IMMUNOGLOBULIN INFUSIONS FOR REPLACEMENT AND IMMUNOMODULATION

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- This document outlines the safe administration of immunoglobulin infusions.
- Immunoglobulin preparations (eg: Intragam® 10, Privigen®, Flebogamma® 5%, Flebogamma® 10%, Kiovig®, Octagam® 5%, Octagam® 10%, Evogam®, Hizentra®, Gammanorm®, Gamunex®, Cuvitru®) are prepared from pooled venous plasma obtained from donors. They contain IgG antibodies and are used to treat primary and secondary immune deficiency diseases (including post allogeneic stem cell transplantation, chemotherapy and other treatment-induced hypogammaglobinaemia) as well as diseases requiring immunomodulation, such as Kawasaki disease and neurological disorders.
- In the case of intravenous infusions, all patients require close monitoring for any potential complications or adverse reactions during the infusion period.
- In the case of intravenous infusions, observations (temperature, heart rate, and respiration rate) should be taken before, during and after the infusion. Blood pressure should be recorded before commencement.
- If there are any adverse reactions the infusion should be ceased and the Medical Officer notified immediately. For home (subcutaneous) infusions, assistance and advice should be sought from treating team or if an emergency, by calling an ambulance.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st August 2021	**Review Period:** 3 years
Team Leader:	Clinical Nurse Consultant	**Area/Dept**: Immunology

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CHANGE SUMMARY

- Addition of immunoglobulin products

READ ACKNOWLEDGEMENT

- Medical staff prescribing/administering immunoglobulin infusions and nursing staff administering immunoglobulin infusions should read and acknowledge this document.
- Pharmacy staff should read this document.

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1 Administration of Intravenous Immunoglobulin (IVIg)

Rationale

- To ensure the safe administration of Immunoglobulin infusions.

Indications

- Replacement therapy for primary and secondary immune deficiency diseases including post allogeneic stem transplantation, chemotherapy and other treatment-induced hypogammaglobinaemia.
- Immunomodulation, e.g. Kawasaki disease and neurological disorders

Immunoglobulins

- **Intragam® 10** is a 10% w/v solution of IgG produced by the CSL Behring from voluntary donors to the Australian Red Cross. Intragam® 10 comes in 2.5 g in 25 mL, 10 g in 100 mL and 20 g in 200 mL.
- **Privigen®** is a 10% solution of IgG produced from imported plasma by CSL Behring, Australia. Privigen® comes in 5 g in 50 mL, 10 g in 100 mL, 20 g in 200 mL and 40 g in 400 mL.
- **Flebogamma®** is in both 5% and 10% solutions of IgG produced by Instituto Grifols, Spain. Flebogamma® 5% comes in 0.5 g in 10 mL, 2.5 g in 50 mL, 5 g in 100 mL, 10 g in 200 mL and 20 g in 400 mL. Flebogamma® 10% comes in 5 g in 50 mL, 10 g in 100 ml and 20 g in 200 mL.
- **Kiovig®** is a 10% solution of IgG produced by Baxalta. Kiovig® comes in 1 g in 10 mL, 2.5 g in 25 mL and 5 g in 50 mL, 10 g in 100 mL and 20 g in 200 mL.
- **Octagam®** is in both 5% and 10% solutions of IgG produced by Octapharma. Octagam® 5% comes in 1 g in 20 mL, 2.5 g in 50 mL, 5 g in 100 ml and 10 g in 200 mL. Octagam® 10% comes in 2 g in 20 mL, 5 g in 50 mL, 10 g in 100 mL and 20 g in 200 mL.
- **Gamunex®** is a 10% w/v solution produced by Grifols and is available in 5g in 50 ml, 10g in 100 mL and 20g in 200 mL
- Donors are screened for antibodies to HIV and Hepatitis B and C. Intragam® 10, Privigen®, Flebogamma®, Kiovig®, Octagam® and Gamunex® are all registered by the Therapeutic Goods Administration (TGA).

General principles

- Intragam® 10 can only be ordered from the Australian Red Cross Lifeblood (ARCLB) (formally Australian Red Cross Blood Service (ARCBS)). Refer to section 3.4.5 of Transfusion of Blood and Blood Components Practice Guideline.
- Privigen®, Flebogamma®, Kiovig® and Octagam® are sometimes supplied by the ARCLB instead of Intragam® 10, but if the indication for IVIG is not eligible for ARCLB supply, these products must be ordered through CHW or SCH Pharmacy.
- Written consent must be obtained from parents or patient.

- Once removed from refrigeration, unopened bottles of **Intragam® 10** must be used within three months; Octagam® 10% must be used within 9 months and Gamunex® within 6 months.
- **Kiovig®, Flebogamma®** and Octagam® 5 have a shelf life of 24 months; **Privigen®** has a shelf-life of 36 months stored at room temperature.
- All opened bottles must be used immediately.
- Do not shake bottles.
- A 'peel-off' identification label with Batch Number and Expiry Date is to be placed on the patient's Blood Component order sheet SCHN 130.310.
- If a premedication is required, it should be given half an hour prior to commencement of the infusion.

Contraindications

- Patients who have had an anaphylactic reaction to a human immunoglobulin preparation.

Administration

- To be checked by two Registered Nurses.
- Requires an aseptic non-touch technique as per the SCHN Aseptic Non-Touch Technique policy
- Given via intravenous cannula or CVAD.
- Administered by infusion pump.
- A blood filter is required.
- Sodium chloride 0.9% may be used as a flush at the end of the infusion.

Nursing Observations

Vital sign monitoring of temperature, heart rate, respiratory rate and blood pressure to be recorded before commencement of infusion.

If the patient is unwell or there are any concerns particularly regarding the baseline observations, the medical officer should be contacted before the infusion commences.

Vital signs (temperature, heart rate, respiratory rate) should then be checked and recorded:

- Within 15 minutes after the start of the infusion
- Hourly during the infusion
- At the end of the infusion

(Refer to section 6.4 of Transfusion of Blood and Blood Components Practice Guideline)

If the patient has ANY adverse reaction, stop infusion and call a medical officer IMMEDIATELY

Adverse reactions

- If adverse reactions occur the first response should be to **stop the infusion**, then notify Medical Officer.
- Severe reactions are uncommon and are most likely to occur during the first infusion, but may occur subsequently.
- Anaphylactic/anaphylactoid reactions are rare: urticaria, angio-oedema, bronchospasm, hypotension. Anaphylactic reactions may require oxygen, adrenaline and steroids depending on severity of the reaction.
- More common reactions are: flushing, fever, headache, pallor, shivering, tachycardia
- Other reported reactions: dyspnoea, chest tightness, tachycardia or hypotension without anaphylaxis, transient haemolytic anaemia, abdominal pain and renal failure
- Milder reactions often resolve after the infusion has been stopped. If so, after discussion with medical staff, the infusion may be recommenced at a slower rate after at least 15 minutes.
- Subsequent infusions should be commenced and escalated at a slower rate.
- Premedication with hydrocortisone, antihistamines +/- paracetamol or ibuprofen can decrease the incidence of side-effects if a child continues to have frequent reactions.

1.1 Procedure: Intravenous Immunoglobulin Infusion for Immune Deficiency (Replacement)

Dose

The dose is usually approximately 400 mg/kg (0.4 g/kg). As children grow their requirements will increase and the dose should be based on weight, number of infections and trough serum IgG level (optimally above 6 g/L, higher (usually above 9 g/L) if there is bronchiectasis or suppurative lung disease)

Allow preparation to reach room temperature and inspect for turbidity or sediments. If so, return to Blood Bank.

Infusion Rates

Individual products recommend different weight based rates of infusion. To avoid confusion, the infusion rates at this centre for 5% and 10% solutions, regardless of product, have been simplified as documented below. These rates are generally well tolerated.

First Infusion

- For the first infusion, **Flebogamma® 5%, and Octagam® 5%** should be infused at a rate of 20 mL/hour (**1 mL/kg/hour for neonates**) for the first hour. Flushing and changes in heart rate and blood pressure could be signs of too rapid an infusion. If there are no adverse reactions (as above), the rate can be increased by up to 50 mL/hour (**1 mL/kg for neonates**) every hour to a maximum infusion rate of 150 mL/hour.
- For the first infusion, **Intragam® 10, Privigen®, Kiovig®, Flebogamma® 10% , Octagam® 10% and Gamunex® (10%)**should be infused at a rate of 10 mL/hour (0.5 mL/kg/hour for neonates) for the first hour. If there are no adverse reactions (as above), the rate can be increased by up to 25 mL/hour **(0.5 mL/kg for neonates)** every hour to a maximum infusion rate of 75 mL/hour.

For example:

	For First infusions only (do not use these rates in neonates)	
	Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 10% Gamunex®**
HOUR	**mL/hour**	**mL/hour**
1	20	10
2	50	25
3	100	50
4	150*	75*

** For the remainder of infusion*

Subsequent infusions

- If no reaction to first infusion, subsequent infusions of **Flebogamma® 5%, and Octagam® 5%** can be commenced at 50 mL/hour, and if there are still no adverse reactions, the rate can be increased by 50 mL/hour every hour to a maximum of 150 mL/hr (**5 mL/kg/hour for neonates**).
- If no reaction to first infusion, subsequent infusions of **Intragam® 10, Privigen®, Kiovig®, Flebogamma® 10% , Octagam® 10% and Gammunex® 10 %** can be commenced at 25 mL/hour, and if there are still no adverse reactions, the rate can be increased by 25 mL/hour every hour to a maximum of 75 mL/hour (**2.5 mL/kg/hour for neonates**).

For example:

	For subsequent infusions only (do not use these rates in neonates)	
	Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 10% Gamunex® 10%**
HOUR	**mL/hour**	**mL/hour**
1	50	25
2	100	50
3	150*	75*

** For the remainder of infusion*

Note: For some children receiving **regular** intravenous immunoglobulin (IVIg) infusions in Turner Medical Day Stay ward (CHW) or C1N (Medical Day Unit) and C2N (SCH) who have tolerated at least 6 infusions, the rate of 100 mL/hour (or 50 mL/hour for 10% solutions) in the second hour can be increased to 150 mL/hour (or 75 mL/hour for 10% solutions) after 30 minutes if tolerated. However the maximum rate of commencement must still remain 50 mL/hour (or 25 mL/hour for 10% solutions) for the first hour. In addition, the rate of infusion of 10% solutions from the 4th hour may be increased to 100 mL/hour if a rate of 75 mL/hour has been tolerated without adverse effects (including in the days post infusion) for at least 6 infusions. These changes can only be initiated after discussion with the medical team and the decision to continue for subsequent infusions depends on the absence of adverse effects in the hours or days following infusion.

Note: ASCIA Guidelines – Standardised infusion rates for intravenous immunoglobulin replacement therapy may be used in conjunction with discussion with medical team.

1.2 Procedure: Intravenous Immunoglobulin for Kawasaki Disease and Other Diseases (Immunomodulation)

This procedure is NOT for children with immune deficiency on replacement IVIg therapy.

Dose

- The dose for Kawasaki disease is usually 2 g/kg which should be given undiluted over **8 to 12 hours.** The dose of IVIg may be different for other diseases, such as Guillain-Barré Syndrome.

Infusion Rate

Kawasaki Disease

- **Flebogamma® 5%, and Octagam® 5%** should be infused at an initial rate of 20 mL/hour (**1 mL/kg for neonates**) for the first hour.
- **Intragam® 10, Privigen®, Kiovig®, Flebogamma® 10%, Octagam® 10%** and Gamunex® **10%** should be infused at an initial rate of 10 mL/hour (**0.5 mL/kg/hour for neonates**) for the first hour
- If there are no adverse reactions, the rate can be increased by 50 mL/hour every hour to a maximum of 150 mL/hour (**5 mL/kg/hour for neonates**) for **Flebogamma® 5%, and Octagam® 5%**, and 25 mL/hour every hour to a maximum of 75 mL/hour (**2.5 mL/kg/hour for neonates**) for **Intragam® 10, Privigen®, Kiovig®, Flebogamma® 10%, Octagam® 10% and Gamunex®10%**.

The final rate of infusion can be calculated by dividing the total volume to be given by 8 to 12, e.g. a 20 kg child with Kawasaki needs 40 g. If Flebogamma® 5% is provided, this is equivalent to 800 mL = 67 mL/hour over 12 hours or 100 mL/hour over 8 hours.

Example of rate escalation towards final infusion rate as calculated above:

	Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 10% Gamunex® 10%**
HOUR	**mL/hour**	**mL/hour**
1	20	10
2	50	25
3	100	50
4	150*	75*

** Maximum rate of infusion*

Other diseases

In other diseases requiring intravenous immunoglobulin for immunomodulation where the patient is not acutely febrile and/or haemodynamically unstable (eg. Guillain-Barré Syndrome and immune thrombocytopenia (ITP)) the rates documented for first and subsequent infusions for replacement therapy can be used (section 1.1). The dose can be given as a single infusion or divided over 3 to 5 days as determined by the ordering clinician.

2 Subcutaneous Immunoglobulin Administration (SCIg)

Subcutaneous administration of immunoglobulin results in negligible fluctuations of IgG levels between infusions and allows home treatment because of minimal significant side effects and simplicity of the procedure with resultant ease of training.

Immunoglobulins

There are four available TGA approved immunoglobulin preparations for subcutaneous infusion. All plasma used is screened for HIV, Hepatitis B and C.

- **Evogam®** is a 16% w/v solution of IgG produced by the CSL Behring. Evogam® comes in 0.8 g in 5 mL and 3.2 g in 20 mL.
- **Hizentra®** is a 20% w/v solution of IgG produced by the CSL Behring. Hizentra® comes in 1 g in 5 mL, 2 g in 10 mL, 4 g in 20 mL and 10 g in 50 mL.
- **Cuvitru®** is a 20% w/v solution of IgG produced by Takeda. It comes in 1.0g in 5 ml, 2.0g in 10 ml, 4.0g in 20 ml and 8.0g in 40 ml.
- **Gammanorm®** is a 16.5% w/v solution of IgG produced by Octapharma. Gammanorm® comes in 1.65 g in 10 mL and 3.3 g in 20 mL.
- **Kiovig®** is a 10% w/v solution of IgG produced by Baxalta. Kiovig® comes in 1 g in 10 mL, 2.5 g in 25 mL and 5 g in 50 mL, 10 g in 100 mL and 20 g in 200 mL. This is the same preparation used for intravenous infusion.
- Prior to the availability of a dedicated product, 16% Human Normal Immunoglobulin (0.8 g/5 mL), a solution of IgG produced by CSL for intramuscular injection had been used.

Dose

The initial monthly dose is equivalent to that previously received, if converting from intravenous administration, or approximately 400 mg/kg/month if not previously treated. This dose is divided and given 1 to 3 times (e.g. Mon, Wed, Fri) each week over the month, although some individuals may tolerate fortnightly infusions. Each infusion will ideally consist of multiples of 5, 10 or 20mL vials to prevent wastage. For example, a child previously receiving 17.5 g/month intravenously will commence with 15mL 2 times a week of Evogam®, giving a total monthly dose of 19.2 g, or 15 mL and 10mL each week of Hizentra® giving a total monthly dose of 20 g. The dose can later be adjusted on the basis of serum IgG levels, clinical response and growth. As infusions are tolerated, doses may be combined resulting in once or twice weekly infusions.

Administration

The immunoglobulin is infused into the subcutaneous tissue of the abdominal wall or front of thigh. EMLA® or amethocaine cream or alternative such as LMX® (4% lidocaine) may be applied for 60 minutes and 30 minutes respectively before commencement but is not essential and if used initially can be abandoned once the child is familiar with the process. Alternatively, a covered cold pack may be applied to the site 15-20 minutes prior to infusion. Discomfort on insertion of the butterfly needle or equivalent device is minimal.

The infusion may be run initially at 5 mL per hour, but depends on the individual. The rate can then be increased as the infusions are tolerated. The site of injection should not be rotated, to allow development of tolerance to local reactions, which are common during the first several weeks after initiation of subcutaneous therapy.

The patient and/or their parents are supervised for the initial infusion in hospital by a member of the Immunology team and documented in the patient's medical record. The patient or their parents are taught how to draw up the product, insert the needle, operate the syringe driver if using one, and commence infusions under supervision. Additionally, they are taught principals of cold chain, logistics of collecting supply of both consumables and Ig product and are given a written treatment plan. In many cases, after 3 supervised procedures, patients and their parents are generally happy and ready to independently undertake them at home, with ready access to telephone and face to face support as required in addition to written instructions.

Although infusions are usually administered using a syringe driver/ pump, it is feasible to administer SCIg by slow manual push technique should the need arise. This seems best tolerated in older children but may be used in any age group.

Adverse reactions

- Although systemic anaphylactoid reactions are theoretically possible, these are very uncommon and the risk has not required routine provision of an adrenalin auto-injector.
- Local irritation commonly occurs during the first few infusions and can continue for some weeks. This can include swelling, redness and pain/discomfort of variable intensity. Most are mild and short lived. Any local reactions reduce in severity with ongoing infusions. We have found the local application of cold-packs very effective in reducing discomfort, paracetamol being rarely necessary. Other strategies such as decreasing the rate of infusion and ensuring needle insertion technique is correct may also be undertaken.
- Periodic assessment of correct technique is extremely useful and this should ideally be undertaken annually if possible.

Follow-up

If SCIg is used for replacement, IgG levels are usually performed after 4-6 weeks to ensure adequate levels are achieved and then 6 monthly. Progress is initially closely monitored by telephone, then at clinic reviews at 6 monthly intervals when immunoglobulin levels, blood count, renal and liver function tests are also performed.

Syringe drivers (Specifically Nikki T34) should be serviced 1 to 2 yearly as per manufacturer's recommendations; this is coordinated by the respective Immunology Departments with Biomedical Engineering. Other devices such as Springfuser and EMED

SCIg 60 do not require servicing and have an expiry date which, when reached, the device must be replaced.

References

1. Berger et al (2010). Improved quality of life, immunoglobulin G levels, and infection rates in patients with primary immunodeficiency diseases during self-treatment with subcutaneous immunoglobulin G. South Med J. 103(9): 856-63
2. Patwa et al (2012). Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders. Neurology; 78:1009-1015.
3. Gardulf et al (2006). Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies--a prospective, multi-national study. J Clin Immunol. 26(2): 177-85
4. Katz et al (2007). Safety of intravenous immunoglobulin (IVIG) therapy Autoimmun Rev. 6(4): 257-9.
5. MIMS online (accessed April 2020).
6. National Blood Authority (Australia): http://www.nba.gov.au/ (accessed February 2021).
7. NSW Health Information Bulletin [IB2014_068} National Policy - Access to Government Funded Immunoglobulin Products in Australia. https://www1.health.nsw.gov.au/pds/Pages/doc.aspx?dn=IB2014_068 (accessed February 2021)
8. National blood Authority issues Ig in accordance with the *Criteria for Immunoglobulin Use in Australia* (the *Criteria*) which undergo periodic review https://www.blood.gov.au/ig-criteria (accessed February 2021)
9. Orange et al (2006). Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. (J Allergy Clin Immunol 117: S525-53)
10. Orange et al (2012). Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clinical and Experimental Immunology 169: 172–181
11. Australasian Society of Clinical Immunology and Allergy (ASCIA) Guidelines – Standardised infusion rates for intravenous immunoglobulin replacement therapy. 2018. https://www.allergy.org.au/hp/papers/ascia-guidelines-for-standardised-ivig-infusion-rates-for-irt

Related Information

- National Blood Authority Australia, BloodSTAR: https://www.blood.gov.au/Bloodstar