are provided for intramuscular (IM) use and for intravenous (IV) use. These have different properties, and the preparations should be given only by the recommended route. Administration of IM immunoglobulin by the IV route will lead to severe reactions.

- **Normal human immunoglobulin (NHIG)**

This is derived from the pooled plasma of blood donors. It contains antibody to microbial agents which are prevalent in the general population.

- **Specific immunoglobulins**

Specific immunoglobulin preparations are obtained from pooled blood donations from patients convalescing from the relevant infection, donors recently vaccinated with the relevant vaccine, or those who, on screening, have been found to have sufficiently high antibody concentrations. These blood-derived specific immunoglobulins therefore contain concentrations of antibody to an individual organism or toxin at a higher titre than would be present in normal immunoglobulin.

Donors of blood used for the production of NHIG and specific immunoglobulin products are screened and products treated to minimise the risk of the immunoglobulin preparations containing HIV, hepatitis A, hepatitis B or hepatitis C viruses, or parvovirus. Two dedicated pathogen inactivation steps are incorporated into the manufacturing process. A pasteurisation step is usually used during manufacture. The risk of prion transmission remains theoretical.

Potential interaction with vaccines

Live attenuated virus vaccines

- Immunoglobulin preparations can interfere with the response to **some** live attenuated virus vaccines by preventing vaccine strain viral replication after vaccine administration. Therefore, administration of live attenuated virus vaccines, such as measles and varicella vaccines (**but not zoster vaccine**), should be deferred for at least 3 months after the IM administration of NHIG, and for at least 9 months after the administration of NHIG (intravenous).⁴ For the same reason, administration of immunoglobulin products should be deferred if possible until at least 2 weeks after a vaccine has been given, unless it is essential that immunoglobulin be given. However, Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR vaccines and the two may be given at the same time in different sites with separate syringes or at any time in relation to each other (see Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.5 *Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination*).

Inactivated vaccines

- Inactivated vaccines such as tetanus, hepatitis B or rabies may be administered concurrently with immunoglobulin preparations, or at any time after, using separate syringes and separate injection sites to induce passive/active immunity. This usually would occur when there has been actual or possible acute exposure.

Availability of immunoglobulins

CSL Bioplasma supplies NHIG for IM use. Rabies immunoglobulin can be obtained only upon application from State/Territory health authorities. Respiratory syncytial virus (RSV) monoclonal antibody (Synagis; Abbott Australia) is available commercially.

The specific immunoglobulins and the CSL Bioplasma NHIG for IV use, which are derived from Australian donated plasma, can be obtained only from the Australian Red Cross Blood Service (ARCBS) with permission from a ARCBS medical officer. The Red Cross Blood Service can be contacted by telephone (ACT 02 6206 6006; NSW 02 9229 4444; NT 08 8927 7855; QLD 07 3835 1333; SA 08 8422 1200; TAS 03 6230 6230; VIC 03 9694 0111; WA 08 9325 3333). The Australian Red Cross Blood Service supplies these products free of charge.

Transport, storage and handling

All immunoglobulins must be protected from light and stored at +2°C to +8°C. Do not freeze.

Normal human immunoglobulin (NHIG) – intramuscular use

NHIG is prepared by plasma fractionation of blood collected from volunteer donors by the Australian Red Cross Blood Service. It is a sterile solution of immunoglobulin, mainly IgG, and contains those antibodies commonly present in adult human blood. In Australia, NHIG is supplied as a 16% solution, in the United States as a 16.5% solution, and in the United Kingdom as a 10% solution.

- **Normal Immunoglobulin-VF (human) (NHIG)** – CSL Bioplasma. A sterile preservative-free solution of immunoglobulin G (IgG) 160 mg/mL prepared from Australian blood donations and made available through the Australian Red Cross Blood Service. It is supplied in 2 mL and 5 mL vials for IM injection.

Administration

NHIG should be given by deep IM injection using a large (19 or 20) gauge needle. The NHIG should be introduced slowly into the muscle, to reduce pain. This product should *not* be administered intravenously because of possible severe adverse events, and hence an attempt to draw back on the syringe after IM insertion of the needle should be made in order to ensure that the needle is not in a small vessel. A special product for IV use (NHIG (intravenous)) has been developed for patients requiring large doses of immunoglobulin.

Recommendations

Immunoglobulin preparations may be given to susceptible individuals as either pre-exposure or post-exposure prophylaxis against specific infections. Normal pooled immunoglobulin contains sufficiently high antibody concentrations to be effective against hepatitis A and measles. The duration of effect of NHIG is dose-related. It is estimated that protection is maintained for 3 to 4 weeks with standard recommended doses of NHIG.

(i) Prevention of hepatitis A (see also Chapter 3.5, *Hepatitis A*)

NHIG contains sufficiently high levels of antibody against hepatitis A to be able to prevent or ameliorate infection in susceptible individuals,⁵ if administered within 2 weeks of exposure.⁶

Because the hepatitis A vaccine is readily available, there is no place for the routine use of NHIG to prevent hepatitis A in travellers. It should be given (at the same time as a dose of hepatitis A vaccine) only to those, such as non-immune aid-workers to be deployed within 2 weeks, who will be living in very inadequate circumstances.^{7,8}

(ii) Prevention of hepatitis B

See Chapter 3.6, *Hepatitis B*, under 'Management of infants born to hepatitis B carrier mothers' and 'Post-exposure prophylaxis for hepatitis B'.

(iii) Prevention of measles (see also Chapter 3.11, *Measles*)

NHIG contains a sufficiently high concentration of antibody against measles to be able to prevent or ameliorate infection in susceptible individuals. NHIG should be given as soon as possible and within 7 days of exposure. Passive protection against measles particularly may be required if the exposed individual has an underlying immunological disorder (HIV/AIDS, immunosuppressive therapy), or to control an outbreak of measles among non-immunised individuals, eg. in a childcare centre. The use of NHIG should be considered in HIV-positive individuals exposed to a patient with measles.

(iv) Prevention of varicella (see also Chapter 3.24, *Varicella*)

Zoster immunoglobulin (ZIG) is able to prevent or ameliorate varicella in infants <1 month of age, in children who are being treated with immunosuppressive therapy, and in pregnant women.^{9,10} ZIG should be given as soon as possible, and preferably within 96 hours, after exposure. ZIG is recommended for non-immune HIV-positive individuals up to 7 days after exposure to clinical cases of either varicella or zoster.

If ZIG is unavailable, large doses of NHIG can be given intramuscularly. This does not necessarily prevent varicella, but it lessens the severity of the disease. The dose of NHIG is 0.4–1.0 mL per kg body weight given by the IM route.

(v) Immune deficiency

Patients with abnormal antibody production (primary hypogammaglobulinaemia, multiple myeloma, chronic lymphoblastic leukaemia) are usually treated with the IV preparation of normal human immunoglobulin (NHIG (intravenous)).²

However, in some cases, NHIG is given by IM injection in a dose of 400–600 mg/kg (0.4–0.6 g/kg) every 2 to 4 weeks. The aim of therapy is to maintain serum IgG levels above 6 g/L. Some patients may receive the IM (160 mg/mL) preparation subcutaneously.

NB. Skin tests with NHIG should not be undertaken. The intradermal injection of concentrated immunoglobulin causes a localised area of inflammation which can be misinterpreted as a positive allergic reaction. True allergic responses to NHIG given by IM injection are extremely rare.

Contraindications

Hypersensitivity reactions occur rarely but may be more common in patients receiving repeated injections. It is recommended that NHIG should not be given to individuals with absolute IgA deficiency, as the small amounts of IgA in NHIG could theoretically lead to the development of anti-IgA antibodies in these individuals. NHIG should not be administered to individuals who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

Adverse events and precautions

Local tenderness, erythema and muscle stiffness at the site of injection sometimes occurs and may persist for several hours after injection. Systemic adverse events such as mild pyrexia, malaise, drowsiness, urticaria and angioedema may occur occasionally. Skin lesions, headache, dizziness, nausea, general hypersensitivity reactions and convulsions may occur rarely.

Anaphylaxis following an injection of NHIG is very rare, but has been reported. Anaphylaxis is more likely to occur if NHIG for IM use is inadvertently given intravenously.

Normal human immunoglobulin (NHIG) – intravenous use

Normal human immunoglobulin (intravenous) is usually abbreviated as NHIG (intravenous).

- **Intragam P** – CSL Bioplasma. A sterile preservative-free solution of immunoglobulin G (IgG) 60 mg/mL prepared from Australian blood donations and made available through the Australian Red Cross Blood Service. Intragam P contains only trace amounts of IgA, and the final solution contains 100 mg/mL maltose. It is supplied as 3 g in 50 mL and 12 g in 200 mL bottles (for intravenous use).
- **Sandoglobulin NF liquid** – CSL Bioplasma (sterile preservative-free solution of immunoglobulin G (IgG), 120 mg/mL). It is supplied as 6 g in 50 mL and 12 g in 100 mL bottles (for intravenous use). A sterile lyophilised preparation for reconstitution, containing human gammaglobulin. The product is reconstituted with sodium chloride 0.9% solution to a sterile 3% or 6% solution. Available in 6 g vials (for intravenous use).
- **Octagam** – Octapharma. A sterile preservative-free solution of immunoglobulin G (IgG) 50 mg/mL prepared from multiple blood donors. It is supplied as 1 g in 20 mL vials, and as bottles of 2.5 g in 50 mL, 5 g in 100 mL and 10 g in 200 mL (for intravenous use).

The available NHIG (intravenous) preparations in Australia have different recommendations for dosage and administration and the product information must be consulted before the use of each individual product. The text below provides an overview of dosage and administration for NHIG (intravenous).

Dosage and administration

The infusion should be commenced slowly and the rate increased gradually. Patients should be closely observed for the duration of the infusion. The patient's pulse, blood pressure and respiration rate should be recorded at 15-minute intervals, and their temperature every hour. All these observations should also be made and recorded before the commencement of the infusion.

The dose for replacement therapy in individuals with immune deficiency is 0.4–0.6 g/kg every 3 to 4 weeks. In Kawasaki disease, a single dose of 2 g/kg given over at least 6 to 8 hours is recommended, repeated once if fever fails to resolve within 48 hours. Doses should be calculated to the nearest (next highest) bottle so as not to waste any immunoglobulin. Giving slightly more than the calculated dose per kilogram will not be harmful.

Recommendations

(i) Antibody deficiency disorders

NHIG (intravenous) is indicated for patients with antibody deficiency disorders requiring large doses of immunoglobulin. Therapy in these patients is usually administered at monthly intervals. NHIG (intravenous) produces higher serum concentrations of IgG after administration than the IM preparation.²

(ii) Kawasaki disease

In clinical studies, NHIG (intravenous) has been found to be effective in the acute phase of Kawasaki disease, as it reduces the risk of coronary artery involvement, and is associated with more rapid resolution of other acute phase features of the disease.¹¹⁻¹⁵

(iii) Other uses

NHIG (intravenous) has been used in the management of immune thrombocytopenia,¹⁶ Guillain-Barré syndrome,^{17,18} chronic inflammatory demyelinating polyneuropathy,¹⁸ toxic shock syndrome,¹⁹ post-transfusion purpura, in patients with bacterial infections associated with secondary immunodeficiency, and in other inflammatory and infective disorders.³

(NB. Some recommendations in this section are not included in the current registered indications for Intragam P. Potential users of NHIG (intravenous) in these circumstances should consult the Australian Red Cross Blood Service or the manufacturer.)

Contraindications

Individuals who are known to have had an anaphylactic or severe systemic response to NHIG should not receive further immunoglobulin. Individuals with selective IgA deficiency should not receive immunoglobulin preparations.

Adverse events and precautions

Adverse events with NHIG (intravenous) consist of shivering, headache, chest and back pains and moderate pyrexia. Severe headache, sometimes attributed to aseptic meningitis, has also been observed with NHIG (intravenous). This can be ameliorated by slowing the infusion or by mixing the 60 mg/mL preparation with an equal volume of normal saline before administration. There have been isolated reports of renal dysfunction and acute renal failure following the administration of NHIG (intravenous). To date, anaphylactic shock has not been experienced with NHIG (intravenous). Subjects with absolute selective IgA deficiency have an increased risk of severe adverse events following NHIG (intravenous).

Specific immunoglobulins

These products are used to protect individuals against specific microbial agents such as hepatitis B,²⁰ rabies and varicella-zoster viruses,^{9,10} and tetanus toxin. Each of these specific immunoglobulins is described in more detail in this *Handbook* in the chapter or section relevant to these specific infections.

In addition, specific immunoglobulins are available for botulism, cytomegalovirus (CMV) and respiratory syncytial virus (RSV) as described below. Adverse events and storage requirements for these specific immunoglobulins are similar to those for NHIG (IM) and, therefore, are not repeated here.

Botulism antitoxin (formerly known as Botulism Immune Globulin, BIG)

Equine antitoxin made in horses has long been used in the treatment of adult botulism, but has not been shown to be effective in infant botulism.²¹

Equine antitoxin is manufactured by major vaccine producing companies such as Chiron. Use in Australia is governed by the Therapeutic Goods Administration's Special Access Scheme and physicians wishing to access this stock should initially contact their State/Territory health authority. Hypersensitivity, presenting as fever, serum sickness or anaphylaxis, may follow its use. Skin testing followed by appropriate dosing should be administered according to the manufacturer's instructions.

A new intravenous botulinum antitoxin, produced in the USA, reduced the duration of mechanical ventilation and hospitalisation significantly in infant botulism.²² It is not currently registered in Australia, but is registered by the US FDA. The sponsor is Californian Department of Health Services. Access to this product should be sought through the Special Access Scheme.

CMV immunoglobulin

CMV immunoglobulin is indicated for the prevention of CMV infection in immunodeficient people at high risk of severe CMV infection, such as after bone marrow and renal transplants.²³⁻³¹ The treatment of established CMV infection is primarily with antivirals such as ganciclovir, and there is scant evidence that the addition of CMV immunoglobulin improves outcome.^{25,26,28} It would seem most logical to reserve the use of CMV immunoglobulin to treat established CMV infection in those patients with hypogammaglobulinaemia.

The product contains no antibacterial agent, and so it must be used immediately after opening. Any unused portion must be discarded. If the solution has been frozen, it must not be used. If the use of CMV immunoglobulin is contemplated, detailed protocols for administration and management of adverse events should be consulted, in addition to the Product Information.

- **CMV Immunoglobulin-VF (human)** – CSL Bioplasma (sterile solution of immunoglobulin prepared from human plasma containing high levels of antibody to CMV). The plasma protein content is approximately 60 mg/mL of which at least 98% is IgG immunoglobulin with a CMV immunoglobulin activity of 1.5 million CMV units per vial. Maltose is added to achieve isotonicity.

RSV immunoglobulin

Several clinical studies of immunoglobulin against RSV have been conducted overseas using hyperimmune polyclonal RSV immunoglobulin (RSVIG) derived from blood donations.³²⁻³⁴ It has been shown to reduce the incidence and severity of RSV infections when given prophylactically in some babies and infants at high risk of severe infection. Benefit has been shown for babies and infants with bronchopulmonary dysplasia (BPD), for those with prematurity without BPD, and children with haemodynamically significant congenital heart disease.^{34,35} RSVIG has caused severe cyanotic episodes and poor outcome after surgery in children with congenital heart disease and is contraindicated in such children.³⁶ RSVIG is not registered in Australia.

A humanised mouse monoclonal antibody to RSV produced by cultured cells – palivizumab – is now registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. This product is given by IM injection each month during periods of anticipated risk of RSV. Palivizumab was found to reduce the absolute risk of hospitalisation from about 10% to about 5% for babies born prematurely,³⁷ for babies with BPD,³⁷ and also for babies with haemodynamically significant congenital heart disease.³⁵ It has not been shown to reduce the incidence of more severe outcomes such as the need for ventilation, nor has it been shown to reduce mortality.^{35,37} Palivizumab is more effective and less costly than RSVIG, but its cost is still prohibitive. Cost-effectiveness analyses have not shown palivizumab to be cost-beneficial, and even analysis of sub-groups of children at high risk has not shown a single subgroup where prophylaxis results in net savings.^{38,39}

- **Synagis** – Abbott Australia (palivizumab). Supplied in single-use vials of powder, to be reconstituted with sterile water for injection; 50 mg in 4 mL vial; 100 mg in 10 mL vial.

Dosage and administration

Palivizumab is administered by IM injection preferably in the anterolateral thigh, in a dose of 15 mg/kg once a month. Where possible, the first dose should be administered before commencement of the RSV season.

Use in pregnancy

Refer to Chapter 2.3, *Groups with special vaccination requirements*, Table 2.3.1 *Vaccinations in pregnancy*.

References

Full reference list available on the electronic *Handbook* or website <http://immunise.health.gov.au>.