Yorkshire and Humber Neonatal Operational Delivery Network Clinical Guideline

ODN South

Thrombocytopaenia in the Neonate

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal Operational Delivery Network. 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.

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1. Aims

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

2. Flow Chart/Summary Page of Recommendations

Thrombocytopenia

Definition; platelet count <150x10^9/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 Treatment; Therapy	Bleeding infant (preterm or term)	<50x10^9/l
	Any infant, not bleeding (preterm or term)	<25x10^9/l
	Platelets 10-15ml/kg	

B Full Guideline & Evidence

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 of Remit

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

4. Evidence/Core guideline

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.

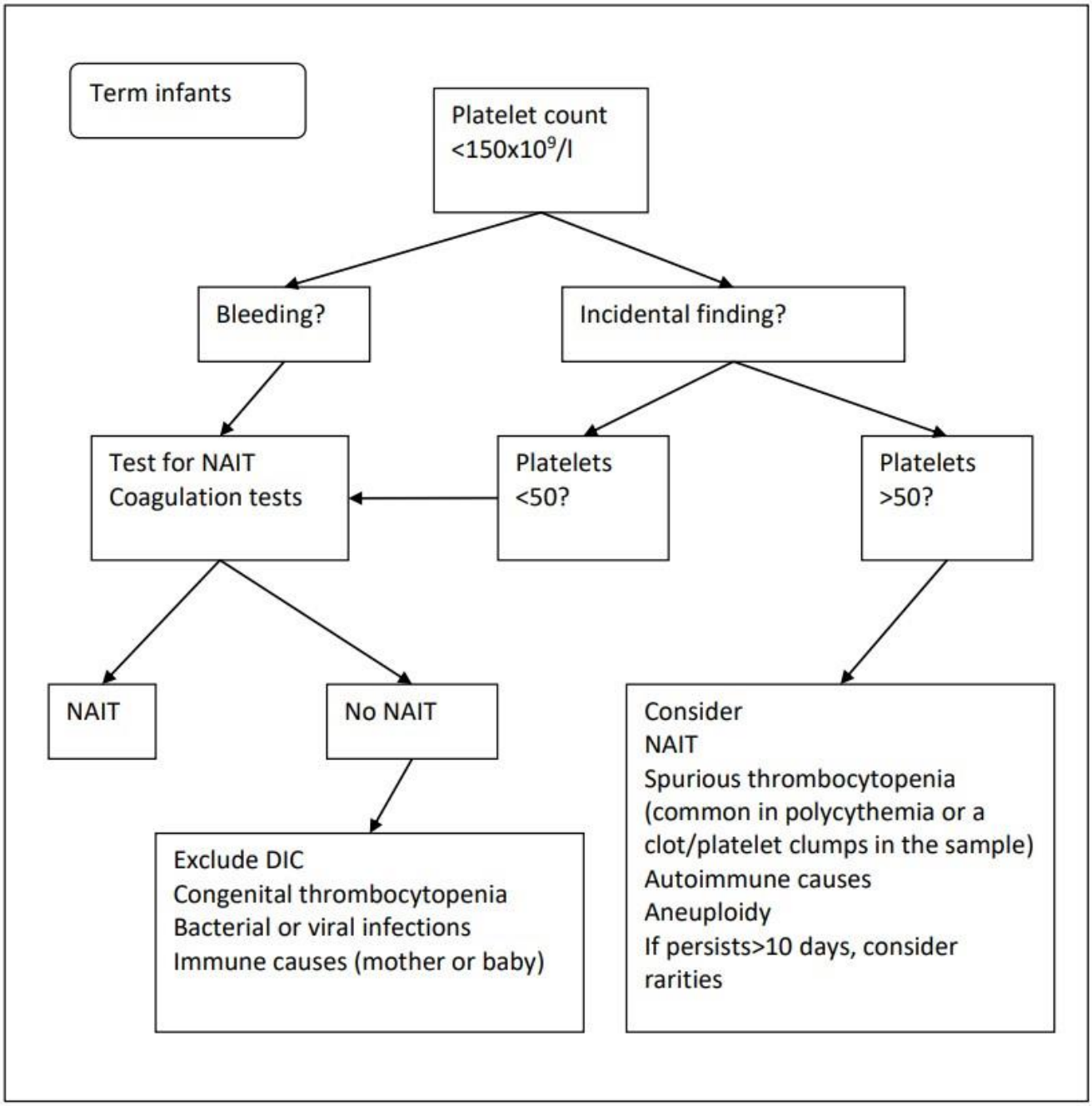
4.1.1 Definition

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<$150x10^9$/l (or below local normal range) can be considered thrombocytopenic[1,2].

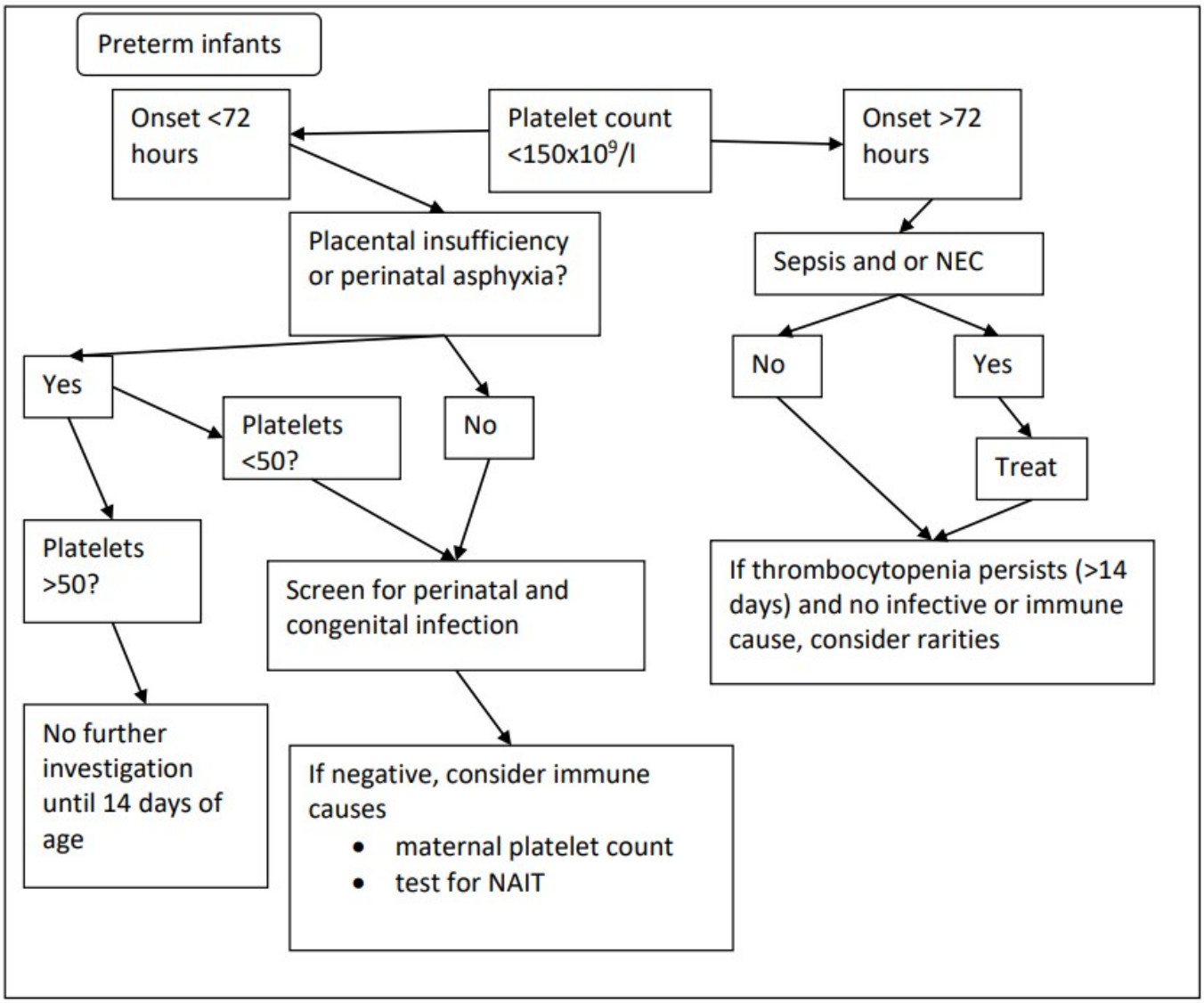
4.1.2 Aetiology

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 A and B[1].

Flow Chart A Investigation of thrombocytopaenia in a term infant



Flow Chart B Investigation of thrombocytopaenia in a preterm infant



4.1.2a Early Onset (<72 hours)

This is usually antenatal in origin and related to fetal hypoxia leading to a reduction in megakaryopoesis, e.g., 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]

Common causes of early thrombocytopaenia

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

A less common cause of early thrombocytopenia (<5%) is neonatal alloimmune thrombocytopenia (NAIT). This should be suspected in term infants with severe thrombocytopenia (<50x10^9/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 RCT[3] 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 study[4] 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 thresholds[5], however this pre-dates the results of the PlaNeT-II trial. This large multi-centre randomised trial randomised 660 infants to a high (50x 10^9/l) or low (25 x 10^9/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)	<50x10^9/l
Any infant, not bleeding (preterm or term)	<25x10^9/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]	> 40x10^9

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 increases the platelet count in term infants by 50-100x10^3.

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 C

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 <50x10^9/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 50x10^9/l if there is any bleeding or above 25 if otherwise well with no IVH. (NSHBT table 2 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 >150x10^9/l no further action is needed. Infants with thrombocytopenia (<150x10^9/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 x10^9/l in the first week of life and <20 x 10^9/l thereafter), The recommended dose of IVIG is 1g/kg daily for 2 days or 400mg/kg daily for 5 days.

4.1.5 Follow up for infants with diagnosis of NAIT
After discharge, the platelet count should be monitored until normalised.
For the large majority of infants diagnosed with NAIT there is no indication for routine outpatient haematology follow up as the platelet count will normalise as maternal antibodies are cleared (may take around 3 months).

4.1.6 Maternal follow up following diagnosis of NAIT
There is risk to future pregnancies and enhanced monitoring will be required with input from the fetomaternal unit. It is important to ensure the mother and obstetric team are aware of the diagnosis. We would recommend a copy of the neonatal discharge summary is sent to the obstetric consultant.

5. Education Resources

None included.

6. Audit Criteria

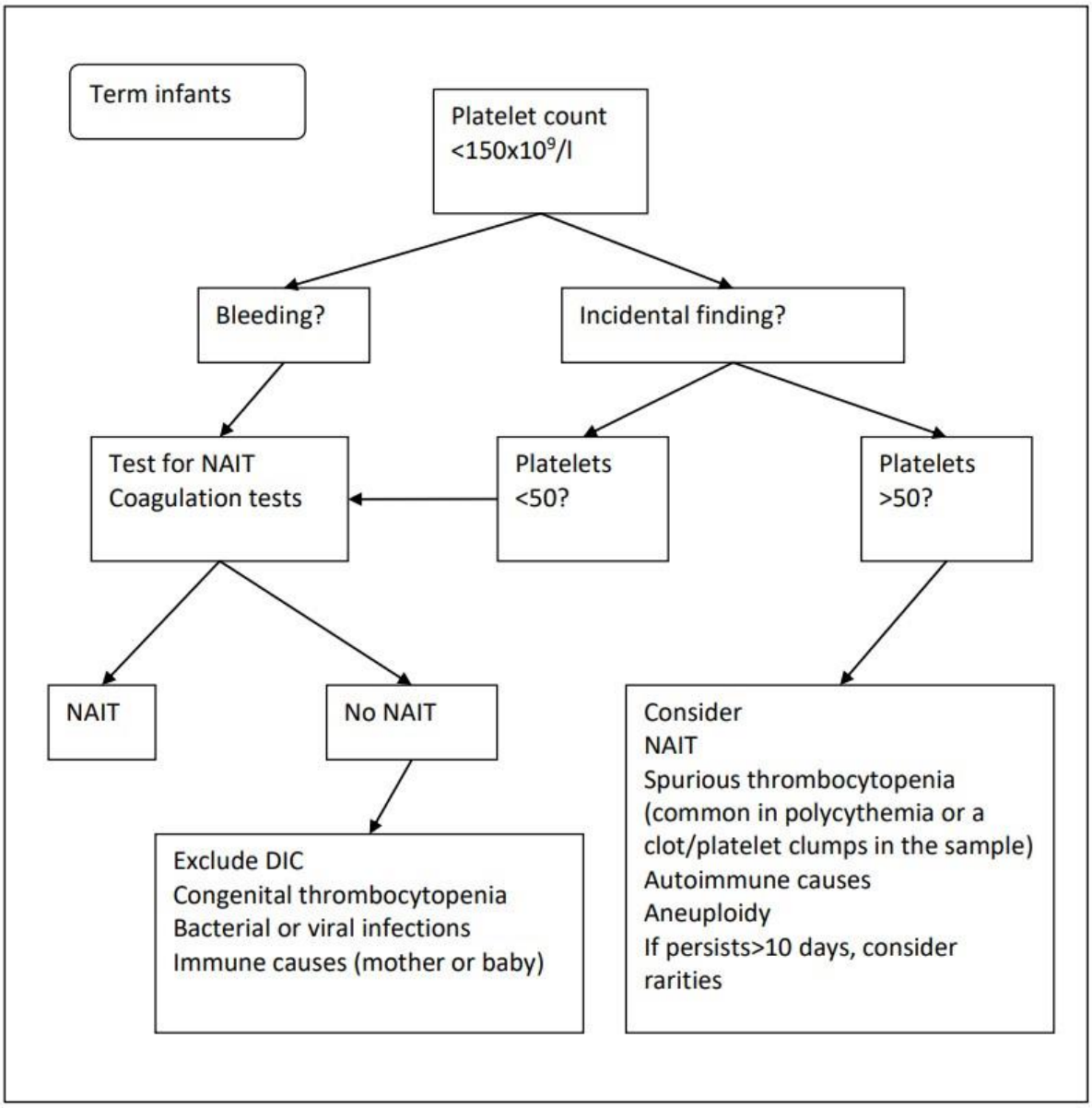
Use of blood products compared with guideline indications.

7. References

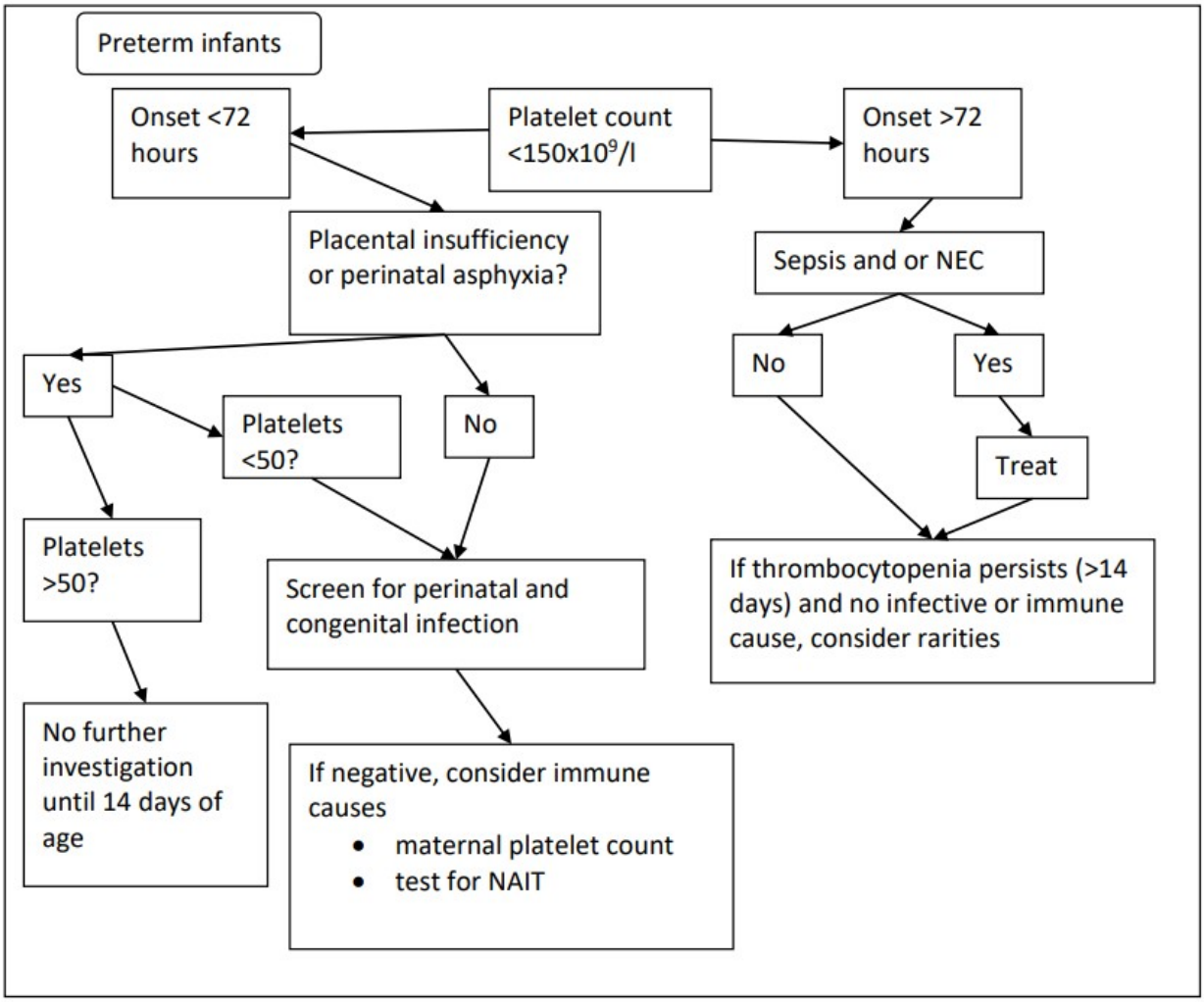
1. Chakravorty, S. How I manage neonatal thrombocytopenia. BJH 2011;*156* 155-162
2. Roberts I. Thrombocytopenia in the neonate. Blood reviews 2008;*22;* 173-186
3. Andrew, M et al. A randomized, controlled trial of platelet transfusion sin thrombocytopenic premature infants. J Pediatr 1993;*123;* 285-291
4. Murray, NA et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. Transfus med 2002;*12;*35-41
5. New, HV et al. Guidelines on transfusion for foetuses, neonates and older children. Br J Haematol. 2016 Dec; 175(5):784-828
6. Curley, A, et al. Randomized trial of Platelet-Transfusion Thresholds in Neonates. N Engl J Med 2019; 380:242-251
7. Sloan S. Neonatal transfusion review. Pediatri Anesthesia 2011; *21;* 25-30
8. Poterjoy B. Platelets, frozen plasma and cryoprecipitate: what is the clinical evidence for their use in the neonatal intensive care unit? Semin Perinatol 2009*;33;*66-74
9. NICE Guideline (CG102) Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management.
10. Frith, L. Letter from NHSBT 'Changes to neonatal platelet pack specification'. 25/11/2019 https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/17387/neonatal-platelets-25-november-2019.pdf and also available on the BAPM website.
11. New, HV et al. British Society for Haematology Guidelines on transfusion for fetuses, neonates and older children (Br J Haematol. 2016;175:784-828) Addendum August 2020 HV New1

8. Appendices

A. Flow Chart 1 Investigation of thromobocytopaenia in a term infant



B. Investigation of thrombocytopaenia in a preterm infant



9. Version Control Table

Version Control Table - Document History			
Date *(of amendment/ review)*	**Issue No.** *(e.g V1)*	**Author** *(Person/s making the amendment or reviewing the Guideline)*	**Detail** *(of amendment/misc notes)*
June 2012	V1.1	E Pilling	New guideline
Sept 2019	V1.2	C Smith/J Payne	Reviewed and updated
Aug 2023	V1.3	C Smith/J Payne	Alteration of platelet count for lumbar puncture and neurosurgical procedure aligned with BSHBT guidance Update to section 4.15 and 4.16 regarding neonatal follow up and care in future pregnancies