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® P, Intragam® 10, Privigen®, Flebogamma® 5%, Flebogamma® 10%, Kiovig®, Octagam® 5%, Octagam® 10%, Evogam®, Hizentra®, Gammanorm®) are prepared from pooled venous plasma obtained from donors. They contain IgG antibodies and are used to treat immune deficiency diseases (including post blood and bone marrow transplantation) as well as diseases requiring immunomodulation, such as Kawasaki disease and neurological disorders.
- During the infusion all patients require close monitoring for any potential complications or adverse reactions.
- Observations (temperature, heart rate, 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.

CHANGE SUMMARY

- Addition of immunoglobulin products

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st April, 2017	**Review Period**: 3 years
Team Leader:	Senior Staff Specialist	**Area/Dept**: Allergy and Immunology

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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 immune deficiency diseases including post allogeneic bone marrow transplantation.
- Immunomodulation, e.g. Kawasaki disease and neurological disorders

Immunoglobulins

- **Intragam® P** is a 6% w/v solution of IgG produced by the CSL Behring from voluntary donors to the Australian Red Cross. Intragam® P comes in 3 g in 50 mL and 12 g in 200 mL.
- **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.
- Donors are screened for antibodies to HIV and Hepatitis B and C. Intragam® P, Intragam® 10, Privigen®, Flebogamma®, Kiovig® and Octagam® are all registered by the Therapeutic Goods Administration (TGA).

General principles

- Intragam® P and Intragam® 10 can only be ordered from via the Australian Red Cross Blood Service (ARCBS). Refer to section 3.8 of Transfusion of Blood and Blood Components Policy and Procedure.
- Privigen®, Flebogamma®, Kiovig® and Octagam® are sometimes supplied by the ARCBS instead of Intragam® P or Intragam® 10, but if the indication for IVIG is not eligible for ARCBS supply, these products must be ordered through CHW or SCH Pharmacy.

- Written consent obtained from parents or patient.
- Once removed from refrigeration, unopened bottles of **Intragam® P, Intragam® 10 and Octagam®** must be used within three months; **Kiovig® and Flebogamma®** within 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 form 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 a surgically clean procedure.
- Given via intravenous cannula, central line, long line or infus-a-port.
- 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 Policy and Procedure)

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 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 if there is bronchiectasis)

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, **Intragam® P, 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% and Octagam® 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)	
	Intragam® P Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 10%**
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 **Intragam® P, 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.
- If no reaction to first infusion, subsequent infusions of **Intragam® 10, Privigen®, Kiovig®, Flebogamma® 10% and Octagam® 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.

For example:

	For subsequent infusions only (do not use these rates in neonates)	
	Intragam® P Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 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 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. This change 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.

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

- **Intragam® P, 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% and Octagam® 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 **Intragam® P, 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% and Octagam® 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:

	Intragam® P Flebogamma® 5% Octagam® 5%	**Intragam® 10 Privigen® Flebogamma®10% Kiovig® Octagam® 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.
- **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 or 10mL vials to prevent wastage. For example, a child previously receiving 18 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 a week of Hizentra® giving a total monthly dose of 20 g. The dose can later be adjusted on the basis of 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. EMLA® or amethocaine cream 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. 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 few weeks after initiation of subcutaneous therapy.

Initiation of initial infusions should be performed supervised in hospital. 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. After 2 to 3 supervised procedures, patients and their parents are generally happy and ready to independently do them at home, with ready access to telephone and face to face support as required.

Although infusions are usually given with a pump, it is feasible to administer SCIg by slow manual push technique should the need arise. This seems best tolerated in older children.

Adverse reactions

- Although anaphylactoid reactions are theoretically possible, none secondary to subcutaneous immunoglobulin have been reported in the available literature, nor experienced in our patients.
- 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. Those with least subcutaneous tissue seem more susceptible. 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.

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 should be serviced annually.

References

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