Intravenous Immunoglobulin
IVIG
For newborn use only

2018

Alert	If the patient has ANY adverse reaction, stop infusion and call a medical officer IMMEDIATELY. This formulary is for Intragam 10. Intragam 10 is the domestically produced intravenous immunoglobulin (IVIg) and is the most likely product that you will receive from the Australian Blood Service. Intragam P (6%) is no longer produced as of June 2018. Flebogamma 5% and 10% should not be given to neonates due to undiagnosed hereditary fructose intolerance. Other preparations such as Privigen 10 are available for paediatric use, but beyond the scope of this formulary.
Indication	1. Neonatal alloimmune thrombocytopenia (NAIT) 2. Haemolytic disease of the newborn (HDN) (isoimmunisation) 3. Immune thrombocytopenic purpura 4. Primary immunodeficiency diseases 5. Secondary hypogammaglobulinaemia 6. Neonatal haemochromatosis – gestational alloimmune liver disease (GALD) 7. Neonatal myasthenia gravis 8. Severe neonatal enterovirus infection including myocarditis or hepatitis 9. Sepsis/infection – prevention and treatment – NOT RECOMMENDED. 1, 3-5, and 7 are approved indications by the National Blood Authority of Australia, 6 is a proposed addition as of June 2018. See https://www.criteria.blood.gov.au/ for a comprehensive list. Indications not funded under the Criteria for the clinical use of intravenous immunoglobulin in Australia (Criteria), may be provided for locally under Jurisdictional Direct Orders (https://www.blood.gov.au/system/files/documents/jdo-factsheet.pdf).
Action	Immunoglobulin G (IgG) provides humoral immunity and is an immune modulator. [19]
Drug Type	Immunoglobulin
Trade Name	Intragam 10. Contains 1 g of immunoglobulin G in 10 mL.
Presentation	**Intragam 10** is a 10% w/v solution of IgG produced by 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. All these strengths provide 1 g of Ig in 10 mL. Donors are screened for antibodies to HIV and Hepatitis B and C.
Dosage / Interval	Medical officer should prescribe (1) brand of IVIg and the % concentration (e.g. Intragam 10), (2) dose in grams and the volume in mL (e.g. 2 g/20 mL) and (3) Rate of infusion (see Administration section) **Isoimmunisation:** 1 g/kg (range 0.5–1.5 g/kg) IV. Dose may be repeated in 12–24 hours if required. **Neonatal alloimmune thrombocytopenia (NAIT):** 1 g/kg IV. Repeat if required. **Immune thrombocytopenic purpura (ITP):** 1 g/kg IV. Repeat if required. **Immunodeficiency:** 0.4 g/kg IV (dose should be based on number of infections and trough serum IgG concentration [optimally above 6 g/L, higher if there is bronchiectasis]). **Neonatal myasthenia gravis:** 1 g/kg IV daily for 2 days (total dose: 2 g/kg). If additional therapy required, titrate against clinical response.[9] **Severe enterovirus infection/myocarditis or hepatitis:** 2 g/kg IV (up to 2.5 g/kg) as a single dose within 3 days of onset.

	Sepsis/infection (prevention or treatment) – not recommended: 0.5 to 1 g/kg IV repeated at intervals when required has been used. **Neonatal haemochromatosis:** 1–2 g/kg/day IV following exchange transfusion in the first 7 days and then 1 g/kg weekly, as required.
Maximum daily dose	2 g/kg/day. Enterovirus infection: 2.5 g/kg/day
Route	Intravenous.
Preparation/Dilution	Obtain written consent from parent or guardian. All opened bottles must be used immediately. Do not shake bottles to avoid foaming. A 'peel-off' identification label with Batch Number and Expiry Date is to be placed on the patient's Blood Component order form. Allow preparation to reach room temperature and inspect for turbidity or sediments. If seen, return to Blood Bank.
Administration	Infusion rate: 0.5 mL/kg/hour for 60 minutes; then 1 mL/kg/hour for next 60 minutes; 2 mL/kg/hour for next 60 minutes; then 4 mL/kg/hour (at a maximum rate of 25 mL/hour). To be checked by two Registered Nurses. • Requires a surgically clean procedure. • Given via intravenous cannula, central line, long line or port. • Administered by infusion pump. • A blood filter is not required, but may be used. • Sodium chloride 0.9% may be used as a flush at the end of the infusion.
Monitoring	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.
Contraindications	Patients who have had an anaphylactic reaction to a human immunoglobulin preparation.
Precautions	
Drug Interactions	Concurrent use of immunoglobulin and live virus vaccines may result in interference with the immune response to the live vaccine. The Australian Technical Advisory Group on Immunisation (ATAGI) recommendations are below: Hepatitis B vaccine is an inactivated vaccine and can be administered at any time before, after or concurrently with IVIg. Rotavirus vaccine may be administered at any time before, after or concurrently with any blood product, including antibody-containing products. BCG vaccine can be given at any time before or after administration of immunoglobulin or any antibody-containing blood product. Following the receipt of IVIg for ITP treatment, an interval of 8–10 months should elapse before vaccination with an MMR, MMRV or varicella vaccine. May result in false-positive Coombs test due to passive transmission of antibodies to erythrocyte antigens. May result in a falsely elevated blood glucose measurement due to assay interference with the glucose dehydrogenase (pyrroloquinoline-quinone) method.
Adverse Reactions	If adverse reactions occur, the first response should be to stop the infusion, then notify Medical Officer.

	• Severe reactions are uncommon especially in neonates. In older patients are most likely to occur during the first infusion, but may occur subsequently. • Anaphylactic reactions are rare: urticaria, angioedema, bronchospasm and hypotension. Anaphylactic reactions may require oxygen, adrenaline (epinephrine) and steroids depending on severity of the reaction. • More common reactions are: flushing, fever, headache, pallor, shivering and 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.
Compatibility	Sodium chloride 0.9% for priming and flushing. Others not tested. Administer through a separate line.
Incompatibility	Compatibility with other drugs not established.
Stability	Do not mix immunoglobulin products of different formulations or from different manufacturers.
Storage	Store at 2 to 8 °C (Refrigerate. Do not freeze). Protect from light. Once removed from refrigeration, unopened bottles of Intragam 10 must be used within three months. Intragam 10 can only be ordered from the Australian Red Cross Blood Service (ARCBS).
Special Comments	Newborn infants with isoimmunisation who are considered at risk of exchange transfusion must have intensive prophylactic phototherapy as this is the intervention most likely to prevent the need for exchange transfusion. If not yet done – newborn screening (NBS) should be performed prior to infusion and repeated as per blood transfusion/NBS policy.
Evidence summary	**Efficacy:** **Newborn infants with isoimmunisation:** Systematic review included 12 studies, 10 trials (n = 463) of Rh isoimmunisation and 2 trials (n = 350) of ABO isoimmunisation. Studies with a high risk of bias showed that IVIg reduced the rate of exchange transfusion (ET) in Rh isoimmunisation (RR 0.23, 95% CI 0.13 to 0.40), whereas studies with a low risk of bias that also used prophylactic phototherapy did not show statistically significant differences (RR 0.82, 95% CI 0.53 to 1.26). [1, 2] (LOE ,I GOR C) For ABO isoimmunisation, only studies with a high risk of bias were available and meta-analysis revealed efficacy of IVIg in reducing ET (RR 0.31, 95% CI 0.18 to 0.55). Role of IVIg in ABO disease is not clear.[1, 3] (LOE I, GOR C) Recommendations: The National Blood Authority Patient Blood Management Guidelines for Neonatal and Paediatrics: In neonates with haemolytic disease of the fetus and newborn, the use of IVIg is not recommended.[4] However, the NICE Practice Guideline recommends: use intravenous immunoglobulin 500 mg/kg over 4 hours as an adjunct to continuous intensified phototherapy in cases of rhesus haemolytic disease or ABO haemolytic disease when the serum bilirubin continues to rise by more than 8.5 µmol/litre per hour [5]. The AAP Subcommittee on Hyperbilirubinemia Clinical Practice Guideline 2004 recommends: In infants with isoimmune haemolytic disease and TSB level rising in spite of intensive phototherapy or within 2–3 mg/dL (34–51 µmol/L) of exchange level, administer intravenous immunoglobulin 0.5–1 g/kg over 2 hours and repeat in 12 hours if necessary.[6] **Intravenous immunoglobulin for suspected or proven infection in neonates:** The results of the INIS trial, which enrolled 3493 infants, and meta-analyses (n = 3973) showed no reduction in mortality during hospital stay or death or major disability at two years of age. Although based on a small sample size (n = 266), IgM-enriched IVIg does not significantly reduce mortality during hospital stay in infants with suspected infection.

	Routine administration of IVIg or IgM-enriched IVIg to prevent mortality in infants with suspected or proven neonatal infection is not recommended.[7] (LOE I, GOR A) **Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants:** IVIg administration results in a 3% reduction in sepsis and a 4% reduction in one or more episodes of any serious infection but is not associated with reductions in other clinically important outcomes, including mortality. Prophylactic use of IVIg is not associated with any short-term serious side effects. The decision to use prophylactic IVIg will depend on the costs and the values assigned to the clinical outcomes.[8] (LOE I, GOR B) **Fetal and neonatal alloimmune thrombocytopenia (F-NAIT):** National Blood Authority Patient Blood Management Guidelines for Neonatal and Paediatrics: There are case reports of IVIg for NAIT. For neonates with F-NAIT, IVIg may be considered. Treatment of the neonate: 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists. [4] (LOE IV, GOR C/D) **Neonatal myasthenia gravis:** Several case reports of variable response to IVIg up to 2 g/kg in infants with neonatal myasthenia gravis.[9-12] (LOE IV, GOR C) **Newborns with severe enterovirus infection:** In infants <7 days age at presentation with severe enterovirus infection (hepatitis with coagulopathy and thrombocytopenia) caused by coxsackievirus B, early IVIg therapy 2–2.5 g/kg was independently associated with a favourable prognosis. [13] (LOE IV, GOR C) **Neonatal hemochromatosis – gestational alloimmune liver disease (GALD):** No controlled clinical trials have assessed the efficacy of IVIg for GALD. Several observational studies reported improved outcomes of pregnancies at risk of GALD with antenatal IVIg. [14–16] There is less evidence for use of postnatal IVIg in infants with GALD. In the largest, historical control study, the majority received either no disease directed therapy (N = 46) or a cocktail of chelation and antioxidants (N = 54). Their overall rate of survival was 13%. IVIg/double volume exchange therapy was applied to 20 patients, with 9 (45%) surviving, and 14 received a liver transplant with 6 (43%) surviving. [17] National Blood Authority proposed recommendation: Neonate with neonatal hemochromatosis – Maintenance IVIg 1–2 g/kg following exchange transfusion in the first 7 days and then 1 g/kg weekly, as required. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1 g/kg per day is contraindicated for some IVIg products. [18] [LOE III-3, GOR C] **Safety:** Donors are screened for antibodies to HIV and Hepatitis B and C. Prophylactic use of IVIg has not been associated with any short-term serious side effects in newborns.[7]
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Authors Contribution

Original author/s	David Osborn
Revision author/s	
Expert review	Helen Lily, Gemma Crighton, Diana Moore
Evidence Review	David Osborn
Nursing Review	Eszter Jozsa, Robyn Richards
Pharmacy Review	Jing Xiao, Cindy Chen, Carmen Burman
NMF Group contributors	Nilkant Phad, Himanshu Popat, Michael Hewson, Arun Sasi, Roland Broadbent
Final content and editing review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty