



Yorkshire & Humber Neonatal ODN (South) Neonatal Network Clinical Guideline

Title: Thrombocytopenia in the Neonate

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal Network (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

A. Summary

1. Aim of guideline

The aim of this guideline is to advise on the initial management and investigation of the neonate with platelet abnormalities.

2. Summary

Thrombocytopenia

Definition; platelet count $<150 \times 10^9/l$ (but check local normal range)

Aetiology; Early onset (<72 hours of age) usually mild
Investigate if bleeding, <50 or persists more than 2 weeks

Late onset (>72 hours of age) more severe
look for underlying cause- sepsis/NEC

Threshold for Bleeding infant (preterm or term) $50 \times 10^9/l$

Treatment; Any infant, not bleeding (preterm or term) $25 \times 10^9/l$

Therapy Platelets 10-15ml/kg

B. Full guideline

1. Background

Thrombocytopenia is commonly seen on the neonatal intensive care unit.

2. Aim

The aim of this guideline is to advise on the initial management and investigation of the neonate with platelet abnormalities.

3. Areas outside remit

Management of infants with suspected/known congenital haematological disorder. Expert advice should be sought from a consultant haematologist/ refer to guideline.

4. Core guideline

- 4.1 Thrombocytopenia
 - 4.1.1 Definition
 - 4.1.2 Aetiology
 - 4.1.2a Early Onset (<72 hours)
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 - 4.1.4 Specific thrombocytopenia conditions
 - 4.1.4.1 Neonatal alloimmune thrombocytopenia (NAIT)
 - 4.1.4.2 Neonatal autoimmune thrombocytopenia

4.1 Thrombocytopenia

Thrombocytopenia is the commonest haematological abnormality, with a prevalence of 1-5% of all newborns, and 22-35% of neonates admitted for intensive care, rising with decreasing gestational age.

4.1.1 Definition

The mean fetal platelet count reaches adult normal range by the end of the 1st trimester, thus infants of all gestations with a platelet count <150x10⁹/l (or below local normal range) can be considered thrombocytopenic.^{1,2}

4.1.2 Aetiology

The aetiology of neonatal thrombocytopenia can be broadly categorized depending on age at onset. Investigations will depend on history, gestation (preterm or term) and clinical condition of the infant- see flow charts 1 and 2.¹

Term infants

Platelet count
$150 \times 10^9 / l$

Bleeding?

Incidental finding?

Test for NAIT
Coagulation tests

Platelets
50?

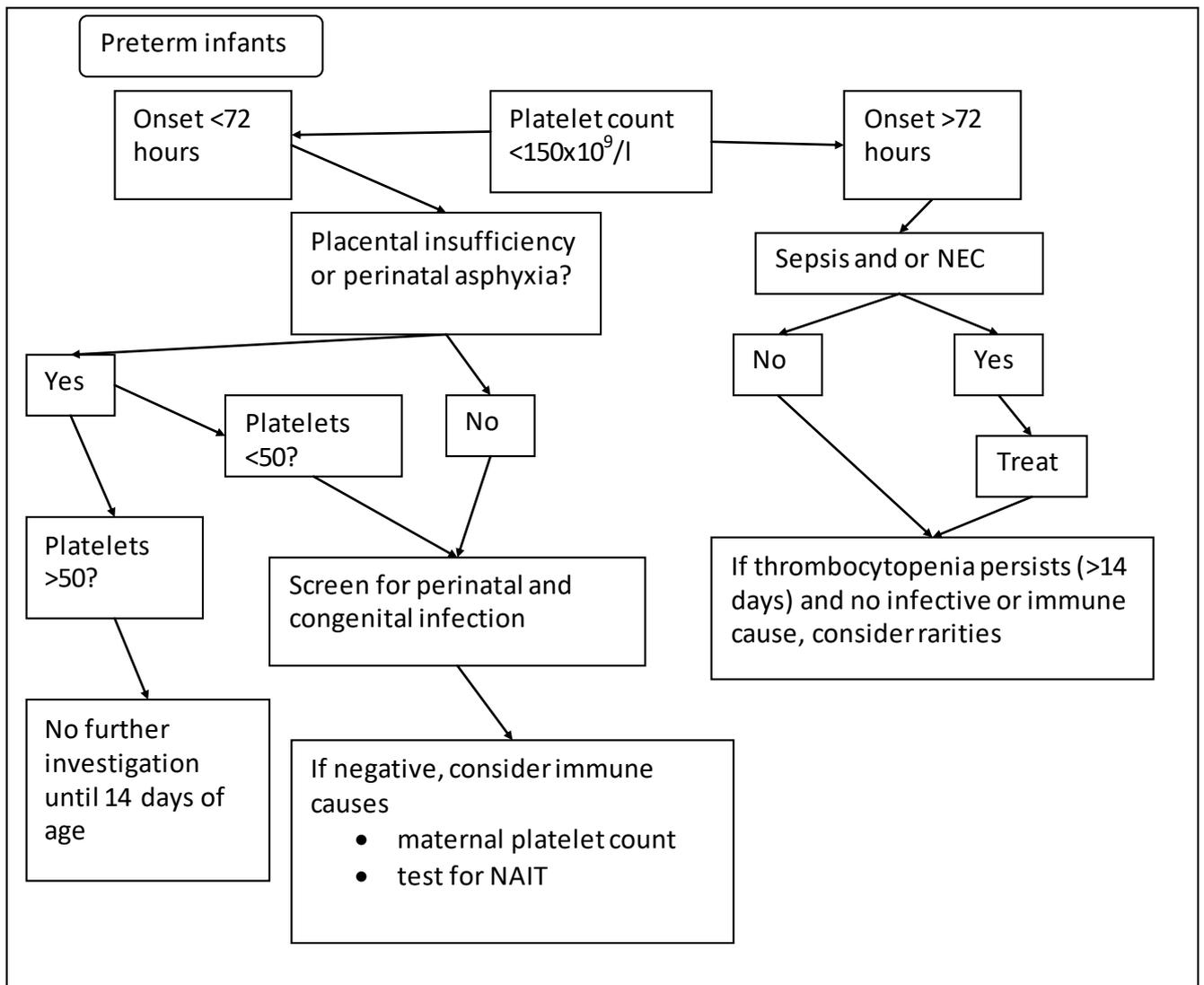
Platelets
>50?

NAIT

No NAIT

Exclude DIC
Congenital thrombocytopenia
Bacterial or viral infections
Immune causes (mother or baby)

Consider
NAIT
Spurious thrombocytopenia
(common in polycythemia or a
clot/platelet clumps in the sample)
Autoimmune causes
Aneuploidy
If persists >10 days, consider
rarities



4.1.2a Early Onset (<math><72</math> hours)

This is usually antenatal in origin and related to fetal hypoxia leading to a reduction in megakaryopoiesis, eg in utero growth restricted infants, hypoxic ischaemic encephalopathy, maternal pregnancy induced hypertension. The natural history is of mild thrombocytopenia, resolving within 10 days. Infants with early onset mild thrombocytopenia persisting beyond 2 weeks of age should be investigated for further causes. Haemorrhage is rare in these cases.^{1,2}

Chronic fetal hypoxia (IUGR, PIH, diabetes)
 Perinatal hypoxia
 Perinatal infection
 DIC
 Alloimmune (NAIT)
 Autoimmune in mother (ITP, SLE)
 Congenital infection (CMV, toxo, rubella, HIV)
 Thrombosis
 Bone marrow replacement
 Kasabach-Merritt syndrome
 Severe Rhesus disease
 Metabolic disease
 Aneuploidy (trisomy 13, 18, 21)
 Inherited thrombocytopenia
 Congenital bone marrow failure

Common causes
 of early
 thrombocytopenia

A less common cause of early thrombocytopenia (<5%) is neonatal alloimmune thrombocytopenia (NAIT). This should be suspected in term infants with severe thrombocytopenia (<50x10⁹/l) or infants who are bleeding with thrombocytopenia without another cause (see box below). See below for further details of investigation/management.

4.1.2b Late Onset (>72 hours)

This is usually a much more severe condition, 80% is due to necrotizing enterocolitis or sepsis. The thrombocytopenia is of rapid onset (over 1-2 days) and can take several weeks to recover. Haemorrhage in this group is more common. Management must include treatment of the underlying cause (see Yorkshire & Humber ODN guidelines on management of sepsis and NEC).^{1,2}

Late onset sepsis NEC Congenital infection Autoimmune in mother Kasabach-Merritt syndrome Metabolic disease Inherited

4.1.3 Treatment

4.1.3a General principles

There have been very few studies to identify the indications and thresholds for treatment of thrombocytopenia.

Prior to publication of the PlaNeT-II, there had been one RCT³ in preterm infants in the first week of life using the triggers of 150 and 50 for transfusion. Infants with counts <50 were excluded. There was no difference in the frequency or severity of IVH and therefore it has been concluded that non bleeding neonates with platelet counts >50 do not need prophylactic transfusions. A further study⁴ looked at neonates transfused with platelet counts between 30 and 50 for clinical instability/previous IVH. In this study 50% of infants received transfusions, however there was no major haemorrhage in either group, suggesting that a platelet count of >30 is probably also a safe threshold.

In the UK, the taskforce for standards in haematology have previously suggested thresholds⁵, however this pre-dates the results of the PlaNeT-II trial. This large multi-centre randomised trial randomised 660 infants to a high (50x 10⁹/l) or low (25 x 10⁹/l) threshold for platelet transfusion. Those transfused at the higher threshold had a statistically significant increase in a new bleeding episode or death compared to those transfused at the lower threshold (26% vs19% OR 1.57; 95% CI 1.06-2.32; P=0.02). This study has recently reported and the following thresholds are now recommended.⁶

Bleeding infant (preterm or term) 50x10⁹/l

Any infant, not bleeding (preterm or term) 25x10⁹/l

In addition for specific procedures to be performed the following are general thresholds. However, where appropriate please discuss with the appropriate team:

General surgical procedures	>50x10 ⁹
Neurosurgical procedures	>90x10 ⁹
Lumbar puncture ⁹	> 100x10 ⁹

Transfused platelets should be CMV negative to reduce the risk of transmission. Infants who have previously received in-utero transfusions (of any blood product) should receive irradiated products.

4.1.3b Dose of platelets^{5, 6}

5-10ml/kg of platelets increase the platelet count in term infants by $50-100 \times 10^3$.

The PlaNeT-II study used a dose of 15ml/kg. A dose of 10-20ml/kg is recommended by the taskforce. There is an argument that since many infants receive just 1 transfusion, and 20ml/kg is generally tolerated well, minimising donor exposure and maximizing increment would support aiming for a dose of 20ml/kg. However, in the PlaNet-II study better outcomes were seen with transfusion at a lower threshold with doses of 15ml/kg transfused. There is potential with further trials that lower platelet transfusion volumes would be demonstrated to be of more benefit.⁶

In January 2020 NHSBT altered the composition of platelet packs to improve stability. They recommend that this should not result in a change to the volume transfused.¹⁰

Recommendation: 10-15ml/kg

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4.1.4 Specific Thrombocytopenia conditions:

4.1.4.1 Neonatal Alloimmune Thrombocytopenia (NAIT)^{1,2}

NAIT is the platelet version of haemolytic disease of the newborn. In this condition there is platelet incompatibility between the parents leading to transplacental transfer of platelet antibodies to the paternal HPA antigens and thrombocytopenia. The most common antibody is HPA-1a, however it can also occur in HPA-5B and HPA-15b. Platelet incompatibility occurs in 1:350 pregnancies, however thrombocytopenia occurs in just 1:1000-1:1500. This is related to the HLA DR subtype of the mother which determines her ability to make antiHPA-1a antibodies.

Unlike Rhesus disease, NAIT can occur in the first pregnancy, due to the early expression of platelet antigens. The thrombocytopenia can be severe and result in intracranial haemorrhage (ICH) and fetal demise. The management of pregnancies affected with NAIT is complex, and requires fetal medicine expertise. Current treatments using high dose steroids and immunoglobulins to the mother seem to reduce the need for the very high risk in-utero transfusions of platelets.

4.1.4.1a Diagnosis

NAIT should be suspected in any term infant with a platelet count $<50 \times 10^9/l$.

Blood should be taken from the infant and both parents and sent for platelet genotyping and antibody testing. Note this can take some time, and while waiting for the results, the infant should be treated as if they have this condition due to the high risk of ICH.

4.1.4.1b Treatment^{1,2}

Cranial USS is mandatory to exclude IVH.

Infants affected with NAIT should have their platelet count maintained above $50 \times 10^9/l$ if there is any bleeding or above 25 if otherwise well with no IVH. (NSHBT table 3 2016)⁵. Ideally HPA 1a and 5b negative platelets should be used, but in an emergency random donor platelets may result in a temporary increase in platelet count. The National Blood service keeps stocks of HPA1a 5b negative platelets for this purpose.⁵

Immunoglobulin can also be used, however this may not increase the count for 12-36 hours. Dose 1g/kg

4.1.4.2. Neonatal autoimmune thrombocytopenia

This occurs in some infants of mothers with idiopathic thrombocytopenia purpura (ITP) or SLE. There is transplacental transfer of antibodies from mother to fetus resulting in thrombocytopenia in 10% of affected pregnancies.

4.1.4.2a Diagnosis^{1,2}

A platelet count should be performed on the cord blood or from the infant on day 1. If this is $>150 \times 10^9/l$ no further action is needed. Infants with thrombocytopenia ($<150 \times 10^9/l$) should have a count repeated at 48 hours. The trough platelet count is often around day 2-4, and rises by day 7. If the expected rise does not occur further platelet counts will be required.

4.1.4.2b Treatment

IVIg may be needed for infants who are bleeding or with a severe thrombocytopenia (e.g. platelet count $<30 \times 10^9/l$ in the first week of life and $<20 \times 10^9/l$ thereafter), The recommended dose of IVIg is 1g/kg daily for 2 days or 400mg/kg daily for 5 days

6. Audit criteria

Use of blood products compared with guideline indications

7. References

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