Intravenous Immunoglobulin (IVIG) – Privigen/Privigen AU

For newborn use only

2024

Alert	If the patient has ANY adverse reaction, stop infusion and call a medical officer IMMEDIATELY. If the indication is in the approved list of NBA, prescriber to request the product through BloodSTAR. BloodSTAR will issue either Privigen AU/Privigen as per the availability. Privigen is not interchangeable with Privigen AU. Flebogamma 5% and 10% should not be given to neonates due to undiagnosed hereditary fructose intolerance - Sorbitol in Flebogamma can be fatal in this patient population.
Indication	**<u>Funded and approved through BloodSTAR</u>** 1. Neonatal alloimmune thrombocytopenia (NAIT) 2. Immune thrombocytopenic purpura 3. Primary immunodeficiency diseases 4. Secondary hypogammaglobulinaemia 5. Neonatal haemochromatosis – gestational alloimmune liver disease (GALD) **<u>Non-funded and may require approval as per local facility</u>** 6. Haemolytic disease of the newborn (HDN). 7. Neonatal myasthenia gravis 8. Severe neonatal enterovirus infection including myocarditis or hepatitis 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, may be provided locally under Jurisdictional Direct Orders (e.g. Individual Patient Usage (IPU) forms in New South Wales) (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	Privigen AU – 10% intravenous immunoglobulin Privigen – 10% intravenous immunoglobulin
Presentation	Privigen AU – Available in vials as 5g (50mL), 10g (100mL), 20g (200mL). Privigen 10% – Available in vials as 5g (50mL), 10g (100mL), 20g (200mL) and 40g (400mL).
Dosage	The medical officer should prescribe in the following manner: (1) Brand of IVIG and the % concentration (e.g. Privigen 10) (2) Dose in grams and the volume in mL (e.g. 2 g/20 mL) (3) Rate of infusion (see Administration section) LOOP DIURETICS SHOULD BE AVOIDED AROUND THE TRANSFUSION TIME TO AVOID VOLUME DEPLETION. **Haemolytic disease of newborn due to Rh- or ABO-incompatibility** 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 as per the advice of paediatric haematologist **Immune thrombocytopenic purpura (ITP):** 1 g/kg IV. Repeat if required as per the advice of paediatric haematologist. **Immunodeficiency/Secondary hypogammaglobulinaemia:** As per the advice of the paediatric immunologist. Suggested dose: 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. **Neonatal haemochromatosis:** 1–2 g/kg/day IV following exchange transfusion in the first 7 days and then 1 g/kg weekly, as required.
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – Commence at the minimum rate of infusion and dose adjusted and infusion rate adjusted based on the clinical judgement.[20] Hepatic impairment – No dose adjustment is required.
Maximum daily dose	2 g/kg/day. Enterovirus infection: 2.5 g/kg/day
Route	Intravenous.
Preparation	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 or pharmacy.
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. The name and batch number of the product should be recorded. • Requires a surgically clean procedure. • Given via a dedicated 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	Continuous cardiorespiratory monitoring of all vital signs for at least 1 hour prior to, during and for at least 1 hour after the 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, blood pressure, SaO_2) should then be checked and recorded:[21] • 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	Renal failure
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 and notify Medical Officer and the Blood bank.
	Severe reactions are uncommon especially in neonates.
	The following adverse reactions have been reported in adults and these can also be applied to neonates:[20]
	• Hypersensitivity and anaphylaxis
	• Haemolytic anaemia
	• Aseptic meningitis syndrome
	  ○ begins within several hours to 2 days following IVIg.
	  ○ Cerebrospinal fluid analysis shows elevated white cell and protein but negative culture.
	• Thromboembolism
	• Acute renal failure – In adults, renal dysfunction have been predominantly associated with IVIG products containing excipients such as sucrose, glucose and maltose. Privigen AU does not contain sucrose, maltose or glucose.
	• Transfusion related lung injury (TALI)

Overdose	Manage circulatory overload. For further information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).
Compatibility	Fluids: Sodium chloride 0.9% for priming and flushing. Can be diluted with glucose 5%.[20] 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. Privigen is not interchangeable with Privigen AU.
Storage	Store below 25^0C. Do not freeze. Protect from light.
Special Comments	If not yet done – newborn screening (NBS) should be performed prior to infusion and repeated as per blood transfusion/Newborn Blood Spot Screening Test (NBST) policy.
Evidence	**Efficacy:** **Rhesus and ABO-mediated haemolytic disease of newborn:** 2018 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 intravenous immunoglobulin (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] 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).[1] The 2016 National Blood Authority Patient Blood Management Guidelines on IVIG for Neonatal and Paediatrics: In neonates with haemolytic disease of the fetus and newborn, the use of IVIG is not recommended.[2] These recommendations are under review as of July 2023. NICE Practice Guideline recommends use of IVIG 500 mg/kg over 4 hours as an adjunct to continuous intensified phototherapy in cases of Rh- or ABO haemolytic disease when the serum bilirubin continues to rise by more than 8.5 µmol/litre per hour.[3] The AAP Subcommittee on Hyperbilirubinemia Clinical Practice Guideline 2004 recommends IVIG 0.5-1.0 g/kg over 2 hours

and repeat in 12 hours if necessary 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.[4] ANMF consensus: 2018 Cochrane review was dominated by two large studies. These two studies included all direct antiglobulin positive (DAT+) neonates regardless of hyperbilirubinaemia severity. This results in their being attributed undue weight and in skewing of the overall analysis toward IVIG ineffectiveness. This is a shortcoming as most infants with haemolytic disease of the newborn (HDN) respond well to intensive phototherapy and never need an exchange transfusion (ET) and do not routinely need IVIG.[1]

2022 International panel of a group of haematologists, neonatologists and transfusion specialists reviewed the role regarding the role of IVIG as an alternative to prevent the use of exchange transfusion. The group acknowledged that ET is invasive and associated with risks. Their recommendations are consistent with 2018 Cochrane review that IVIG should not be routinely used to treat Rh or ABO antibody-mediated HDN. However, the panel did not provide specific guidance in situations where hyperbilirubinaemia is severe (and ET is imminent), or when ET is not readily available.[5] While ANMF group and New South Wales agree with their conclusion that high-quality studies are urgently needed to assess the optimal use of IVIG in patients with HDN, we need to consider the current consensus of the senior clinicians working at tertiary academic NICUs, which is along the lines of the American Academy of Pediatrics 2004 guidelines and NICE 2010 guidelines.[3,4]

ANMF group and the New South Wales and the Australian Capital Territory NICU directors consensus (June 2023): While waiting for the outcomes of any future studies, the targeted use of IVIG for selected neonates with immune-mediated HDN in whom the TSB is rising despite intensive phototherapy or the TSB level is within 35–50 µmol/L of the exchange level is on balance more likely to provide benefit than harm and remains a prudent approach at bedside.[6]

Intravenous immunoglobulin for suspected or proven infection in neonates: The updated Cochrane 2020 review identified a total of 9 studies evaluating 3973 infants. Mortality during hospital stay in infants with clinically suspected infection was not significantly different after IVIG treatment. Death or major disability at 2 years corrected age was not significantly different in infants with suspected infection after IVIG treatment. Mortality during hospital stay was not significantly different after IVIG treatment in infants with proven infection. Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with proven infection. Mortality during hospital stay in infants with clinically suspected or proven infection was not significantly different after IVIG treatment. Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with suspected or proven infection. Length of hospital stay was not reduced for infants with suspected or proven infection. No significant difference in mortality during hospital stay after administration of IgM-enriched IVIG for suspected infection was reported. The undisputable results of the INIS trial, which enrolled 3493 infants, and he updated meta-analyses (n = 3973) showed no reduction in mortality during hospital stay, or death or major disability at two years of age in infants with suspected or proven infection. The latest update also provided additional evidence that 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. No further research is 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.[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.[2] (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.[2]
Practice points	
References	1. Zwiers C et al. Immunoglobulin for alloimmune hemolytic disease in neonates. Cochrane Database Syst Rev. 2018 Mar 18;3:CD003313. doi: 10.1002/14651858.CD003313.pub2. PubMed PMID:29551014 2. National Blood Authority (NBA). Patient Blood Management Guidelines: Module 6 – Neonatal and Paediatrics. NBA, Canberra, Australia. 2016. 3. NICE Guideline. Jaundice in newborn babies under 28 days. Clinical guideline Published: 19 May 2010 nice.org.uk/guidance/cg98. 4. American Academy of Pediatrics Subcommittee. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316. 5. Lieberman L, Lopriore E, Baker JM, Bercovitz RS, Christensen RD, Crighton G, et al. International guidelines regarding the role of IVIG in the management of Rh-and ABO-mediated haemolytic disease of the newborn. British Journal of Haematology. 2022;198(1):183-95. 6. Hansen TWR, Akkök CA, Watchko JF. International guidelines regarding the role of intravenous immunoglobulin in the management of RhD-and ABO-mediated haemolytic disease of the newborn—reconsidering the recommendations. British Journal of Haematology. 2022;199(3):452-3. 7. Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or proven infection in neonates. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub6. Accessed 29 June 2023. 8. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD000361. DOI: 10.1002/14651858.CD000361.pub4. Accessed 29 June 2023. 9. Zifman E, Litmanovitz I, Segal G, Regev R, Watemberg N. Marked hypotonia in an infant of a mother with Devic disease. J Child Neurol. 2010;25:746-7. 10. O'Carroll P, Bertorini TE, Jacob G, Mitchell CW, Graff J. Transient neonatal myasthenia gravis in a baby born to a mother with new-onset anti-MuSK-mediated myasthenia gravis. J. 2009;11:69-71. 11. Tagher RJ, Baumann R, Desai N. Failure of intravenously administered immunoglobulin in the treatment of neonatal myasthenia gravis. J Pediatr. 1999;134:233-5.

	12. Bassan H, Muhlbaur B, Tomer A, Spirer Z. High-dose intravenous immunoglobulin in transient neonatal myasthenia gravis. Pediatr Neurol. 1998;18:181-3. 13. Yen MH, Huang YC, Chen MC, Liu CC, Chiu NC, Lien R, Chang LY, Chiu CH, Tsao KC, Lin TY. Effect of intravenous immunoglobulin for neonates with severe enteroviral infections with emphasis on the timing of administration. J Clin Virol. 2015;64:92-6. 14. Whitington PF, Kelly S, Taylor SA, Nobrega S, Schreiber RA, Sokal EM, Hibbard JU. Antenatal Treatment with Intravenous Immunoglobulin to Prevent Gestational Alloimmune Liver Disease: Comparative Effectiveness of 14-Week versus 18-Week Initiation. Fetal Diagnosis and Therapy. 2018;43:218-25. 15. Lee SS, Lee CH, Kawada P, O'Loughlin E V, Magoffin A, Gaskin KJ, Stormon MO. Long term outcome of neonatal hemochromatosis: A review of two decades of experience. Journal of Gastroenterology and Hepatology (Australia). 2014;2):152. 16. Baruteau J, Heissat S, Broue P, Collardeau-Frachon S, Bouvier R, Fabre M, Debiec H, Ronco P, Uzan M, Narcy P, Cordier MP, Lachaux A, Lamireau T, Elleau C, Filet JP, Mitanchez D, Dupuy MP, Salaun JF, Odent S, Davison J, Debray D, Guigonis V. Transient neonatal liver disease after maternal antenatal intravenous IG infusions in gestational alloimmune liver disease associated with neonatal haemochromatosis. Journal of Pediatric Gastroenterology and Nutrition. 2014;59:629-35. 17. Taylor SA, Kelly S, Alonso EM, Whitington PF. The Effects of Gestational Alloimmune Liver Disease on Fetal and Infant Morbidity and Mortality. Journal of Pediatrics. 2018;196:123-8. 18. National Blood Authority Specialist Working Group for Haematology. Proposed changes to the criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition 2012. https://www.blood.gov.au/ accessed 13/06/2018. 19. Basta M, Branch DR. 7th International Immunoglobulin Conference: Mechanisms of action. Clin Exp Immunol. 2014;178 Suppl 1:87-8 and 111. 20. Privigen AU. Product info. Accessed online on 6 July 2023. 21. Australian and New Zealand Society of Blood Transfusion. Australian College of Nursing. Guidelines for the administration of blood products. 3rd Edition, Revised February 2024.

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