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REVIEW

Thrombocytopenia in the Neonate

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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.

Definition

Studies of fetal blood obtained by cordocentesis show that the mean fetal platelet count reaches 150×10^9/L by the end of the first trimester of pregnancy[6], and rises to $175—250 \times 10^9$/L by end of the second trimester.[7—9] Several population studies also show that >98% of term neonates born to mothers with normal platelet counts have platelets above 150×10^9/L at birth.[10—13] 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.[14—17] 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.[1,19] In these clinical situations thrombocytopenia usually develops very rapidly over 1—2 days, is often very severe (platelets $<30 \times 10^9$/L) and may take several weeks to recover.[1] 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).[17,18] This form of thrombocytopenia is usually mild or moderate and it is self-limiting, resolving within 10 days in the majority of cases.[17,18] The mechanism of thrombocytopenia is reduced megakaryopoiesis[17,20] 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).[18,21] Although representing <5% of cases of early thrombocytopenia, an important cause of early thrombocytopenia is neonatal alloimmune 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).