Appendix 6: Passive immunisation

A6.1 Introduction

Passive immunisation involves administering pre-formed antibody as human immunoglobulin to a recipient who is thought to have either no natural immunity to one or more infections, or who has impaired antibody production. CSL Behring Australia is the primary manufacturer of immunoglobulin products for the New Zealand Blood Service (NZBS). These products are prepared by fractionating large pools of plasma collected from blood donors to NZBS.

In New Zealand, blood donations are only collected from voluntary, unpaid donors who are in good health and who do not have any conditions identifiable by the standard questionnaire that all blood donors complete or by the mandatory testing for HIV/AIDS, hepatitis B, hepatitis C and syphilis on each donation. Blood donations are only used if the tests show no evidence that these infections are present. Similar standards apply to the manufacture of rabies immunoglobulin (RIG), which is obtained from an overseas commercial source but is not registered as a medicine in New Zealand.

A6.2 Preparations available in New Zealand

Immunoglobulin products available in New Zealand include human normal immunoglobulin for intramuscular (IM) use, specific immunoglobulins for intramuscular use, human normal immunoglobulin for intravenous use (IVIG) and human normal immunoglobulin for subcutaneous use (SCIG). All of these products have an excellent safety record in both Australia and New Zealand.

A6.2.1 Human normal immunoglobulin for intramuscular use

Human normal immunoglobulin for intramuscular use (available as Normal Immunoglobulin-VF) is a sterile, preservative-free, pasteurised solution containing 160 mg/mL human plasma proteins and 22.5 mg/mL glycine. The solution has a pH of 6.6. At least 98 percent of the protein comprises immunoglobulins, mainly immunoglobulin G (IgG). Normal Immunoglobulin-VF is intended for IM injection and is available in 5 mL preservative-free vials. It is prepared by Cohn cold ethanol fractionation of human plasma. The manufacturing process involves specific viral removal steps to reduce the possibility of virus transmission, and includes pasteurisation for viral inactivation and nanofiltration for virus removal.

A6.2.2 Specific immunoglobulin for intramuscular use

Specific human immunoglobulin preparations for IM use are available, including those for tetanus, hepatitis B, varicella zoster and anti-D. These are manufactured from plasma pools containing donations from individuals known to have high levels of the appropriate antibody. These preparations are available in single vials containing the specific antibody. The volume of the product will be determined by the potency for the appropriate antibody. In unusual circumstances, when supplies of specific immunoglobulin products manufactured from New Zealand plasma are not available, commercial products from alternative donor sources may be supplied by NZBS.

RIG is imported from a commercial source and is held at NZBS sites in Auckland, Christchurch and Wellington. The product is not registered as a medicine in New Zealand. It may be accessed and supplied under section 29 of the Medicines Act 1981 after discussion with an NZBS medical officer.

A6.2.3 Human normal immunoglobulin for intravenous use

The current human normal immunoglobulins for intravenous use in New Zealand are Intragam P and Privigen. Intragam P is produced by CSL Behring Australia and Privigen is produced by CSL Behring in the US. The latter commercial product has been introduced as stocks of IVIG from New Zealand plasma have not been sufficient to meet overall clinical requests for IVIG.

Intragam P is a sterile, preservative-free solution containing 6 g of human protein and 10 g of maltose in each 100 mL. The solution has a pH of 4.25. Isotonicity is achieved by the addition of maltose. At least 98 percent of the protein has the electrophoretic mobility of IgG. At least 90 percent of the protein is IgG monomer and dimer. Intragam P contains only trace amounts of immunoglobulin A (IgA) (nominally <0.025 mg/mL).

Intragam P and Privigen are produced by chromatographic fractionation of large pools of human plasma obtained from voluntary blood donors. The protein has not been chemically or enzymatically modified. The manufacturing process contains special steps to reduce the possibility of virus transmission, including pasteurisation (heating at 60°C for 10 hours) and incubation at low pH.

Note: In New Zealand, Intragam P is used to provide intravenous (high dose) tetanus immunoglobulin. Because the level of immunoglobulin in each batch varies and this indication is not included in the product registration, consultation with an NZBS medical officer is required prior to issuing a prescription.[1]

Privigen is a sterile, preservative-free 10 percent solution containing 10 g/100 mL of normal immunoglobulin; it is available in 50 mL, 100 mL and 200 mL vials. The solution has a pH of approximately 4.8, has a low sodium content, contains 250 mmol/L of proline, a non-essential amino acid, as a stabiliser and is approximately isotonic. It contains no carbohydrate stabiliser.

Privigen is made by cold ethanol fractionation, octanoic acid fractionation and anion exchange chromatography of large pools of human plasma obtained from blood donors in Europe and the US. The distribution of IgG subclasses in Privigen is similar to that in plasma;

only trace amount of IgA are present, typically <0.025 mg/mL. The protein has not been enzymatically modified. The manufacturing process involves special steps to reduce the possibility of virus transmission including pasteurisation (heating to 60°C for 10 hours) and nanofiltration.

A6.2.4 Human normal immunoglobulin for subcutaneous use

Human normal immunoglobulin for subcutaneous use (Evogam) is produced by CSL Behring, Australia, from NZBS New Zealand-sourced plasma. It is a sterile solution containing 16 g per 100 mL of human immunoglobulin with a purity of at least 98 percent immunoglobulin G (IgG). At least 85 percent consists of monomers and dimers (typically >90 percent), and less than 10 percent of the IgG is aggregates. The distribution of the IgG subclasses closely resembles that found in normal human plasma.

The pH value of the solution is 6.6. It contains 2.25 g/100 mL of glycine as a stabiliser. It does not contain a carbohydrate stabiliser (eg, sucrose, maltose) and contains no preservative. Evogam contains only trace amounts of IgA, typically <0.025 mg/mL.

Evogam is produced by chromatographic fractionation of large pools of human plasma obtained from New Zealand's voluntary blood donors. The manufacturing process involves special steps to reduce the possibility of virus transmission, including pasteurisation (heating at 60°C for 10 hours) and nanofiltration.

A6.2.5 Accessing immunoglobulin or contacting NZBS for advice

NZBS operates a 24-hour on-call service for medical advice and access to these products. Details of the medical officer on call can be obtained from any DHB hospital blood bank in New Zealand.

Product can be requested using the NZBS request form. This can be accessed online (www.nzblood.co.nz/Clinical-information/Transfusion-medicine/Information-for-Health-Professionals/Request-forms), or by contacting your local blood bank, or writing to:

New Zealand Blood Service
Private Bag 92071
Victoria Street West
Auckland 1142

or by telephone (during normal office hours): (09) 523 5744.

A6.3 Indications for use

A6.3.1 Passive immunisation

For advice on the use of immunoglobulin products and specific dosages of these products, please contact a medical officer at NZBS. Copies of the product data sheet are available on the NZBS website (www.nzblood.co.nz/Clinical-information/Transfusion-medicine/Health-professionals-medicine-datasheets/Immunoglobulins).

Normal Immunoglobulin-VF is available for passive immunisation (pre- or post-exposure prophylaxis) against measles (see section 11.8.2) and hepatitis A (see section 7.8) where active vaccination is not appropriate or is contraindicated. It is not recommended for the prevention of rubella or mumps. Guidance on the use of specific preparations is provided in other sections of this *Handbook*: for pre- or post-exposure prophylaxis against hepatitis B (sections 8.5.2 and section 8.8.1), tetanus (section 19.5.5) and varicella zoster (section 21.8.2).

A6.3.2 Management of primary and acquired immune deficiency

Recurrent infections can occur in individuals who have low or absent levels of circulating immunoglobulins – so-called humoral immune deficiency. This can arise as a congenital disorder, or it can be acquired as a consequence of a number of diseases. Humoral immune deficiency can exist alone or as part of a wider immune deficiency syndrome. Immunoglobulin products can be used to prevent recurrent infections in these patients.

Until recently, IVIG was the product of choice for managing these patients. A subcutaneous IgG product (Evogam) is also now available, which can be infused by patients at home. This avoids the need for outpatient or day-case admission for infusion of IVIG and is preferred by some patients. The subcutaneous preparation is not suitable for use in prophylaxis against hepatitis A or measles infection.

For replacement therapy in antibody deficiency disorders, monthly administration of IVIG is given, usually at a dosage of 0.2 to 0.6 g/kg of body weight.[2] Subcutaneous product is administered one to two times per week, with the overall monthly dosage similar to that of IVIG. For both types of product, the dosage and frequency of infusion should be based on the effectiveness in the individual patient. In general, however, the aim of treatment should be to maintain the serum IgG at or above a level of 5 g/L.

A6.4 Storage and administration

Immunoglobulin products must be stored at +2°C to +8°C and must not be frozen. They should also be protected from light. If the product appears turbid or contains sediment, it must not be used. Always check and observe the manufacturer's expiry date before injecting the product. The product does not contain an antimicrobial preservative and must be used immediately after opening the vial; any unused portions should be discarded. Information on the batch number and dose injected must be kept in the recipient's records.

The intramuscular and subcutaneous forms of normal immunoglobulin should be brought to room temperature before use. They *must not* be given intravenously because of the possible reactions discussed in section A6.7.[2]

The intramuscular product, Normal Immunoglobulin-VF, should be given slowly by deep IM injection, using a needle of appropriate gauge and length. If a large volume (more than 5 mL) is required, administration in divided doses at different sites is recommended.

The subcutaneous product, Evogam, is normally given using an infusion pump. Information on infusion rates is provided in the medicine's data sheet.

A6.4.1 Interactions with other drugs

Immunoglobulin should not be mixed with other pharmaceutical products, except as indicated by the manufacturer.

Passively acquired antibody can interfere with the response to live attenuated virus vaccines. Live virus vaccines should be given at least three weeks before, or deferred for up to 11 months after, doses of human normal immunoglobulin or other blood products. The interval will be determined by the blood product and dose received (Table A6.1).

Table A6.1: Suggested intervals between immunoglobulin product administration or blood transfusion and MMR or varicella vaccination (does not apply to rotavirus vaccine)

Product or indication	Route	Dose	Interval (months)[a]
Tetanus immunoglobulin (250 IU/vial)	IM	250 IU if <24h 500 IU if >24h or gross contamination or burns	3
Hepatitis A prophylaxis (with human normal immunoglobulin)			
• Contact and short-term travel (<3 months prophylaxis)	IM	0.03 mL/kg	3
• International travel (>3 months)[b], other requirement for long-term prophylaxis – repeated 6-monthly	IM	0.06 mL/kg	3
Hepatitis B immunoglobulin (A different low-volume product is provided for neonatal use)	IM	Adults 400 IU Neonates 100 IU	3
Rabies immunoglobulin	IM	20 IU/kg	4
Varicella prophylaxis (with zoster immunoglobulin, 200 IU/vial)	IM	125 IU/10 kg (max 625 IU) 0–10 kg: 1 vial 10.1–30 kg: 2 vials >30 kg: 3 vials	5
Measles prophylaxis (with human normal immunoglobulin)			
• standard contact	IM	0.2 mL/kg	5
• immunocompromised contact	IM	0.6 mL/kg	6
Blood transfusion:			
• washed RBCs	IV	10 mL/kg	0
• RBCs, resuspended	IV	10 mL/kg	3
• whole blood, allogeneic	IV	10 mL/kg	6
• platelets in PAS	IV	1 unit	5
• plasma	IV	10 mL/kg	7
• platelets suspended in plasma	IV	1 unit	6

Continued overleaf

Product or indication	Route	Dose	Interval (months)[a]
Cytomegalovirus immunoglobulin[c]	IV	Contact NZBS MO to discuss product and dose	6
Replacement (or therapy) of immune deficiencies (with IVIG)	IV	0.3–0.4 g/kg occasionally higher	8
IVIG therapy for autoimmune or inflammatory disorders	IV	0.4 g/kg	8
		1–1.5 g/kg	10
		1.6–2 g/kg	11
Monoclonal antibody (as palivizumab[d]) to respiratory syncytial virus	IM	15 mg/kg	None

Key: IM = intramuscular; IU = international units; IV = intravenous; IVIG = intravenous immunoglobulin; NZBS MO = New Zealand Blood Service medical officer; PAS = platelet additive solution; RBCs = red blood cells.

Notes

a Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of immunoglobulin or measles vaccine might be indicated after measles exposure.

b Immunoglobulin is not normally available or recommended in New Zealand for pre-travel use.

c Cytomegalovirus immunoglobulin is not available in New Zealand. Contact NZBS MO to discuss access to an alternative product.

d Palivizumab contains antibody only to respiratory syncytial virus and does not interfere with the immune response to live or inactivated vaccines.

Adapted from: Centers for Disease Control and Prevention. 2011. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 60(RR2): 1–61. Table 5. Deferral interval for vaccination after blood components and products calculated from NZBS data.

Note: The above does not apply to rotavirus vaccines.

Inactivated vaccines may be administered concurrently with passive antibody (although in separate syringes) to induce active immunity, as is done for some tetanus-prone wounds and for babies born to HBsAg-positive mothers.

A6.4.2 Passive transfer of antibodies and interference with serological testing

Serological testing after the administration of immunoglobulin may detect transfused antibodies for several months after administration. Serological testing for any infection after immunoglobulin should therefore be discussed with an expert.

A6.5 Duration of effect

The estimated half-life of *intramuscular* human normal immunoglobulin is 27 ± 7 days (mean ± standard deviation [SD]).[2] The duration of effect is linked to the initial dosage.

The estimated half-life of *intravenous* human normal immunoglobulin is 40 ± 8 days (mean ± SD).[2]

The estimated half-life of *subcutaneous* human normal immunoglobulin is 55 days (range 14–165 days).[2]

A6.6 Contraindications and precautions

A6.6.1 Contraindications

> Immunoglobulin products intended for subcutaneous and intramuscular injection must not be administered intravenously because of the potential for anaphylactic reactions.

Health professionals should check the package insert for the immunoglobulin product to be administered.

Skin tests should not be conducted with immunoglobulin preparations. Intradermal injection of any concentrated immunoglobulin product may cause a local inflammatory reaction, which can be misinterpreted as a positive allergic reaction. Allergic responses to normal immunoglobulin given in the prescribed IM route are extremely rare, but may occur in those with complete immunoglobulin A (IgA) deficiency in whom anti-IgA is present.

Intramuscular injection of immunoglobulin products should be avoided in patients with a low platelet count or with any coagulation disorder that would contraindicate IM injections. In these circumstances, the injection may be given subcutaneously, with a lightly applied pressure pad if prone to bruising; for example, if thrombocytopenia or von Willebrand disease is present.[1]

A6.6.2 Precautions

Injections of Normal Immunoglobulin-VF must be IM, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel (see section 2.2.3).

As with any injection, there is a risk of anaphylaxis. Adrenaline and other means of treating acute reactions should therefore be immediately available (see section 2.3.3).

A6.7 Expected responses and adverse events following passive immunisation

Clinicians in New Zealand are requested to notify all adverse reactions arising from, or in association with, the use of blood products. Reactions to any immunoglobulin product should be reported on a form obtainable from NZBS or any local DHB hospital blood bank.

Local tenderness, erythema and muscle stiffness occasionally occur at the site of injection and may persist for several hours after intramuscular injection. An occasional recipient may react more strongly, with a low-grade fever. Systemic reactions, including nausea, urticaria and generalised hypersensitivity reactions, may occur.[1, 2]

Reactions to IVIG tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. However, delayed reactions can occur, and include nausea, vomiting, chest pains, rigors, dizziness or aching legs. Systemic and local reactions are more common in those being treated for hypogammaglobulinaemia than in those with normal gammaglobulin levels who are being treated with immunoglobulin preparations for autoimmune conditions.

Occasional reports exist of renal failure following infusion of IVIG. These largely relate to sucrose-containing products. Intragam P and Privigen, the IVIG products available in New Zealand, do not contain sucrose, but patients should be adequately hydrated prior to their administration. Renal function should be monitored in patients considered to be at increased risk.

Aseptic meningitis has been reported following treatment with IVIG. This may present up to two days following treatment. Anaphylactic reactions, although rare, have been reported following injection of immunoglobulin products, although anaphylaxis is more likely to occur following intravenous infusion. Other significant adverse events that have been observed in New Zealand and are mostly associated with large or ongoing treatment with high dose IVIG or SCIG include: haemolysis, rashes, febrile events, pain or hypotension.

Immunoglobulin products may interfere with the immune response to live virus vaccines. In general, live vaccines should be given at least 3 weeks before or up to 11 months after the immunoglobulin preparation (see Table A6.1). This does not apply to the yellow fever vaccine, because New Zealand blood donors are very unlikely to have antibodies to this virus. For travellers abroad, the necessary interval may not be possible. No evidence of adverse interaction with rotavirus vaccine has been reported.

See section 1.6.3 for further information about adverse events and reporting.

References

1. New Zealand Blood Service. 2016. Transfusion Medicine Handbook Third Edition, 2016: A guide to the clinical use of blood components, blood products and blood transfusion procedures in New Zealand. URL: www.nzblood.co.nz/clinical-information/transfusion-medicine/transfusion-medicine-handbook

2. CSL Behring. 2013. CSL Immunoglobulin Product Data Sheets. URL: www.nzblood.co.nz/Clinical-information/Transfusion-medicine/Health-professionals-medicine-datasheets/Immunoglobulins