Fetal and neonatal alloimmune thrombocytopenia (FNAIT)

Conditions for which IVIg has an established therapeutic role.

Specific Conditions	• Fetal alloimmune thrombocytopenia (FAIT) • Neonatal alloimmune thrombocytopenia (NAIT)
Indication for IVIg Use	• Prevention or treatment of fetal thrombocytopenia or haemorrhage where no previous pregnancy affected by FNAIT • Prevention or treatment of fetal alloimmune thrombocytopenia where unexplained previous fetal death or previous sibling affected by FNAIT • Prevention or treatment of neonatal thrombocytopenia or haemorrhage
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Fetal alloimmune thrombocytopenia (FAIT) and neonatal alloimmune thrombocytopenia (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 disease of the newborn due to red cell antigen–antibody incompatibility. The aim of management of the thrombocytopenic fetus or neonate is to treat or prevent severe bleeding by increasing the platelet count. Instances of neonatal thrombocytopenia can also occur in situations where the mother has idiopathic (autoimmune) thrombocytopenic purpura (ITP). If fetal blood sampling reveals thrombocytopenia, intravenous immunoglobulin (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 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 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. Pacheco et al 2011 recommended a management and treatment algorithm based on risk stratification where previous pregnancies have been variably affected by FNAIT and maternal alloantibodies are demonstrated against current paternal/fetal antigens. This approach was endorsed by Petersen et al, 2013 through the publishing of the UK guideline.

Qualifying Criteria for IVIg Therapy

Prevention or treatment of fetal thrombocytopenia or haemorrhage where no previous pregnancy affected by FNAIT

This indication relates only to prevention or treatment of fetal thrombocytopenia or haemorrhage. Neonates with neonatal alloimmune thrombocytopenia (NAIT) are eligible under the indication for **prevention or treatment of neonatal thrombocytopenia or haemorrhage.**

- Evidence of fetal thrombocytopenia

  OR

- Evidence of spontaneous fetal haemorrhage

Where fetal blood sampling demonstrates there has been a failure to improve the platelet count, national guidelines recommend the consideration of intrauterine platelet transfusion rather than further Ig therapy.

Ref: Patient Blood Management Guidelines – Module 6 –Neonatal and paediatric (Section 4.2)

Prevention or treatment of fetal alloimmune thrombocytopenia where unexplained previous fetal death or previous sibling affected by FNAIT

This indication relates only to prevention or treatment of fetal thrombocytopenia or haemorrhage. Neonates with NAIT are eligible under the indication for **prevention or treatment of neonatal thrombocytopenia or haemorrhage.**

- Unexplained previous fetal death or previously affected sibling

  AND

- Maternal platelet-specific alloantibodies known or suspected to cause this condition (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 4.2)

Prevention or treatment of neonatal thrombocytopenia or haemorrhage

This indication relates only to prevention or treatment of neonatal thrombocytopenia or haemorrhage. Pregnant women with FAIT are eligible under the indication for **prevention or treatment of fetal alloimmune thrombocytopenia**.

- 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 for Assessing the Effectiveness of IVIg Use

Prevention or treatment of fetal thrombocytopenia or haemorrhage where no previous pregnancy affected by FNAIT

This indication relates only to prevention or treatment of fetal alloimmune thrombocytopenia. Neonates with NAIT are eligible under the indication for **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.

- Fetal or neonatal morbidity or mortality in the context of maternal alloantibodies

  AND

- 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**.

Prevention or treatment of fetal alloimmune thrombocytopenia where unexplained previous fetal death or previous sibling affected by FNAIT

This indication relates only to prevention or treatment of fetal alloimmune thrombocytopenia. Neonates with NAIT are eligible under the indication for **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.

- Fetal or neonatal morbidity or mortality in the context of maternal alloantibodies

  AND

- Occurrence and severity of thrombocytopenia in the neonate

Prevention or treatment of neonatal thrombocytopenia or haemorrhage

This indication relates only to prevention or treatment of neonatal thrombocytopenia or haemorrhage. Pregnant women with FAIT are eligible under the indication for **prevention or treatment of fetal alloimmune thrombocytopenia.**

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy.

- Occurrence and severity of thrombocytopenia in the neonate

  AND

- Maximum platelet count achieved within 7 days of Ig treatment

Dose	
	Prevention or treatment of fetal thrombocytopenia or haemorrhage where no previous pregnancy affected by FNAIT • **Dose during pregnancy** - 1 g/kg (up to a maximum maternal weight of 100 kg) weekly throughout pregnancy. 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 on dose, administration and contraindications.
	Prevention or treatment of fetal alloimmune thrombocytopenia where unexplained previous fetal death or previous sibling affected by FNAIT • **Dose during pregnancy** - 1 to 2 g/kg (up to a maximum maternal weight of 100 kg) weekly throughout pregnancy, with starting time and dose tailored to individual risk profile and history. Pacheco et al, 2011 recommends Ig treatment (at times in conjunction with steroids): ○ Previous infant with thrombocytopenia but no intracranial haemorrhage – from 20 weeks at 1 to 2 g/kg, increasing to 2 g/kg at 32 weeks until birth; ○ Previous fetus or neonate with intracranial haemorrhage diagnosed at 28 or more weeks gestation – from 12 weeks at 1g/kg; 1 to 2 g/kg from 20 weeks, increasing to 2 g/kg from 28 weeks until birth; ○ Previous fetus or neonate with intracranial haemorrhage diagnosed at less than 28 weeks gestation - from 12 weeks at 2 g/kg until birth; 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 on dose, administration and contraindications.
	Prevention or treatment of neonatal thrombocytopenia or haemorrhage • **Neonatal dose** - 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 on dose, administration and contraindications.

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. https://www.ncbi.nlm.nih.gov/pubmed/16394045

Bussel, JB, Berkowitz, RL, Lynch, L, et al 1996, 'Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomised trial of the addition of low dose steroid to intravenous gamma globulin', *American Journal of Obstetrics & Gynecology*, vol. 174, no. 5, pp. 1414–23.

Bibliography

https://www.ncbi.nlm.nih.gov/pubmed/9065105

Bussel, JB, Zabusky, MR, Berkowitz, RL, et al 1997, 'Fetal Alloimmune Thrombocytopenia', *The New England Journal of Medicine*, vol. 337, no. 1, pp. 22–26.
https://www.nejm.org/doi/full/10.1056/nejm199707033370104

Bussel, JB, Berkowitz, RL, Hung, C, et al 2010, 'Intracranial haemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus', *American Journal of Obstetrics and Gynaecology*, vol. 203, no. 2, pp. 113–114.
https://www.ncbi.nlm.nih.gov/pubmed/20494333

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.
https://www.ncbi.nlm.nih.gov/pubmed/16403916

Ontario Regional Blood Coordinating Network 2016, 'Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0' [online]. Available from: http://transfusionontario.org/en/

Pacheco, LD, Berkowitz, RL, Moise, KJ, et al 2011, 'Fetal and Neonatal Alloimmune Thrombocytopenia: A Management Algorithm based on Risk Stratification', *Obstetrics and Gynecololgy*, vol. 118, no. 5, pp. 1157–63.
https://www.ncbi.nlm.nih.gov/pubmed/22015886

Petersen, J, McFarland, J, Curtis, BR, et al 2013, 'Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management', *British Journal of Haematology*, vol.161, no. 1, pp. 3–14.
https://www.ncbi.nlm.nih.gov/pubmed/23384054

Rayment, R, Brunskill, SJ, Soothill, PW, et al 2005, 'Antenatal interventions for fetomaternal alloimmune thrombocytopenia', *Cochrane Database of Systematic Reviews*, Issue 1.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004226.pub3/pdf

Salomon, O & Rosenberg N 2013, 'Predicting risk severity and response of fetal neonatal alloimmune thrombocytopenia', *British Journal of Haematology*, vol. 162, no. 3, pp. 304–312.
https://www.ncbi.nlm.nih.gov/pubmed/23672281

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.
https://www.ncbi.nlm.nih.gov/pubmed/11284646

Winkelhorst, D, Murphy, MF, Greinacher, A, et al 2017, 'Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review', *Blood*, vol. 129, no. 1, pp. 1538–1547.
https://www.ncbi.nlm.nih.gov/pubmed/28130210, http://www.bloodjournal.org/content/early/2017/01/27/blood-2016-10-739656

UK Department of Health 2011, 'Clinical Guidelines for Immunoglobulin Use: Second Edition Update', Available from:
https://www.gov.uk/government/publications/clinical-guidelines-for-immunoglobulin-use-second-edition-update

UK Department of Health 2011, 'Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster'. Available from:
http://igd.mdsas.com/clinical-info/

Yinon, Y, Spira, M, Solomon, O, et al 2006, 'Antenatal noninvasive treatment of patients at risk for alloimmune thrombocytopenia without a history of intracranial haemorrhage', *American Journal of Obstetrics & Gynecology,*vol.195, no.4, pp.1153–7.
https://www.ncbi.nlm.nih.gov/pubmed/17000248

Generated on: 10 July 2018