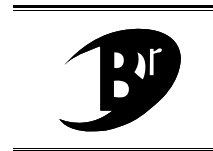




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REVIEW

## Thrombocytopenia in the Neonate

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### KEYWORDS

Thrombocytopenia;  
Neonates;  
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**Summary** Thrombocytopenia is one of the commonest haematological problems in neonates, affecting at least 25% of all admissions to neonatal intensive care units (NICUs) [Murray NA, Howarth LJ, McCloy MP et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit patients. *Transfus Med* 2002;12:35–41; Garcia MG, Duenas E, Sola MC et al. Epidemiologic and outcome studies of patients who received platelet transfusions in the neonatal intensive care unit. *J Perinatol* 2001;21:415–20; Del Vecchio A, Sola MC, Theriaque DW et al. Platelet transfusions in the neonatal intensive care unit: factors predicting which patients will require multiple transfusions. *Transfusion* 2001;41:803–8]. Although a long list of disorders associated with neonatal thrombocytopenia can be found in many textbooks, newer classifications based on the timing of onset of thrombocytopenia (early vs. late) are more useful for planning diagnostic investigations and day-to-day management. The mainstay of treatment of neonatal thrombocytopenia remains platelet transfusion although it is important to note that no studies have yet shown clinical benefit of platelet transfusion in this setting. Indeed some reports even suggest that there may be significant adverse effects of platelet transfusion in neonates, including increased mortality, and that the effects of transfusion may differ in different groups of neonates with similar degrees of thrombocytopenia [Bonifacio L, Petrova A, Nanjundaswamy S, Mehta R. Thrombocytopenia related neonatal outcome in preterms. *Indian J Pediatr* 2007;74:269–74; Kenton AB, Hegemier S, Smith EO et al. Platelet transfusions in infants with

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necrotizing enterocolitis do not lower mortality but may increase morbidity. *J Perinatol* 2005;25:173–7]. There is also considerable variation in transfusion practice between different countries and between different neonatal units. Here we review recent progress in understanding the prevalence, causes and pathogenesis of thrombocytopenia in the newborn, the clinical consequences of thrombocytopenia and developments in neonatal platelet transfusion.

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## Definition

Studies of fetal blood obtained by cordocentesis show that the mean fetal platelet count reaches  $150 \times 10^9/L$  by the end of the first trimester of pregnancy<sup>6</sup>, and rises to  $175\text{--}250 \times 10^9/L$  by end of the second trimester.<sup>7–9</sup> Several population studies also show that >98% of term neonates born to mothers with normal platelet counts have platelets above  $150 \times 10^9/L$  at birth.<sup>10–13</sup> Therefore thrombocytopenia in a neonate of any viable gestational age can be defined as a platelet count of  $<150 \times 10^9/L$ .

## Prevalence of neonatal thrombocytopenia

Previous studies report a prevalence of thrombocytopenia of 1–5% of all newborns. However, the prevalence varies depending upon the population studied. In neonates admitted to intensive care units, thrombocytopenia develops in 22–35% of all admissions, with the rate increasing as gestational age decreases.<sup>14–17</sup> The majority of neonates will have mild or moderate thrombocytopenia. However, 5–10% will have severe thrombocytopenia at birth (platelets  $<50 \times 10^9/L$ ) and require urgent investigation to identify the cause and institute prompt treatment to prevent long-term disability or death.

## Causes of Neonatal Thrombocytopenia

The underlying cause of neonatal thrombocytopenia can often be predicted by the timing of the onset of the thrombocytopenia and its natural history (Table 1). Thrombocytopenia which presents after the first 3 days of life is due to sepsis or necrotizing enterocolitis in >80% of cases.<sup>1,19</sup> In these clinical situations thrombocytopenia usually develops very rapidly over 1–2 days, is often very severe (plate-

lets  $<30 \times 10^9/L$ ) and may take several weeks to recover.<sup>1</sup> By contrast, sepsis and necrotizing enterocolitis are uncommon causes of early neonatal thrombocytopenia (presenting in the first 3 days of life).

The most frequent cause of early-onset thrombocytopenia is associated with chronic fetal hypoxia, as occurs in infants born to mothers with pregnancy-induced hypertension or diabetes and/or in those with intrauterine growth restriction (IUGR).<sup>17,18</sup> This form of thrombocytopenia is usually mild or moderate and it is self-limiting, resolving within 10 days in the majority of cases.<sup>17,18</sup> The mechanism of thrombocytopenia is reduced megakaryopoiesis<sup>17,20</sup> and affected neonates also have a number of additional associated haematological abnormalities which help to confirm the diagnosis, including transient neutropenia, increased numbers of circulating nucleated red cells with or without associated polycythaemia, increased erythropoietin levels and evidence of hyposplenism (spherocytes, target cells and Howell-Jolly bodies).<sup>18,21</sup> Although representing <5% of cases of early thrombocytopenia, an important cause of early thrombocytopenia is neonatal allo-immune thrombocytopenia (NAIT) [see later].

A number of less common disorders may also present with thrombocytopenia at birth. When NAIT has been excluded and there is no evidence for chronic fetal hypoxia due to common maternal disorders and/or idiopathic IUGR, the most likely causes of thrombocytopenia are prenatal viral infections (e.g. cytomegalovirus, CMV), perinatal bacterial infections (e.g. group B *Streptococcus*, *Escherichia coli*, and *Haemophilus influenzae*), perinatal asphyxia or aneuploidy (particularly trisomies 18, 13, and 21 or triploidy). Early-onset neonatal thrombocytopenias that persist for more than 2 weeks are also unusual and warrant further investigation. As most other forms of thrombocytopenia will have resolved by this time, the likely causes of prolonged, unexplained thrombocytopenia are inherited thrombocytopenias, all of which are rare (Table 1).

**Table 1** Classification of fetal and neonatal thrombocytopenias.

	Condition
Fetal	<b>Alloimmune</b> <b>Congenital infection</b> (e.g. CMV, toxoplasma, rubella, HIV) <b>Aneuploidy</b> (e.g. trisomies 18, 13, 21) Autoimmune (e.g. ITP, SLE) Severe Rhesus haemolytic disease Inherited (e.g. Wiskott-Aldrich syndrome)
Early-onset neonatal (<72 hours)	<b>Chronic fetal hypoxia</b> (e.g. PIH, IUGR, diabetes) <b>Perinatal asphyxia</b> <b>Perinatal infection</b> (e.g. E. coli, GBS, Haemophilus influenzae) DIC Alloimmune Autoimmune (e.g. ITP, SLE) Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Thrombosis (e.g. aortic, renal vein) Bone marrow replacement (e.g. congenital leukaemia) Kasabach-Merritt syndrome Metabolic disease (e.g. propionic and methylmalonic acidemia) Inherited (e.g. TAR, CAMT)
Late-onset neonatal (>72 hours)	<b>Late-onset sepsis</b> <b>NEC</b> Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g. propionic and methylmalonic acidemia) Inherited (e.g. TAR, CAMT)

CMV – cytomegalovirus, HIV – human immunodeficiency virus, ITP – idiopathic thrombocytopenic purpura, SLE – systemic lupus erythematosus, PIH – pregnancy-induced hypertension, IUGR – intrauterine growth restriction, E. coli - Escherichia coli, GBS - group B Streptococcus, TAR – thrombocytopenia with absent radii, CAMT – congenital amegakaryocytic thrombocytopenia, NEC - necrotising enterocolitis. The most frequently occurring conditions are highlighted.

## Clinical and laboratory features of specific thrombocytopenias

### Neonatal alloimmune thrombocytopenia (NAIT)

In NAIT, the platelet equivalent of haemolytic disease of the newborn, thrombocytopenia results from transplacental passage of maternal antibodies to fetal platelets expressing paternal human platelet antigens (HPA) that the mother lacks. HPA antigens are uniquely expressed on platelets, and sixteen HPAs have been identified although fetomaternal incompatibility between only 3 (HPA-1a, HPA-5b and HPA-15b) cause 95% of cases in Caucasian populations.<sup>22</sup> Other antibodies, for example anti-HPA-3a, are occasionally involved.<sup>23,24</sup> Fetomaternal incompatibility for HPA-1a is the commonest being responsible for ~75% of cases in Caucasians.<sup>22–24</sup> HPA-1a incompatibility occurs in 1:350 pregnancies although thrombocytopenia develops

in only 1:1000–1500 pregnancies.<sup>22</sup> The ability of an HPA-1a-negative woman to form anti-HPA-1a is controlled by the HLA DRB3\*0101 allele such that HLA DRB3\*0101-positive women are 140 times more likely to make anti-HPA-1a than HLA DRB3\*0101-negative women<sup>25</sup>, thereby explaining the frequency of the clinical problem. This is an example of a very strong association with HLA.

NAIT occurs in the first pregnancy in almost 50% of cases. Thrombocytopenia is often extremely severe (platelet count  $<20 \times 10^9/L$ ) and may result in major bleeding, particularly intra-cranial haemorrhage (ICH). While the incidence of ICH is difficult to ascertain precisely, large series report ICH in 10–20% of untreated pregnancies.<sup>22,26,27</sup> ICH may also occur during fetal development, as thrombocytopenia may occur from 20 weeks onwards particularly in untreated pregnancies.<sup>24,28–32</sup> The course of NAIT in otherwise well neonates is variable with thrombocytopenia resolving in most cases within one week without long-term sequelae. However, in some cases thrombocytopenia lasts for

several weeks and may require repeated platelet transfusion. In a minority of neonates ICH occurs for the first time following birth; some recent data indicate that this may be more common in neonates whose mothers received no antenatal therapy.<sup>32</sup> The neurodevelopmental outcome of neonates with untreated NAIT has also been reported to be inferior to their siblings where maternal treatment is given.<sup>33</sup> Overall two thirds of cases with NAIT-associated ICH develop neurodevelopmental problems, approximately half of which are severe e.g. severe cerebral palsy and/or sensory impairment.<sup>22</sup>

The morbidity and mortality of NAIT mean that this disorder requires expert management with close collaboration between fetal medicine specialists, haematologists and neonatologists. An important guiding principal of therapy has been the knowledge that for mothers with known HPA antibodies the fetal and neonatal course in subsequent pregnancies (with an antigen-positive fetus) closely reflect that in previously affected pregnancies. Thus, mothers with previous neonates suffering an ICH are at high risk of future children also having a severe course.

#### Antenatal management of NAIT

Although antenatal management of pregnancies at risk of NAIT remains controversial, most centres now rely mainly on non-invasive strategies. Three general approaches are used (reviewed in 24,34,35). The invasive approach, focused on 'high-risk' mothers with previous severely affected children, uses repeated fetal blood samples (FBS) and intrauterine transfusions (IUT) of HPA-compatible platelets in thrombocytopenic fetuses, combined with preterm delivery at 32–34 weeks. Secondly, a non-invasive approach relies on monitoring by fetal ultrasound (USS) and maternal intravenous weekly high dose intravenous immunoglobulin (IVIg) ± steroids. A third approach uses combination therapy of high dose maternal IVIg together with infrequent FBS to monitor the response to therapy during pregnancy and decide on the mode of delivery. It has recently become clear that the rate of fetal loss and emergency preterm delivery with repeated FBS and IUT is similar to the rate of fetal ICH in untreated pregnancies and exceeds that in 'low-risk' pregnancies treated with IVIg.<sup>22,36,37</sup> As a result therapy for NAIT, even in high-risk cases, is increasingly moving towards the non-invasive approach. In a recent study 52 pregnant women (5 with a previous sibling with ICH) with known HPA-incompatibility were treated with IVIg alone at a dose of 1 g/kg weekly, beginning at

16 weeks if the previous sibling had an ICH and 32 weeks if not.<sup>38</sup> All the pregnancies resulted in live births, there were no ICHs and no neonatal deaths. This group have now adopted this non-invasive regimen as their standard protocol for antenatal therapy for all mothers with known HPA incompatibilities.<sup>34</sup> Other centres are now following these more conservative approaches, compared to the interventionist ones based around IUT of HPA-compatible platelets.

#### Presentation and management of neonates with NAIT

Affected neonates may present with asymptomatic thrombocytopenia, with petechiae or purpura or with symptoms of ICH (e.g. neonatal seizures). Important clinical criteria for a diagnosis of NAIT include unexplained severe thrombocytopenia  $< 50 \times 10^9/l$  in the first day in term infants without apparent cause and a relevant family history.<sup>27</sup> The diagnosis of NAIT is made by demonstrating platelet antigen incompatibility between mother and baby serologically. The monoclonal antibody – specific immobilisation of platelet antigens (MAIPA) assay is the main technique used for HPA antibody detection and identification of maternal platelet-specific antibodies. The MAIPA assay is not straightforward and quality control exercises have revealed variation between laboratories undertaking the assay.<sup>39</sup> The parents and infant are also genotyped for the HPA alloantigens. In general, there are no validated laboratory parameters (eg titre of antibody) which predict the severity of NAIT, and therefore prediction of severity tends to be based on history of previously affected pregnancies and estimation of fetal platelet counts.<sup>40</sup>

The most important aspect of management of new cases is to consider NAIT as a possible diagnosis in any case of unexpected severe thrombocytopenia presenting at birth. Since the majority of affected neonates (~80%) will not have suffered an ICH before birth, preventing ICH during neonatal thrombocytopenia should be considered an emergency. The best way of treating NAIT is unclear. The threshold for platelet transfusion and the regimen to achieve and maintain a 'safe' platelet count for neonates with NAIT is unclear.<sup>41</sup> In addition, recent evidence suggests that neonates with HPA-5b incompatibility may bleed at higher platelet counts than other HPA incompatibilities.<sup>22</sup> Neonates with NAIT, or those with an unexplained platelet count  $\leq 50 \times 10^9/L$  and presumed NAIT, have a high risk of ICH and should have their platelet count maintained above  $50 \times 10^9/L$  for

**Table 2** Guidelines for platelet transfusion thresholds for neonates.

Platelet count x 10 <sup>9</sup> /L	Non-bleeding neonate (1 <sup>st</sup> week of life)	Non-bleeding neonate (week 2 onwards)	Neonate with major bleeding	Auto-IT	NAIT (new case suspected)	NAIT (known case)
<30	Transfuse all patients	Transfuse all patients	Transfuse	Transfuse if bleeding present or IVIG unavailable	Transfuse using HPA-1a/5b negative platelets (Random donor platelets only if compatible platelets unavailable)	Transfuse using HPA compatible platelets
30–49	Do not transfuse if clinically stable Transfusion appropriate if: <ul style="list-style-type: none"> <li>• &lt; 1000 g and &lt; 1 week of age</li> <li>• clinically unstable (e.g. high ventilation requirements or fluctuating BP/hypovolaemia)</li> <li>• previous major bleeding tendency (e.g. grade 3–4 IVH)</li> <li>• concurrent coagulopathy</li> <li>• surgery or exchange transfusion</li> </ul>	Do not transfuse	Transfuse	Do not transfuse if stable and not bleeding	Transfuse using HPA-1a/5b negative platelets (Random donor platelets only if compatible platelets unavailable)	Transfuse using HPA compatible platelets (if minor bleeding)
50–99	Do not transfuse	Do not transfuse	Transfuse	Do not transfuse	Transfuse using HPA-1a/5b negative platelets (if major bleeding)	Transfuse using HPA compatible platelets (if major bleeding)

Auto-IT – Autoimmune thrombocytopenia; NAIT – Neonatal alloimmune thrombocytopenia; HPA – Human platelet antigen

the first 2 weeks of life pending diagnosis (Table 2). All babies with severe thrombocytopenia due to NAIT should also have a cranial USS to look for evidence of ICH. The initial treatment of choice for NAIT is transfusion with HPA-1a and 5b negative platelets (available 'off the shelf' from transfusion centres in the UK and many other European countries) whilst the results from laboratory investigations to provide serological confirmation of the diagnosis are undertaken.<sup>42</sup> Alternatives are random donor platelet transfusion, IVIG, steroids, an expectant approach monitoring the count until thrombocytopenia resolves and washed maternal platelets. Where there is a delay in obtaining HPA-compatible platelets, random donor platelet transfusions can be used in an emergency as they can produce a significant platelet increment in NAIT<sup>43</sup> or IVIG although the rise in platelet count may be delayed for 12–36 hours.<sup>26,29</sup> In new cases without major bleeding with an initial count  $>50 \times 10^9/L$  an expectant approach is appropriate. It is important to note that thrombocytopenia often worsens over the first few days making close monitoring of the platelet count essential. In thrombocytopenic neonates with active bleeding (e.g. new or worsening ICH, gastrointestinal, frank haematuria) it seems reasonable to maintain the platelet count above  $100 \times 10^9/L$  (Table 2).

Pregnant women and mothers with HPA antibodies are at risk of post-transfusion purpura, and should be transfused with HPA-compatible red cells and platelets if these are readily available, unless in an emergency. Close liaison with obstetricians is essential.

### Neonatal autoimmune thrombocytopenia

Maternal platelet auto-antibodies (principally immune thrombocytopenic purpura and systemic lupus erythematosus) occur in 1–2:1,000 pregnancies.<sup>44–46</sup> Transplacental passage of maternal auto-antibodies in this setting is much less of a clinical problem than NAIT. Thrombocytopenia only occurs in ~10% of neonates whose mothers have autoantibodies and the incidence of ICH is 1% or less.<sup>47</sup> Therefore fetal blood sampling or cesarean delivery in mothers with autoimmune thrombocytopenia is not normally necessary irrespective of the platelet count during pregnancy.<sup>44,48</sup> Maternal disease severity and/or platelet count during pregnancy or the occurrence of severe thrombocytopenia in a previous neonate are the most useful indicators of the likelihood of significant fetal and neonatal thrombocytopenia complicating the current pregnancy.<sup>49</sup> Interestingly, a recent retrospec-

tive study, which included a high proportion mothers who were thrombocytopenic during their pregnancy, showed a higher incidence of affected babies: 25% of infants had thrombocytopenia, 9% had a platelet count of  $<50 \times 10^9/L$ , 15% of infants received treatment for bleeding in association with thrombocytopenia and 2 fetuses died, one with extensive haemorrhage.<sup>50</sup>

All neonates of mothers with autoimmune disease should have their platelet count determined at birth either by cord blood sampling, which is often difficult, or by a peripheral blood sample since artefactual thrombocytopenia due to clots from heel-prick samples are common. In neonates with normal platelet counts ( $>150 \times 10^9/L$ ), no further action is necessary. In those with thrombocytopenia, a platelet count should be repeated after 2–3 days as platelet counts are often at their lowest at this time before rising spontaneously by day 7 in most cases.<sup>51</sup> It is important to note that thrombocytopenia may persist in a small number of cases for several weeks.<sup>44,51</sup> In this situation, where the thrombocytopenia is severe (platelet count  $<30 \times 10^9/L$ ) treatment with IVIG (2 gm/kg over 2–5 days), to which most babies promptly respond, may be useful.<sup>52</sup>

### Neonatal thrombocytopenia associated with aneuploidies

Thrombocytopenia is seen in neonates with trisomy 21, trisomy 18 and trisomy 13 and also in Turner syndrome and in triploidies. The prevalence of thrombocytopenia in this setting is not known, although useful data come from a series of fetal blood samples which found a high frequency of thrombocytopenia in association with trisomy 18 (86%) and triploidy (75%) and a lower frequency in Turner syndrome (31%), trisomy 13 (31%), and trisomy 21 (6%).<sup>53</sup> Although severe thrombocytopenia is uncommon in trisomy 21, mild thrombocytopenia is frequent in neonates with trisomy 21.<sup>55</sup> Thrombocytopenia may also occur with partial trisomies, such as isochromosome 18q.<sup>[54]</sup> For trisomy 13 and 18 the mechanism of thrombocytopenia is unknown, although the frequent association of the thrombocytopenia with neonatal polycythaemia, neutropenia and IUGR suggests that it is likely to be due to reduced platelet production and that the pathogenesis may be similar to that seen in chronic fetal hypoxia.<sup>18</sup> For trisomy 21, there have been several recent studies which provide insight into the possible mechanism of thrombocytopenia (reviewed in 55).

Thrombocytopenia in neonates with Down syndrome may present in one of two ways. The majority of such neonates have haematological features typical of those seen in chromosomally normal infants with IUGR (neutropenia, thrombocytopenia and increased circulating normoblasts with or without polycythaemia).<sup>55</sup> Blast cells are not increased in this situation. However, ~10% of neonates with Down syndrome develop a clonal preleukaemic disorder (transient abnormal myelopoiesis; TAM), characterised by increased myeloblasts and a variable degree of thrombocytopenia.<sup>55</sup> In most cases this resolves spontaneously, but in 20–30% acute megakaryoblastic leukaemia (AMKL) develops at some time in the first 5 years of life.<sup>55</sup> Recent studies have shown that neonates with TAM have mutations in the key megakaryocyte transcription factor GATA1 which lead to the transcription of a short GATA1 mRNA (GATA1s) and protein.<sup>56–61</sup> Infants who progress from TAM to AMKL have the same GATA1 mutation at both stages and since GATA1 mutations disappear when TAM/AMKL enter remission, GATA1s plays a key role in the pathogenesis of the leukaemia although it is clearly not fully responsible for the transformation of TAM into AMKL. Studies in human fetal liver suggest that trisomy 21 perturbs fetal haemopoiesis and predisposes to the development and maintenance of GATA1 mutations.<sup>62</sup>

### Inherited thrombocytopenia

Most inherited thrombocytopenias are due to reduced platelet production secondary to abnormal haemopoietic stem or progenitor cell development. There are often associated congenital anomalies which may be useful in guiding investigations and establishing the diagnosis. There have been many recent advances in identifying the molecular basis of a number of these disorders which inform both the diagnosis and management of neonates with unexplained, persistent thrombocytopenia. Disorders which present with thrombocytopenia in the neonatal period are shown in Table 2 and are briefly discussed below (reviewed in 63,64).

#### Bernard-Soulier Syndrome (BSS)

BSS may present in the neonatal period although bleeding is not usually severe in neonates.<sup>65</sup> A diagnosis of BSS is suggested where there is mild to moderate thrombocytopenia together with giant platelets and an autosomal recessive pattern of inheritance. BSS is due to qualitative or quantita-

tive defects in the glycoprotein (GP) Ib-IX-V complex.<sup>65</sup> Most mutations are in the GPIb $\alpha$  gene; some are also found in the GPIb $\beta$  and GPIX genes.<sup>66</sup> Treatment by platelet transfusion is effective but should be reserved for life-threatening haemorrhage since transfused patients may form allo-antibodies against GPIb, GPIX, or GPV.<sup>67</sup> Fetal/neonatal thrombocytopenia may also occur in the offspring of women with BSS due to the formation of allo-antibodies against GPIb-IX-V and may, as in other forms of NAIT, be a cause of severe fetal ICH.<sup>68</sup>

#### Wiskott-Aldrich Syndrome (WAS)

WAS and X-linked thrombocytopenia are a spectrum of disorders due to mutations in the WAS protein (WASP) gene on the short arm of the X chromosome.<sup>69</sup> Over 100 different mutations have been identified and genotype and phenotype are closely linked.<sup>70</sup> WAS, which is characterized by microthrombocytopenia, eczema, recurrent bacterial and viral infections, and a propensity to develop autoimmune disorders, usually presents during the first year of life with bleeding problems; most cases do not present in the neonatal period unless there is a known family history.<sup>71,72</sup> Bleeding is due to abnormal platelet function as well as reduced platelet survival and thrombocytopenia.<sup>71</sup> In X-linked thrombocytopenia the other clinical features are absent and the thrombocytopenia is usually milder.<sup>69,71</sup>

#### Fanconi anaemia

Although, rarely presenting until after infancy, thrombocytopenia has been reported in neonates with Fanconi anaemia and the diagnosis should always be considered in unexplained neonatal thrombocytopenia, particularly if there are typical dysmorphic features such as malformations of the skin, thumb, face or eyes, and/or if there is parental consanguinity.<sup>73–76</sup> The diepoxybutane test is nearly always diagnostic.<sup>77</sup> Treatment is rarely necessary in the neonatal period. The molecular basis of Fanconi anaemia is heterogeneous and complex, with 12 different genes, identified to date (reviewed in 78).

#### Thrombocytopenia absent radii (TAR) syndrome

TAR syndrome is characterised by bilateral absence of the radii and thrombocytopenia which is either present at birth or which develops within the first 4 months of life.<sup>79</sup> In contrast to Fanconi anaemia, both thumbs are present and normal.<sup>79</sup> The platelet count is usually  $<50 \times 10^9/L$  and the white cell count is elevated in >90% of patients, sometimes

exceeding  $100 \times 10^9/L$  and mimicking congenital leukemia.<sup>80</sup> A fairly recent review of 34 patients with TAR found a high prevalence of associated abnormalities including cow's milk intolerance (47%), lower limb anomalies (47%), renal anomalies (23%) and cardiac anomalies (15%).<sup>81</sup> Infants that survive the first year of life generally do well since the platelet count spontaneously improves to low normal levels which are then maintained. The molecular basis of TAR syndrome has not yet been identified although inheritance appears to be autosomal recessive. Megakaryocytes and their progenitors are reduced.<sup>80,81</sup> However TPO levels are increased and no abnormalities of the TPO receptor, c-mpl, have been identified implicating defects in the TPO signalling pathway in the pathogenesis of TAR syndrome.<sup>82–84</sup>

#### **Amegakaryocytic thrombocytopenia with radio-ulnar synostosis (ATRUS)**

ATRUS presents at birth with severe thrombocytopenia, absent bone marrow megakaryocytes and radio-ulnar synostosis; affected infants may also have clinodactyly and shallow acetabulae.<sup>85</sup> Two kindreds show that ATRUS is caused by mutations in the HOXA11 gene thus distinguishing it from TAR.<sup>85,86</sup>

#### **Congenital amegakaryocytic thrombocytopenia (CAMT)**

CAMT nearly always presents in the neonatal period since the platelet count is usually  $<20 \times 10^9/L$  at birth. Most affected babies have petechiae and/or other evidence of bleeding and physical anomalies are present in approximately 50% of children.<sup>87</sup> Although CAMT presents with isolated thrombocytopenia, ~50% of patients later develop aplastic anaemia and there are several reports of leukaemia or myelodysplasia developing later in childhood.<sup>87</sup> Bleeding episodes in neonates with CAMT are treated by platelet transfusion; stem cell transplantation is curative for those patients with severe disease or aplasia.<sup>88</sup> CAMT is autosomal recessive and caused, in most patients, by mutations in c-mpl<sup>89–92</sup> leading to reduced numbers of megakaryocytes and their progenitors.<sup>93</sup>

#### **X-linked macrothrombocytopenia due to GATA-1 mutation**

Several families with a familial macrothrombocytopenia, with or without associated anaemia, have been described in which there is a mutation in the FOG-1 binding site of GATA-1.<sup>94,95</sup> This form of

thrombocytopenia may present with severe thrombocytopenia and profound bleeding at birth.<sup>95</sup>

#### **Giant platelet syndromes**

Several of the rare giant platelet syndromes may present with thrombocytopenia in the neonatal period or in the fetus, including the May-Hegglin anomaly which is characterised by thrombocytopenia, giant platelets, and leucocyte Dohle-like inclusion bodies.<sup>96</sup> Thrombocytopenia may develop *in utero* and May-Hegglin anomaly is a rare cause of fetal or neonatal ICH.<sup>97,98</sup> The platelet count varies from  $<20 \times 10^9/L$  up to normal, but is usually  $40–80 \times 10^9/L$ . The May-Hegglin anomaly is due to mutations in the MYH9 gene on chromosome 22q which encodes non-muscle myosin heavy chain A.<sup>99</sup> MYH9 mutations are also seen in two other giant platelet syndromes, Fechtner syndrome and Sebastian syndrome.<sup>99,100</sup>

#### **Other causes of congenital thrombocytopenia presenting in the neonatal period**

##### **Kasabach-merritt syndrome**

This typically presents in the neonatal period with profound thrombocytopenia together with microangiopathic anaemia, DIC and an enlarging vascular lesion.<sup>101,102</sup> The diagnosis is usually straightforward since the haemangiomas are cutaneous but in ~20% there is visceral involvement, e.g. in the liver, without any cutaneous signs.<sup>101,103</sup> Thrombocytopenia in Kasabach-Merritt syndrome is mainly due to trapping of platelets on the endothelium of the haemangioma but is exacerbated in some cases by the development of DIC.<sup>104,105</sup> When required, treatment with steroids followed by interferon and/or vincristine is effective in over 50% of cases, although the mortality, even in fairly recent series, is 20–30%.<sup>101,102</sup>

##### **Thrombotic disorders**

Several thrombotic disorders well known in adults and older children have recently been reported in neonates, including thrombotic thrombocytopenic purpura (TTP), haemolytic-uremic syndrome (HUS) and heparin-induced thrombocytopenia (HIT).<sup>106–109</sup> Inherited deficiency of the von Willebrand factor cleaving protease ADAMTS13 may present in the neonatal period with thrombocytopenia, hyperbilirubinaemia and anaemia (106.107). The diagnosis is often delayed since the condition is rare and these signs are all common in sick neonates. HUS



has also been reported in a neonate, possibly triggered by *Bordetella pertussis*.<sup>108</sup> HIT has also been reported in neonates, often with associated arterial thrombosis.<sup>109–111</sup> Neonatal thrombocytopenia may also occur as a secondary event after thrombosis of a major vessel. Renal vein thrombosis in particular is associated with a high incidence of thrombocytopenia and should be considered in any neonate with thrombocytopenia in association with renal failure.<sup>112</sup>

### Metabolic disorders

Thrombocytopenia is a common presenting feature in certain inborn errors of metabolism, including propionic, methylmalonic and isovaleric acidemia<sup>113,114</sup> and Gaucher disease.<sup>115</sup> Thrombocytopenia may also complicate induced hypothermia used to improve outcome in neonates with hypoxic ischaemic encephalopathy.<sup>116,117</sup>

## General principles for treatment of neonatal thrombocytopenia

### Thrombocytopenia and the risk of bleeding in neonates

The majority of bleeding problems seen in neonates will be a consequence of acquired disorders such as in sepsis or DIC, in particular those related to secondary consumption of platelets or coagulation factors. Occasionally this may manifest itself as major bleeding, for example, pulmonary or gastrointestinal. Minor patterns of bleeding in these infants may only be manifest as blood-stained endotracheal secretions, or mild oozing from mouth or nose, blood streaking in nasogastric secretions, or longer than expected oozing from sites used for taking blood samples. These forms of bleeding are very common in sick neonates and may be overlooked or considered clinically of low importance, particularly in the context of only minor changes in platelet counts or coagulation tests.<sup>118</sup> Whether the manifestations of minor bleeding are predictors of more severe bleeding remains unknown. It has also long been recognised by clinicians that the risk of bleeding varies widely in neonates despite similar degrees of thrombocytopenia. The risk of bleeding appears to be higher, for example, in neonates with NAIT and in those with sepsis or NEC, especially those born at very early gestations.

Until recently, there has been very little evidence from which to accurately measure the risk of bleeding in individual neonates or groups of neonates (for example, those with IUGR). We have recently completed a detailed prospective observational survey on over 169 severely thrombocytopenic neonates at 7 different neonatal intensive care units in southern and eastern England (the PlaNeT study) to help define objective measures of bleeding risk according to the cause of thrombocytopenia.<sup>119</sup> Major haemorrhage occurred in 13% of the severely thrombocytopenic neonates (IVH 53%, pulmonary 26%, renal 11%, other 10%), the vast majority affecting neonates of <30 weeks gestation at birth (84%). The PlaNeT study confirms previous data that sepsis and NEC are a common underlying diagnosis in thrombocytopenic neonates who bleed in contrast to the lack of major haemorrhage in neonates with thrombocytopenia secondary to IUGR or pregnancy-induced hypertension, despite severe thrombocytopenia.

### Neonatal platelet transfusion: effects on haemorrhage

The only specific therapy for neonatal thrombocytopenia is platelet transfusion. Bleeding in association with marked thrombocytopenia in these neonates is a clear indication for platelet transfusion. In contrast to this therapeutic indication for platelet transfusions, platelet transfusions may also be given prophylactically to non-bleeding neonates, and in fact this is by far the most common indication for platelet transfusion in current neonatal practice. However there have been no trials to show whether transfusion reduces haemorrhage or improves outcome in neonates. The one randomised controlled trial of platelet transfusion in neonates showed no reduction in major haemorrhage.<sup>120</sup> However, this trial was carried out more than 15 years ago when the NICU patient population was very different. In addition, the trial aimed to raise the platelet count to normal ( $>150 \times 10^9/L$ ) and was confined to neonates with platelet counts above  $50 \times 10^9/L$ , thereby excluding most neonates receiving platelet transfusions using present day guidelines (see below).

Despite the lack of clinical trials of platelet transfusion in neonates, many countries have developed consensus guidelines or protocols.<sup>2,3,121</sup> However, as illustrated by 3 recent studies in the USA, UK and Mexico respectively, there is evidence of a wide variation in platelet

transfusion rates between units (from 2% up to 9.4% of admissions) despite the fact that the majority of platelet transfusions in all 3 studies were given prophylactically to non-bleeding neonates and that most transfused neonates received only one platelet transfusion.<sup>1–3</sup> A recent electronic survey of neonatal platelet transfusion usage received responses from 1044 neonatologists also revealed evidence of significant variability in platelet transfusion thresholds across Canada and the US. In this survey, platelet transfusion appeared to be frequently administered to non-bleeding infants with platelet counts  $>50 \times 10^9/L$ , higher thresholds than currently practiced in the UK.<sup>122</sup>

These studies also found that the thrombocytopenic neonates who received platelet transfusion(s) were up to 10 times more likely to die than those who were not transfused, raising the possibility that platelet transfusion, at least in some settings, may be harmful. It is not yet clear whether the excess mortality in thrombocytopenic neonates receiving platelet transfusions<sup>1–3,119</sup>, reflect the severity of the conditions causing severe thrombocytopenia (e.g. sepsis and NEC) or whether it is a direct effect of platelet transfusion.<sup>4,5</sup> Nevertheless, the potential for adverse effects from platelet transfusion underlines the need for randomised controlled trials to define the optimal threshold and regimen for platelet transfusion in neonates. Preliminary data from the PlaNeT study<sup>119</sup> showed that 69% of all neonates with a platelet count below  $60 \times 10^9/L$  were given a platelet transfusion even though fewer than 1 in 5 of these babies had overt haemorrhage, and, surprisingly, that two thirds of these babies received a single platelet transfusion suggesting that many of the transfusions may have been unnecessary.

### Guidelines for platelet transfusion in neonates

Until data from controlled trials become available, decisions about platelet transfusion in neonates will be based on consensus guidelines, a number of which are available.<sup>121</sup> Recent data suggest that most neonates who bleed (particularly those with IVH) do so in the first days of life.<sup>119</sup> By contrast, most episodes of severe thrombocytopenia, especially in preterm infants, develop after the first few days of life (due to sepsis/NEC) when major haemorrhage is relatively rare even in severely thrombocytopenic neonates.<sup>119</sup> This suggests that

prophylactic platelet transfusions are not required outside the first week of life for thrombocytopenic neonates of any gestational age until the platelet count falls below  $30 \times 10^9/L$  (Table 2). Recommendations for neonates during the first week of life are more difficult but it seems reasonable to continue to recommend that for patients in the first week of life with the greatest risk of haemorrhage, (e.g. unstable extremely preterm neonates) prophylactic platelet transfusions using trigger thresholds up to  $50 \times 10^9/L$  represent acceptable and safe clinical practice. Platelet transfusions in neonates with platelet counts  $>50 \times 10^9/L$  should be reserved for patients with active major bleeding, such as new or extending IVH, pulmonary, gastrointestinal or renal haemorrhage (since there is no evidence that higher platelet counts are of any benefit in non-bleeding neonates).

No trial evidence is currently available regarding the optimal dose of platelets to administer or when to administer further transfusions. Larger volumes (20 ml/kg) appear to produce larger and more sustained rises in platelet count compared to smaller volumes (10 ml/kg), and are generally well tolerated (personal observations). Since most neonates only receive one platelet transfusion it seems prudent to ensure this results in a good platelet increment by using a larger volume to minimize donor exposure. For guidance on appropriate platelet products for transfusion in neonates the reader is referred to the British Committee for Standards in Haematology website.<sup>121</sup>

### Conclusion

Thrombocytopenia is a common problem in the newborn, particularly those born prematurely. Most episodes of neonatal thrombocytopenia are mild or moderate and resolve spontaneously without clinical sequelae. For more severe episodes, the recent demonstration of impaired megakaryocytopoiesis and platelet production offers the potential for improved therapies, although no thrombopoietic agents have yet been used in controlled clinical trials in neonates. Instead the focus of clinical studies is on the relationship between platelet count and the different causes of thrombocytopenia and on the role of platelet transfusion. Future studies should define more clearly the safe lower limit for platelet counts within these different groups of neonates in tandem with defining which neonates will benefit from platelet transfusion.

## Practice points

- The underlying cause of neonatal thrombocytopenia can usually be predicted by timing of onset.
- The most frequent cause of early onset thrombocytopenia (presenting within 72 hours of birth) is chronic fetal hypoxia (eg due to IUGR); this form of thrombocytopenia is self-limiting and rarely severe.
- Most episodes of severe thrombocytopenia develop after the first few days of life and are secondary to sepsis and/or NEC.
- NAIT is the commonest cause of otherwise unexplained severe thrombocytopenia at birth; >95% of cases are due to HPA-1a, 5b, 15b incompatibility.
- Bleeding risk is in order of NAIT > sepsis/NEC > chronic fetal hypoxia.
- The risk of bleeding is highest in the first week of life, especially in very preterm neonates; a threshold for platelet transfusion of  $50 \times 10^9/L$  is reasonable at this time.
- Prophylactic transfusions are not required after the first week of life for any gestational age unless platelet count  $< 30 \times 10^9/L$ .
- Platelet transfusion for neonates with platelets  $> 50 \times 10^9/L$  should be reserved for those with active major bleeding.
- Incidence of ICH in neonates born to mothers with ITP is  $< 1\%$ .
- Antenatal treatment of NAIT increasingly relies on administration of maternal IVIG rather than intrauterine fetal platelet transfusion.

## Research agenda

- Clinical trials to establish the optimum management of pregnancies at risk for NAIT are needed to minimise the high neonatal mortality and morbidity.
- Further investigation of the fetal pathogenesis of Down syndrome-associated thrombocytopenias should provide insight into paediatric acute leukaemias.
- Further studies of the correlation between neonatal thrombocytopenia and bleeding are required to identify a bleeding risk score to aid treatment decisions.
- Studies to identify the neonates most likely to benefit from platelet transfusion and the optimal transfusion regimen to use are urgently needed.

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