PART 5 PASSIVE IMMUNISATION

5.1 PASSIVE IMMUNISATION USING IMMUNOGLOBULIN PREPARATIONS

Immunoglobulin preparations are used to provide passive immunisation, that is, the direct administration of antibodies to a non-immune person to provide immediate protection against infection or disease.

Immunoglobulin infusions are also indicated for some immunocompromised persons who are antibody-deficient. In addition, immunoglobulins are also used in the treatment of a number of specific immune-mediated conditions in order to modulate the disease course. For further information regarding the use of intravenous immunoglobulins, refer to Criteria for the clinical use of intravenous immunoglobulin in Australia (www.nba.gov.au/ivig/index.html).

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. For more information on intravenous immunoglobulin, refer to Criteria for the clinical use of intravenous immunoglobulin in Australia.

There are two types of immunoglobulin:

- normal human immunoglobulin
- specific immunoglobulins.

Normal human immunoglobulin (NHIG) is derived from the pooled plasma of blood donors. It contains antibody to microbial agents that are prevalent in the general population.

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 the products are 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 (see www.transfusion.com.au/adverse_events/risks/estimates for further details).

5.1.1 Availability of immunoglobulins

CSL Limited supplies NHIG for IM use both directly to hospitals and to the Australian Red Cross Blood Service. Rabies immunoglobulin, tetanus immunoglobulin and botulism antitoxin can only be obtained by application to state/territory health authorities. Respiratory syncytial virus (RSV) monoclonal antibody (Synagis; Abbott Australia) is available commercially.

Other specific immunoglobulins (for hepatitis B, cytomegalovirus, tetanus and varicella-zoster), which are derived from Australian donated plasma, can be obtained only from the Australian Red Cross Blood Service with permission from an Australian Red Cross Blood Service medical officer. The Australian Red Cross Blood Service supplies these products free of charge.

The Blood Service can be contacted by telephone nationally on 13 14 95; callers will then be connected to the relevant state or territory Australian Red Cross Blood Service branch.

Individual state or territory contact numbers:

- Australian Capital Territory 02 6206 6024
- New South Wales 1300 478 348
- Northern Territory 08 8928 5116
- Queensland 07 3838 9010
- South Australia 08 8422 1201
Store all immunoglobulins at +2°C to +8°C. Do not freeze. Protect from light.

**5.1.3 Normal human immunoglobulin for intramuscular use**

Normal human immunoglobulin (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 and made available through the Australian Red Cross Blood Service.

- **Normal Immunoglobulin-VF (human)** (NHIG; for intramuscular use) – CSL Limited. 160 mg/mL immunoglobulin (mainly IgG) prepared from Australian blood donations. Supplied in 2 mL and 5 mL vials. Also contains glycine.

**Administration**

NHIG should be given by deep IM injection, using an appropriately sized needle. The NHIG should be introduced slowly into the muscle, to reduce pain. This product must 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. For further information regarding the use of intravenous immunoglobulins, refer to **Criteria for the clinical use of intravenous immunoglobulin in Australia**.1

**Recommendations**

Immunoglobulin preparations may be given to susceptible persons, 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. Both hepatitis A and measles are notifiable diseases and further instructions about their management and the need for immunoglobulin can be found in national guidelines (www.health.gov.au/cdnasongs) and obtained from state/territory public health authorities (see Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

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.

**Prevention of hepatitis A**

Hepatitis A vaccination (see 4.4 Hepatitis A) is recommended in preference to NHIG for post-exposure hepatitis A prophylaxis in persons ≥12 months of age who are immunocompetent.

NHIG can be used when hepatitis A vaccine administration is contraindicated, in infants <12 months of age, or in persons who are immunocompromised and who might not mount a sufficient response following vaccination.2 NHIG contains sufficiently high levels of antibody against hepatitis A to be able to prevent or ameliorate infection in susceptible persons, if administered within 2 weeks of exposure.2

**Prevention of measles**

Measles vaccination (see 4.9 Measles) within 72 hours of case contact is recommended in preference to NHIG for post-exposure measles prophylaxis in many instances (see Table 4.9.2 in 4.9 Measles).

NHIG contains a sufficiently high concentration of antibody against measles to be able to prevent or ameliorate infection in susceptible persons. NHIG should be given as soon as possible and within 7 days of exposure.3 Passive protection, against measles particularly, may be required if the exposed person has an underlying immunological disorder (HIV/AIDS, immunosuppressive therapy), or to control an outbreak of measles among non-immunised persons, for example, in a childcare centre. The use of NHIG should be considered in HIV-positive persons exposed to a patient with measles.

**Immune deficiency**

Patients with abnormal antibody production (primary hypogammaglobulinaemia, multiple myeloma, chronic lymphoblastic leukaemia) usually receive therapy with the IV preparation of normal human immunoglobulin (NHIG
[intravenous]). However, in some cases, NHIG is given by IM injection. 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. For further information regarding the use of intravenous immunoglobulins, refer to Criteria for the clinical use of intravenous immunoglobulin in Australia.¹

Note: 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.

5.1.4 Specific immunoglobulins

Specific immunoglobulins are used to protect against specific microbial agents such as hepatitis B, rabies and varicella-zoster viruses, and tetanus. Further instructions about the management of these diseases and the need for immunoglobulin should be obtained from state/territory public health authorities (see Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control), and the national guidelines for management of disease from rabies and other lyssaviruses, including Australian bat lyssavirus (www.health.gov.au/cdnasongs).

Specific immunoglobulins for botulism and cytomegalovirus (CMV) and a monoclonal antibody preparation for respiratory syncytial virus (RSV) are available as described below. Potential interactions, adverse events and storage requirements for these specific immunoglobulins are similar to those for NHIG (IM).

**Hepatitis B specific immunoglobulin**

Hepatitis B specific immunoglobulin (HBIG) is prepared from plasma donated through routine blood bank collection. Stocks of HBIG are very limited, and use should be strictly reserved for those who are at high risk, such as babies born to mothers with chronic hepatitis B infection and non-immune persons who are exposed through occupational exposure to the blood of unidentified persons, or to persons who are chronically infected with hepatitis B or whose hepatitis status cannot be ascertained in time.⁴ Requests for HBIG should be directed to the Australian Red Cross Blood Service in your state/territory (see 5.1.1 Availability of immunoglobulins above).

See 4.5 Hepatitis B, ‘Management of infants born to mothers who are HBsAg-positive’ in 4.5.7 Recommendations and 4.5.11 Public health management of hepatitis B, for more information.

**Rabies specific immunoglobulin**

Rabies specific immunoglobulin (HRIG) is prepared from the plasma of hyperimmunised human donors. HRIG is only administered in persons who have not received a previous course of rabies vaccine. HRIG is also administered as part of the post-exposure prophylaxis used following potential Australian bat lyssavirus or other lyssaviruses exposures in previously unvaccinated persons.⁵ A single dose of HRIG is given to provide localised anti-rabies antibody protection while the patient responds to the rabies vaccine. It should be given at the same time as the 1st post-exposure dose of vaccine (day 0). If not given with the 1st vaccine dose, it may be given up to day 7. From day 8 onwards, an antibody response to rabies vaccine is presumed to have occurred.

The dose of HRIG is based on body mass and should be infiltrated in and around all wounds, using as much of the calculated HRIG dose as possible. The remainder of the HRIG dose should be administered intramuscularly at a site away from the injection site of rabies vaccine.

See 4.16 Rabies and other lyssaviruses (including Australian bat lyssavirus) for more information.

**Varicella-zoster specific immunoglobulin**

Zoster immunoglobulin (ZIG) is highly efficacious, but is often in short supply. Normal high-titre zoster immunoglobulin is available from the Australian Red Cross Blood Service on a restricted basis for the prevention of varicella in high-risk subjects who report a significant exposure to varicella or herpes 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. ZIG has no proven use in the treatment of established varicella or zoster infection. ZIG must be given early in the incubation period (within 96 hours of exposure), but may have some efficacy if administered out to as late as 10 days post exposure. 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.⁶ ⁷ Patients suffering from primary or acquired diseases associated with cellular immune deficiency and those receiving immunosuppressive therapy should be tested for varicella-zoster antibodies following contact with a person with confirmed varicella. However, this should not delay ZIG administration, preferably within 96 hours and up to 10 days after initial exposure.⁷

See 4.22 Varicella for more information.
**Botulism antitoxin**

An equine antitoxin (derived from horses) has long been used in the treatment of adult botulism, but has not been shown to be effective in infant botulism. Equine antitoxin is manufactured by pharmaceutical companies such as Chiron. Use in Australia is governed by the Therapeutic Goods Administration’s Special Access Scheme and physicians wishing to access this product should initially contact the relevant state/territory health authority (see Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control). Hypersensitivity, presenting as fever, serum sickness or anaphylaxis, may follow the use of equine antitoxin. Skin testing followed by appropriate dosing should be administered according to the manufacturer’s instructions.

An intravenous botulinum antitoxin, produced in the United States (BabyBIG; its sponsor is the Californian Department of Health Services), significantly reduces the duration of mechanical ventilation and hospitalisation in infant’s with botulism. This product has been administered to Australian children with infant botulism. It is not currently registered in Australia, but is registered by the United States Food and Drug Authority. Access to this product should be sought through the TGA’s Special Access Scheme.

**Cytomegalovirus immunoglobulin**

Cytomegalovirus (CMV) immunoglobulin is indicated for the prevention of CMV infection in immunocompromised persons at high risk of severe CMV disease, such as after bone marrow and renal transplants. The treatment of established CMV infection and disease is primarily with antivirals, such as ganciclovir or valganciclovir, and there is contradictory evidence whether the addition of CMV immunoglobulin improves outcome.

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 Limited. 55–65 mg/mL immunoglobulin (mainly IgG) prepared from human plasma with high levels of antibody to CMV. Single vials contain 1.5 million units of CMV immunoglobulin activity. Contains maltose.

**Respiratory syncytial virus monoclonal antibodies**

A humanised mouse monoclonal antibody to respiratory syncytial virus (RSV) produced by cultured cells, palivizumab, is registered in Australia for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. There is no consensus regarding the use of palivizumab in Australia. This product is given by IM injection each month to children at high risk of severe RSV disease, during the seasonal period of exposure to RSV. Palivizumab has been found to reduce the absolute risk of hospitalisation from about 10% to about 5% for babies born prematurely, for babies with chronic neonatal lung disease, and also for babies with haemodynamically significant congenital heart disease, particularly when complicated by large left-to-right shunts leading to pulmonary hypertension. 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. There are currently a number of clinical trials assessing a recombinant humanised antibody, motavizumab.

- **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.

The dose of palivizumab is 15 mg/kg once a month, to be given by IM injection, preferably in the anterolateral thigh. Where possible, the 1st dose should be administered before commencement of the RSV season.

**Tetanus immunoglobulin**

Tetanus immunoglobulin (human) for intramuscular use

Tetanus immunoglobulin (TIG) should be used for passive protection of persons who have sustained a tetanus-prone wound, where the person has not previously received 3 or more doses of a tetanus toxoid-containing vaccine or where there is doubt about their tetanus vaccination status. In persons who have a humoral immune deficiency, TIG should be provided after a tetanus-prone injury, regardless of the time since their last dose of tetanus-containing vaccine. TIG provides immediate protection that lasts for a period of 3 to 4 weeks. For wounds not categorised as tetanus-prone, such as clean cuts, TIG is unnecessary. Detailed information on appropriate tetanus prophylaxis measures in wound management, including use of TIG, are outlined in Table 4.19.1 in 4.19 Tetanus.
The recommended dose for TIG is 250 IU, to be given by IM injection as soon as practicable after the injury. If more than 24 hours have elapsed, 500 IU should be given. Because of its viscosity, TIG should be given to adults using a 21 gauge needle. For children, it can be given slowly using a 23 gauge needle. A tetanus toxoid-containing vaccine should be given at the same time in the opposite limb with a separate syringe, and arrangements should be made to complete the full course of tetanus toxoid-containing vaccinations. Details for accessing TIG should be obtained from the Australian Red Cross Blood Service (see 5.1.1 Availability of immunoglobulins above).

**Tetanus immunoglobulin (human) for intravenous use**

- **Tetanus Immunoglobulin-VF (human, for intravenous use)** – CSL Limited. 55–65 mg/mL immunoglobulin (mainly IgG) prepared from human plasma containing high levels of antibody to the toxin of *Clostridium tetani*. Single vials containing 4000 IU human tetanus antitoxin. Contains maltose.

Tetanus immunoglobulin for IV use (TIVG) is used in the management of clinical tetanus. The recommended dose is 4000 IU, to be given by slow intravenous infusion. Detailed protocols for administration of this product and management of adverse events should be consulted if its use is contemplated. Requests for TIVG should be directed to the Australian Red Cross Blood Service in your state/territory (see 5.1.1 Availability of immunoglobulins above).

**Diphtheria antitoxin**

Diphtheria antitoxin is prepared by immunising horses against the toxin produced by *Corynebacterium diphtheriae*. Advice should be sought with respect to diphtheria antitoxin access and dosage, and special arrangements made if hypersensitivity is suspected; this can be coordinated through the relevant state/territory health authority (see Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

### 5.1.5 Potential interaction with vaccines

**Live attenuated viral vaccines**

Immunoglobulin preparations can interfere with the response to certain live attenuated viral vaccines by preventing vaccine virus replication after administration. Therefore, administration of live attenuated viral vaccines, such as measles and varicella vaccines (but not rotavirus, zoster or yellow fever vaccines), should be deferred, dependent on the clinical status of the patient, for at least 3 months after the IM administration of NHIG, and for at least 8 months after the administration of intravenous NHIG. For detailed information on recommended intervals, see 3.3 Groups with special vaccination requirements, Table 3.3.6 Recommended intervals between either immunoglobulins or blood products and MMR, MMRV or varicella vaccination. For the same reason, if vaccination has occurred, administration of immunoglobulin products should be deferred if possible until at least 3 weeks after a measles-containing or varicella-containing vaccine has been given, unless it is essential that immunoglobulin be administered. However, Rh (D) immunoglobulin (anti-D) does not interfere with the antibody response to MMR- or varicella-containing 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 3.3 Groups with special vaccination requirements, Table 3.3.6 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 before or after receipt of immunoglobulin, using separate syringes and separate injection sites. This usually would occur when there has been actual or possible acute exposure to one of these infectious agents.

### 5.1.6 Use in pregnancy

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

### 5.1.7 Contraindications

Hypersensitivity reactions to immunoglobulin preparations occur rarely but may be more common in patients receiving repeated injections. Intramuscular immunoglobulins should not be administered to persons who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

### 5.1.8 Adverse events and precautions

Local tenderness, erythema and muscle stiffness at the site of injection occur very commonly (in over 10% of recipients) and may persist for several hours after injection. Systemic adverse events such as mild pyrexia, malaise,
drowsiness, urticaria and angioedema are uncommon, occurring in fewer than 1% of recipients). 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.

References
A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


