Specialist Working Group for Haematology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT):**	**Fetal and neonatal alloimmune thrombocytopenia (FNAIT)**	Revised condition name. Up to date spelling of fetal.
Specialty	Haematology	Haematology	
Chapter	6	6	
Specific Conditions		Fetal alloimmune thrombocytopenia (FAIT) Neonatal alloimmune thrombocytopenia (NAIT) Neonate - mother with ITP	
Level of Evidence	Small case studies only; insufficient data (Category 4a).	Small case studies only; insufficient data (Category 4a).	
Description and Diagnostic Criteria	FMAIT/NAIT develops because of maternal sensitisation to foetal platelets that possess a paternally inherited antigen. In Caucasians, the antigen is human platelet antigen (HPA) 1a in 80% of cases and HPA-5b in 15%, but other antigens are also implicated. The mother's antibodies cross the placenta and coat the baby's platelets, with accelerated platelet clearance leading to thrombocytopenia. This may result in serious and potentially life-threatening bleeding in the foetus or neonate. Pathogenesis is analogous to that of haemolytic disease of the newborn due to red cell	FAIT & NAIT develops because of maternal sensitisation to fetal platelets that possess a paternally inherited antigen. In Caucasians, the antigen is human platelet antigen (HPA) 1a in 80% of cases and HPA-5b in 15%, but other antigens are also implicated. The mother's antibodies cross the placenta and coat the baby's platelets, with accelerated platelet clearance leading to thrombocytopenia. This may result in serious and potentially life-threatening bleeding in the fetus or neonate. Pathogenesis is analogous to that of haemolytic	Update to diagnostic description to address the occasional instance where neonate will present with thrombocytopenia due to maternal ITP. This requires one-off treatment.

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	antigen-antibody incompatibility. The aim of management of the thrombocytopenic foetus or neonate is to increase the platelet count. If foetal blood sampling reveals thrombocytopenia, IVIg may be administered weekly to the mother, with or without steroids, until delivery. Recent studies using IVIg weekly from around 20 weeks gestation, without foetal blood sampling, have shown reduced foetal and neonatal morbidity. This approach may be used for current pregnancies where the condition in a previous pregnancy was not associated with a foetal death or severe haemorrhage. Testing on maternal blood for foetal DNA or early genetic testing of the foetus (for platelet genotype) may predict the need to use IVIg. Management of this condition is a specialised area and may include administration of HPA-compatible intrauterine and/or neonatal platelet transfusions. Further information regarding specialised platelet support is available from the Blood Service. Random (non-HPA-matched) platelets may be of benefit in the neonatal setting	disease of the newborn due to red cell antigen–antibody incompatibility. The aim of management of the thrombocytopenic fetus or neonate is to increase the platelet count. Instances of neonatal thrombocytopenia can occur in situations where the mother has idiopathic (autoimmune) thrombocytopenic purpura (ITP). If fetal blood sampling reveals thrombocytopenia, IVIg may be administered weekly to the mother, with or without steroids, until delivery. Recent studies using intravenous immunoglobulin (IVIg) weekly from around 20 weeks gestation, without fetal blood sampling, have shown reduced fetal and neonatal morbidity. This approach may be used for current pregnancies where the condition in a previous pregnancy was not associated with a fetal death or severe haemorrhage. Where a previous pregnancy was affected in the context of demonstrated maternal antibodies, the subsequent pregnancy is likely to be more severely affected where the fetus is positive to the relevant paternal antigen. Testing on	Amendments to highlight the risks of subsequent pregnancies in line with expert opinion points from the Patient Blood Management guidelines – Module 6 – neonatal and paediatric.

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	when matched platelets are not available (Kiefel 2006).	maternal blood for fetal DNA or early genetic testing of the fetus (for platelet genotype) by amniocentesis may predict the need to use IVIg. Management of this condition is a specialised area and may include administration of HPA-compatible intrauterine and/or neonatal platelet transfusions. Further information regarding specialised platelet support is available from the Blood Service. Random (non-HPA-matched) platelets may be of benefit in the neonatal setting when matched platelets are not available (Kiefel et al 2006).	
Justification for Evidence Category	Evidence from randomised trials (Berkowitz et al 2006, Bussel et al 1996), case series (Kiefel et al 2006, Yinon et al 2006) and a review (Spencer and Burrows 2001) shows that IVIg modulates the course of this condition. A 2004 Cochrane review (Rayment et al 2005) reported on one randomised controlled trial (RCT) comparing IVIg plus dexamethasone with IVIg alone. This RCT was methodologically sound, but too small to detect differences among comparison groups.	Evidence from randomised trials (Berkowitz et al 2006, Bussel et al 1996), case series (Kiefel et al 2006, Yinon et al 2006) and a review (Spencer and Burrows 2001) shows that IVIg modulates the course of this condition. A 2004 Cochrane review (Rayment et al 2005) reported on one randomised controlled trial (RCT) comparing IVIg plus dexamethasone with IVIg alone. This RCT was methodologically sound, but too small to detect differences among comparison groups.	
Diagnosis is required		No / Which Speciality	

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Diagnosis must be verified		No / Which Specialty	
Exclusion Criteria			
Indication for use	Prevention or treatment of foetal or neonatal thrombocytopenia or haemorrhage.	**Prevention or treatment of fetal thrombocytopenia or haemorrhage.** **Prevention or treatment of neonatal thrombocytopenia or haemorrhage.**	Indication has been split due to the differing eligibility criteria and evidence requirements for the relevant patient populations.
Qualifying Criteria	Clinical suspicion of FMAIT in antenatal or neonatal setting based on clinical and laboratory features, including: 1. Thrombocytopenia or spontaneous haemorrhage in the foetus; OR 2. Thrombocytopenia with or without haemorrhage in the neonate; OR 3. Unexplained foetal death in a previous pregnancy and the presence of maternal platelet-specific alloantibodies that are known or suspected to cause this condition (most commonly HPA-1a or	**Prevention or treatment of fetal thrombocytopenia or haemorrhage.** Clinical suspicion of FAIT in the antenatal setting based on clinical and laboratory features: • Evidence of foetal thrombocytopenia OR • Evidence of spontaneous fetal haemorrhage OR • Unexplained previous fetal death or previous affected sibling and maternal platelet-specific alloantibodies known or suspected to cause this condition and directed against current paternal antigens (most commonly HPA-1a or HPA-5b). **Where fetal blood sampling demonstrates a failure to improve the platelet count, national guidelines recommend the consideration of intrauterine platelet transfusion rather than Ig therapy.** *Ref: Patient Blood Management Guidelines – Module 6 –Neonatal and paediatric (Section*	Criteria are largely consistent with existing criteria, with the addition of acknowledgement of the unusual instance of neonates becoming thrombocytopenic due to maternal ITP. While an infrequent occurrence, it does occur and is treated under the current indications. Modified in response to feedback from the public consultation including a qualification to confirm the same paternity of this pregnancy and thus continued risk to this fetus. In addition, a script has been added to reflect the Expert opinion point 24 of the Patient Blood Management Guidelines – Module 6 –Neonatal and paediatric.

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	HPA-5b).	*4.2)* **Prevention or treatment of neonatal thrombocytopenia or haemorrhage.** • Evidence of thrombocytopenia <30 x 10^9/L in a neonate with NAIT or where a diagnosis of NAIT is highly suspected. OR • Evidence of thrombocytopenia <30 x 10^9/L in offspring of a mother with ITP.		
Review Criteria	• Foetal or neonatal morbidity and mortality in the context of maternal alloantibodies.	**Prevention or treatment of fetal thrombocytopenia or haemorrhage.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. **Outcome data to be measured** • Fetal/neonatal morbidity and/or mortality in the context of maternal alloantibodies. • Occurrence and severity of thrombocytopenia in the neonate. Neonates with NAIT are eligible under the indication for prevention or treatment of neonatal thrombocytopenia or haemorrhage.	Data on fetal or neonatal outcome will be collected and maternal alloantibodies.	

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	• Occurrence and severity of thrombocytopenia in the neonate. • Maternal HPA-1a antibody level (if assay is available). Note that the strength/titre of maternal antibody level, even if available, is not proven clinically relevant and not able to be compared readily between laboratories at this time.	**Prevention or treatment of neonatal thrombocytopenia or haemorrhage.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. **Outcome data to be measured** • Occurrence and severity of thrombocytopenia in the neonate. • Maximum platelet count achieved within 7 days of Ig treatment.	Script added to advise prescribes that neonates are also eligible under a different indication, if required. This is one-off treatment - outcome data can be collected but will not be mandatory. Period for response amended from within 72 hours to within 7 days.
Dose	Maternal dose: 1 g/kg weekly throughout pregnancy, with starting time tailored to individual risk profile and history if relevant. Other doses and schedules have been used and some studies have used IVIg in conjunction with steroids. Treatment of the neonate: 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical**	**Prevention or treatment of fetal thrombocytopenia or haemorrhage.** **Maternal dose:** 1 g/kg (up to a maximum weight of 100 kg) weekly throughout pregnancy, with starting time tailored to individual risk profile and history if relevant. Other doses and schedules have been used and some studies have used IVIg in conjunction with steroids. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. **Refer to the current product information sheet for further information.** **Prevention or treatment of neonatal**	Dosing is unchanged. SWG recommends a maximum maternal weight of 100Kg be introduced due to the high incidence of obesity on the pregnant population.

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	outcome for each patient.	**thrombocytopenia or haemorrhage.** **Treatment of the neonate** - 1 g/kg. Occasionally more than one dose is required if thrombocytopenia persists. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient **Refer to the current product information sheet for further information.**	

BIBLIOGRAPHY

Berkowitz, RL, Kolb, EA, McFarland, JG, et al 2006, ‚Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia', *Obstetrics & Gynecology*, vol. 107, no. 1, pp. 91–6.

Bussel, JB, Berkowitz, RL, Lynch, L, et al 1996, 'Antenatal management of alloimmune thrombocytopenia with intravenous immunoglobulin: a randomised trial of the addition of low dose steroid to intravenous gamma globulin', *American Journal of Obstetrics & Gynecology*, vol. 74, no. 5, pp. 1414–23.

Bussel J.B, Zabusky MR, Berkowitz RL et al, 1997. 'Fetal Alloimmune Thrombocytopenia.' *N Engl J Med*. vol. 337(1):pp22-26.

Kiefel, V, Bassler, D, Kroll, H, et al 2006, 'Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia', *Blood*, vol. 107, no. 9, pp. 3761–3.

Rayment, R, Brunskill, SJ, Stanworth, S, et al 2005, 'Antenatal interventions for fetomaternal alloimmune thrombocytopenia (Cochrane Review)', in *The Cochrane Library*, Issue 1, John Wiley & Sons, Ltd, Chichester, UK.

Spencer, JA & Burrows, RF 2001, 'Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis', *Australia New Zealand Journal of Obstetrics and Gynaecology*, vol. 41, no. 1, pp. 45–55.

Yinon, Y, Spira, M, Solomon, O, et al 2006, 'Antenatal noninvasive treatment of patients at risk for alloimmune thrombocytopenia without a history of intracranial hemorrhage', *American Journal of Obstetrics & Gynecology,* vol. 195, no. 4, pp. 1153–7.

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