NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)

This LOP is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this LOP. This LOP has been developed in partnership with the Haematology team at Sydney Children's Hospital and the Australian Red Cross.

1. AIM

- To identify potential cases of neonatal alloimmune thrombocytopenia (NAIT)
- To assist in immediate clinical management of the neonates affected with NAIT
- To arrange appropriate follow up

2. BACKGROUND

- Neonatal alloimmune thrombocytopenia or "NAIT" or fetomaternal alloimmune thrombocytopenia (FMAIT) is a rare but serious condition
- It is associated with significant neonatal morbidity and mortality, including a 20% risk of intracranial haemorrhage (ICH)
- Platelet antigens, inherited from the father and expressed on neonatal platelets, are destroyed by maternal alloantibodies, which cross into the neonatal circulation via transplacental transfer
- Immediate management includes confirmation of diagnosis, use of specific platelets (mostly HPA-1bb) to keep the platelet count above 30 x 10^9/L and immune-modulatory treatment
- There are risks to subsequent offspring, which are higher if the first offspring with identified NAIT experienced an ICH

3. CLINICAL PRACTICE

When to suspect NAIT:

- Severe thrombocytopenia in an otherwise well neonate even if no history of NAIT in previous pregnancies (< 50 x 10^9/L) although NAIT can occur with mild/moderate thrombocytopenia (< 150 x 10^9/L)
- Exclude alternative diagnoses, such as infection, collection error, maternal auto-antibodies (especially maternal ITP), maternal medications, neonatal liver disease
- NAIT in a prior pregnancy (although NAIT can occur in the first pregnancy)

Diagnosis and immediate management:

- Arrange neonatal full blood count if thrombocytopenia is suspected on history or clinical examination
- If the diagnosis is suspected, treat as NAIT (confirmatory tests may take a few days)
- Contact Paediatric Haematology Fellow/Consultant
- Call Australian Red Cross Blood Service (ARCBS) – 1300 478 348
    - 24 hour phone line, request the Medical Officer on call
    - Request rare platelets type HPA-1bb, unless prior platelet genotyping on the parents is available to suggest use of another HPA group
    - Transfuse to keep neonatal platelet count above 30, preferably above 50 x 10^9/L
    - Rare platelets will always be available from ARCBS (usually HPA-1bb platelets)
    - Rare HPA-1bb platelets are also genotyped for other HPA types
    - It may be possible to provide another HPA-type if the HPA antibody is known
- Urgently collect blood from both parents
    - Samples required are indicated on the ARCBS cover page for requests (see appendix A) or can be downloaded from the ARCBS website www.transfusion.com.au

Authors: Marion Mateos (Haem/Onc Fellow, SCH), Glenn Marshall, Sue Russell, David Ziegler, Helen Pearson – Sydney Children's Hospital and the Australian Red Cross
RHW NICU version: Tim Schindler, Srinivas Bolisetty, Antonia Shand
Original: 11 January 2013
Approved by the Newborn Quality Committee 4th February 2013

        - Mother – 20ml clot tube (no gel) and 30ml EDTA tube, Father – 40ml whole blood EDTA tube only
    - The form is available below (see appendix B) or can be downloaded from the ARCBS website www.transfusion.com.au
    - Please use a form for each parent and indicate in "Tests Required Section" that NAIT testing is needed
        - Fresh samples (collected within the last 24 hours) must be delivered, transported at ambient temperature, to ARCBS within working hours Monday to Friday (testing will not occur on a weekend)
    - Advise SEALS Blood Bank and ARCBS about urgency and transport of samples
    - Blood can be couriered to ARCBS, to arrive as early as possible. Preliminary results will be available on the same day if samples arrive by mid-morning
- If preliminary results are positive (for example if maternal serum alloantibodies to HPA-1a are present) then the neonate needs URGENT TREATMENT to reduce the risk of ICH
- Solid Phase platelet (intact platelet panels) antibody investigations and HPA genotyping are performed urgently and results sent out as a preliminary result, which is followed up with definitive MAIPA assays (Monoclonal Antibody-specific Immobilisation of Platelet Antigens assay)
- MAIPA assays have been developed to allow identification and characterisation of antibodies directed against platelets (with platelet glycoproteins)

Treatment:

It is important to maintain platelet counts above 30 x 10^9/L and preferably above 50 x 10^9/L

- Platelet transfusions are the mainstay of initial therapy, followed by IVIG and possibly steroids (platelets are ideally CMV negative and irradiated – if CMV negative platelets are not available, then discuss with the haematologist)
- Volumes advised are 10-20ml/kg
- HPA antigen negative platelets are preferred, but random donor platelets (HPA antigen positive) can also be used safely and effectively if HPA antigen negative platelets are not available
- Repeat testing for platelet level is required (for neonates with severe NAIT, a one-hour post-platelet increment may be useful)
- Please advise ARCBS of the neonate's clinical status and likely need for further rare platelets
- Maternal platelet collection is also a possibility however this procedure is rarely performed (please speak to Blood Bank and ARCBS)
- In addition to platelet transfusion, treatment with IVIG is strongly recommended – the dose is 1g/kg x 2 days (ordered from ARCBS and administered intravenously)
- Consider addition of steroids for severe/ refractory NAIT (suggested dose: IV methylprednisone 1-2mg/kg/ day in 2-3 divided doses x 5 days)
- Seek further advice from Haematology in severe/refractory NAIT cases
- Treatment side effects to be discussed with the parents include (but are not limited to):
    - IVIG – allergic/anaphylactic reactions, fever, headache, aseptic meningitis (rare)
    - Steroids – hypertension (that may require additional treatment), hyperglycaemia, irritability, mood changes, avascular necrosis, transient adrenal suppression
- Arrange head ultrasound to exclude ICH (further imaging may be required)

Follow up:

- As NAIT is purely a consequence of maternal antibodies directed against paternal platelet antigens NAIT will resolve after 1-3 weeks
- Monitoring of platelet counts for at least 2-6 weeks post delivery is recommended
- Consider reporting the case to the Australian NAIT registry to inform epidemiological studies
- Arrange haematology follow-up as an outpatient

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- Arrange referral for parents to a maternal foetal medicine specialist for follow up
- Advise parents that subsequent pregnancies are at risk and early antenatal, or preferably pre-conception, counselling with a maternal foetal medicine subspecialist is recommended

4. EDUCATIONAL NOTES

Epidemiology:

- NAIT accounts for 3% of all fetal and neonatal thrombocytopenia (defined as platelets < 150 x 109/L) and 27% of severe cases (platelets < 50 x 109/L)
- NAIT is associated with significant neonatal morbidity and mortality, including a 20% risk of intracranial haemorrhage (ICH)
- NAIT can occur in the first pregnancy

Risk factors:

- NAIT in a prior pregnancy is a risk factor for NAIT in subsequent pregnancies, especially where there is known discordance between parental HPA (human platelet antigen) types (see table below)
- HPA types vary in frequency across racial groups. The most frequent cause of NAIT in a Caucasian population is anti-HPA-1a antibodies and in Asian populations are anti-HPA-4a antibodies
- Other HPA antibodies implicated in NAIT include anti-HPA-3a, anti-HPA-5b, anti-HPA-15a and anti-HPA-15b
- Severe NAIT and ICH in a prior pregnancy greatly increases the risk of ICH in subsequent pregnancies

Future pregnancies:

- Through NAIT testing, parental HPA typing is determined and the risk to future pregnancies can be predicted (see table below)
- In-utero HPA genotyping can be performed on DNA extracted from amniocytes (DNA extraction, and confirmatory testing that DNA is of foetal origin, is performed by the Molecular Genetics Unit at Prince of Wales Hospital) –the DNA is then referred to the Tissue Typing Department at the ARCBS for HPA-genotyping
- Amniocytes should also be cultured in the cytogenetic laboratory to allow for subsequent retesting if needed
- If NAIT is considered likely either from history and/or prenatal invasive diagnosis, antenatal therapy may be instituted (this may include IVIG and/or steroids and possible in-utero platelet transfusion)
- Treatment depends on the previous history of severity of thrombocytopenia, including any history of previous ICH
- ARCBS can be contacted peri-partum to ensure availability of specific platelets. A follow-up antibody screen post-partum is often useful, to confirm genotyping and determine if additional HPA antibodies have developed

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Causative Maternal HPA allo-antibody	Maternal HPA type	Paternal HPA type	Offspring HPA type	Platelets required for transfusion
Anti-HPA-1a antibody These maternal antibodies are directed against HPA-1a antigens expressed on the neonatal platelets	HPA-1bb	HPA-1aa *or* HPA-1ab	If father HPA-1aa, then 100% of offspring are HPA-1ab, therefore 100% affected If father HPA-1ab, then 50% of offspring affected (HPA-1ab) Offspring who are HPA-1bb will be unaffected	HPA-1bb These are negative for HPA-1a antigens, to which the maternal alloantibodies are directed

5. REFERENCES

1. Bonacossa IA, Jocelyn LJ. Alloimmune thrombocytopenia of the newborn: neurodevelopmental sequelae. American Journal of Perinatology. 1996;13(14): 211-215
2. McQuilten Z, Wood EM, Savoia H et al. A review of pathophysiology and current treatment for neonatal alloimmune thrombocytopenia (NAIT) and introducing the Australian NAIT registry. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011;51:191-198
3. Serrarens-Janssen VM, Semmekrot BA, Novotny VM et al. Fetal/neonatal allo-immune thrombocytopenia (FNAIT): past, present, and future. Obstetrical & Gynecological Survey. 2008; 63(4):239-52
4. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. New England Journal of Medicine. 1993;329(20):1463-1466
5. Bassler D, Greinacher A, Okascharoen C et al. A systematic review and survey of the management of unexpected neonatal alloimmune thrombocytopenia. Transfusion. 2008; 48(1):92-98
6. Kiefel V, Bassler D, Kroll H et al. Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT). Blood. 2006;107 (9): 3761-3763

APPENDIX A: Parental blood sample information

Transplantation & Immunogenetics Services- (NSW)
Red Cross Blood Service
17 O'Riordan St ALEXANDRIA, NSW, 2015
Phone: (02) 9234-2322
Fax: (02) 9234-2326
Email: bookings and samples :ttcbo@redcrossblood.org.au
general enquiries : nswtransplant@redcrossblood.org.au
Web: www.transplantservices.com.au
•ASHI accredited •ASEATTA accredited

REQUEST FORM FOR TISSUE TYPING INVESTIGATIONS

REQUEST FORM:

The request form must be completed accurately and legibly
Information on the form must match that on the sample tube(s).
Sample labels and request forms must have legible handwriting
Ensure that all tubes, at a minimum, are clearly labelled with:

- the patient's full name (family name and given names),
- date of birth
- and date of collection, as shown on the Request Form.

If these are not provided, testing may not proceed.

SPECIMENS:

The quality of typing cannot be guaranteed for samples that are not received at room temperature or not received within 24 hours of collection. Samples (other than frozen samples) should be maintained at room temperature

Paediatric patients/donors: Initial and confirmatory testing-1ml/ACD/birth year up to 8yo, (+ 1/2ml serum for patients at CT).

Samples sent for flow cytometric crossmatching or for final crossmatching (stage 3 testing) prior to living renal transplantation must be pre-booked (please email ttcbo@redcross.org.au).

DELIVERIES: Samples should be sent to:

Transplantation & Immunogenetics Services-NSW
Australian Red Cross Blood Service
Dock A
17 O'Riordan Street ALEXANDRIA NSW 2015.

For any concerns or queries:
Please consult the laboratory for sample requirements (ttcbo@redcrossblood.org.au

SPECIMEN REQUIREMENTS

Bone Marrow Transplantation

Testing	Specimen	Volume	Collection
Initial patient testing	Whole blood	40 mL	ACD tubes
Parental testing	Whole blood	20 mL	ACD tubes
Related donor testing	Whole blood	20 mL	ACD tubes
Confirmatory patient testing	Whole blood	40 mL	ACD tubes
	Clot	10 mL	with gel
Confirmatory related donor testing	Whole blood	40 mL	ACD tubes
Cellular assays Patient Donor	Whole Blood	60-80 mL 40 mL	ACD tubes

Solid Organ Transplantation

Testing	Specimen	Volume	Collection
Recipient entry – NSW/ACT waiting list	Whole blood	60 mL	ACD tubes
	Whole blood	7 mL	EDTA tubes
	Clot	10 mL	with gel
Monthly serum sample for solid organ crossmatch trays. (not required for Liver transplantation)	Clot	10 mL	with gel

Live Donor Kidney Workups

Testing	Specimen	Volume	Collection
Recipient - Stages 1, 2 and 3	Whole blood	60 mL	ACD tubes
	Whole blood	7 mL	EDTA tubes
	Clot	10 mL	with gel
Live donor - Stages 1, 2 and 3	Whole blood	60 mL	ACD tubes
	Whole blood	7 mL	EDTA tubes

Platelet Immunology

Testing	Sample details	Volume	Collection
Fetomaternal Alloimmune Thrombocytopenia (FMAIT)	Mother Whole blood and clot	20 mL	Clot – no gel
		30 mL	EDTA tubes
	Father Whole Blood only	40 mL	EDTA tubes
Refractoriness to Platelet Transfusion	Clot	20mL	Clot no gel
	Patient WBC ct >1x109/L	20mL	ACD
	Patient WB Cct <1x109/L	60mL	ACD
Platelet autoantibodies, Post Transfusion Purpura, Quinine dependent antibodies	Clot	20mL	Clot no gel
	Patient platelet ct <20x10^9/L	nil	nil
	Patient platelet ct.>20x109/L	30 mL	EDTA tubes
	Patient platelet ct.>50x109/L	20mL	EDTA tubes

Non-transplant Patients / Research Samples
Please consult the laboratory (ttcbo@redcrossblood.org.au

APPENDIX B: Parental sample request form

NEW SOUTH WALES TRANSPLANTATION AND IMMUNOGENETICS SERVICE

Australian Red Cross BLOOD SERVICE

RCPA The Royal College of Pathologists of Australasia

NATA

Bookings +61 2 9234 2322
Fax +61 2 9234 2326
Email ttcbo@redcrossblood.org.au
Website www.transplantservices.com.au

Delivery: Dock A, 17 O'Riordan Street
Alexandria, Sydney NSW 2015

Dr P Coghlan

SURNAME (Please print)

GIVEN NAMES **DOB** / / **SEX**

ADDRESS

TELEPHONE **UR No**

Name of Collector, Date and Time

TRANSPLANT CENTRE

REQUESTING DOCTOR PROVIDER No

SURNAME AND INITIALS

TT Specimen No. and Date (for lab use only)

ADDRESS POSTCODE

TELEPHONE FACSIMILE

REPORTS TO BE SENT TO

NAME

ADDRESS

TELEPHONE FACSIMILE

NAME

ADDRESS

TELEPHONE FACSIMILE

CLINICAL NOTES

PROVISIONAL DIAGNOSIS

REASON FOR REQUEST/TYPE OF TRANSPLANT

TEST/S REQUESTED (Please see reverse for code list)

PLEASE COMPLETE RECIPIENT DETAILS BELOW IF SPECIMEN ABOVE IS FROM A POTENTIAL DONOR:

PATIENT NAME

PATIENT DOB / /

RELATIONSHIP OF DONOR TO PATIENT

FOR NON-TRANSPLANT/TRANSFUSION TESTING

ACCOUNT TO BE SENT TO (please tick) ☐ N/A ☐ PATIENT ☐ INTERHOSPITAL ☐ PRIVATE PATH

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FILE COPY

PLEASE USE THE FOLLOWING TEST CODES WHEN REQUESTING TESTS

CL1	Class I Typing (Please specify eg., HLA-A, B or C)
CL2	Class II Typing (Please specify eg., DR, DQ,DP)
CYT	Cytotoxic Antibody Screening (monthly dry tube)
LUM	Luminex HLA Antibody Screen (Please specify eg., if Class I and/or Class II antibody specificity is required)
XM	Crossmatch (Please specify CDC XM or Flow XM)
NAB	Neutrophil Antibody
PAB	Platelet Antibody
PGEN	Platelet Genotyping
B27	Specific Class I Typing
GM	Gene Mutation Testing (Please specify eg., HFE)
	Cellular Assays (Please specify eg. CTLp)

FOR MORE INFORMATION ON TESTING, CODES OR BLOOD VOLUMES:

PHONE 02 9234 2322
EMAIL ttcbo@redcrossblood.org.au
WEB transplantservices.com.au

PLEASE DO NOT DETACH THIS PAGE FROM ORIGINAL REQUEST AND FORWARD WITH SAMPLE.