Neonatal Thrombocytopenia

General Presentation:

Thrombocytopenia is one of the most common haematological problems encountered in the neonatal period presenting in 1-5% of newborns at birth. It is particularly common in newborns admitted to the neonatal intensive care units (NICU) presenting in 22-35% of these neonates. Neonatal thrombocytopenia is defined as a platelet count of less than 150 x 10^9/l. This definition is the same for older children and adults as studies have shown that the fetal platelet count is above 150 x 10^9/l by the second trimester of pregnancy. The hallmark of platelet disorders is mucocutaneous bleeding however newborns may present more severely with, petechiae, purpura, and intra-cranial hemorrhages.

Causes and Mechanisms:

There are many neonatal and maternal factors that are associated with thrombocytopenia of the newborn. A decreased platelet count can result from a variety of mechanisms:

1. Impaired Platelet Production → This is the major mechanism underlying neonatal thrombocytopenia. Thrombocytopenia is either present at birth or develops in the first 72 hours of life in 75% of the neonates. Only a small number of these infants have immunological disorders or coagulopathy; the majority of newborns with thrombocytopenia are born prematurely after pregnancies complicated by placental insufficiency and/or fetal hypoxia (ie maternal pre-eclampsia and intra-uterine growth retardation of the fetus). These pre-term infants with early-onset thrombocytopenia have impaired megakaryocytopoeisis and platelet production. The megakaryocytes (platelet precursors) and their progenitors are reduced at birth.

2. Consumption and/or Sequestration → An increase in platelet consumption and/or sequestration to the spleen and other organs is the mechanism in 25-35% of cases of neonatal thrombocytopenia. Transplacental passage of maternal platelet alloantibodies and

autoanitbodies account for 15-20% of thrombocytopenia present at birth. Disseminated intravascular coagulapathy (DIC) associated with perinatal asphyxia and sepsis is responsible for 10-15%, almost always in neonates who are extremely ill.

3. Combination → Most neonates probably develop thrombocytopenia due to an adverse fetal environment that leads to impaired megakarycytopoeisis at birth. This predisposes them to a further decrease in their platelet count when the neonate is exposed to concurrent consumptive stress. ie as in an infection.

Classification:

Thrombocytopenia of the newborn can be classified by different methods. Some classify it based on pathophysiological factors such as Immune-Mediated, Asssociated with Infection, Increased Consumption, Genetic and Congenital Anomalies and Miscellaneous. The classification scheme presented here is based on time of presentation of thrombocytopenia adapted from *Roberts and Murray, 2003*:

1. **Fetal**
    - Alloimmune (see below)
    - Congenital infection – TORCH infections (toxoplasmosis, other (syphilis, viral infections), rubella, cytomegalovirus, herpes simplex, and HIV)
    - Aneuploidy – trisomies 18, 13, or 21
    - Autoimmune – Immune Thrombocytopenia Purpura (ITP), Systemic Lupus Erythematous (SLE)
    - Others: severe Rh hemolytic disease, congenital/inherited (Wiscott-Aldrich syndrome) [Wiscott-Aldrich Syndrome = an X-linked disorder characterized by hypogammaglobulinemia, eczema and thrombocytopenia caused by a defect in a cytoskeletal protein common to lymphocytes and platelets. Small platelets are seen on the smear. Thrombocytopenia may be improved by splenectomy.]
2. **Early Onset Neonatal (< 72hours after birth)**
    - Placental Insufficiency – pre-eclamspsia, intra-uterine growth retardation, maternal diabetes
    - Perinatal asphyxia
    - Perinatal infection – group B streptococcus, *Escheria coli*, *Haemophilus influenzae*
    - Disseminated Intravascular Coagulopathy
    - Alloimmune (see below)
    - Autoimmune – ITP and SLE
    - Congenital/Inherited – Thrombocytopenia with absent radii (TAR) [TAR = severe thrombocytopenia in association with orthopedic abnormailities, especially of the upper extremity. The thrombocytopenia improves over time], Congenital amegakaryocytic thrombocytopenia (CAMT) [CAMT = severe

thrombocytopenia presenting at birth or shortly thereafter with no other congenital anomalies. The marrow is devoid of megakaryocytes]

- Others – congenital infection (TORCH), thrombosis, bone marrow replacement (congenital leukemia), metabolic disease (proprionic and methylmalonic academia – both organic acid disorders), Kasabach-Merrit syndrome

3. **Late Onset Neonatal (>72 hours after birth)**
   - Late onset sepsis
   - Necrotizing enterocolitis (NEC) [NEC = an acquired condition in which the lining of the intestinal wall dies and sloughs off. Its cause is unknown and it is much more common in premature infants. Symptoms include abdominal distention, feeding intolerance, lethargy, diarrhea and blood in stool. Signs include thrombocytopenia, elevated white blood cells and positive fecal occult blood test.]
   - Others – congenital infectionn, autoimmune, metabolic disease (ie proprionic and methymalonic academia), congenital/inherited (TAR, CAMT)

Clinical Presentation and Diagnosis:

a) **Fetal Thrombocytopenia** → Can be identified during assessment of fetuses with ultrasound demonstrating hydrops as a result of congenital infections or aneuploidy. Thrombocytopenia of the fetus may also be discovered following primary diagnostic investigations for either inherited or alloimmune thrombocytopenia.

b) **Thrombocytopenia in an otherwise healthy term baby** → These neonates usually present with hemorrhage and purpura. It is uncommon and usually caused by alloimmune or autoimmune thrombocytopenia but needs to be treated as an emergency due to the risk of hemorrhage.

c) **Neonatal Alloimmune Thrombocytopenia (NAIT)** → Sometimes known as isoimmune thrombocytopenia, this is the result of sensitization of the mother to antigens present on fetal platelets during gestation. These antigens are inherited from the father and are thus absent on maternal platelets. The antibodies created then cross the placenta and attack the fetal platelet. The incidence of NAIT is approximately 1 in 1500 pregnancies and is the platelet equivalent of haemolytic disease of the newborn.
   - Suspect NAIT in a thrombocytopenic newborn that is otherwise well, normal maternal platelets, no history of maternal autoimmune disease or ITP. The neonate with NAIT is at risk for intracranial hemorrhage in utero and during delivery.
   - NAIT varies in severity from mild/moderate which typically resolves in the first week of life without sequelae, to severe with extensive intracranial hemorrhage (up to 20% of cases) leading to either death or serious neurological sequelae.

- The most common presentations in severe NAIT are petechiae, purpura, and cephalohematoma at birth.
- The diagnosis depends on demonstrating platelet antigen incompatibility between mom and neonate or mom and father.
- The most commonly detected antibodies are those directed again human platelet antigen (HPA) -1a (80%) and HPA-5b (10-15%) – this permits prenatal diagnosis in at risk fetuses.

d) Neonatal Autoimmune Thrombocytopenia → This form of neonatal thrombocytopenia occurs in neonates whose mothers have Idiopathic Thrombocytopenia Purpura (ITP) or Systemic Lupus Erythematous (SLE). These mothers carry antibodies directed against platelets. The platelet associated IgG antibody can passively cross the placenta and cause thrombocytopenia in the fetus and the newborn in 10% of cases.

- The clinical manifestations are less severe than in NAIT; the risk of intracranial hemorrhage is less than 1%, greatest during passage through the birth canal. Most cases usually resolve by 4-6 weeks.
- All neonates of moms with an autoimmune disease should have a cord blood platelet count determined at birth.
- Fetal scalp sampling can also be used to measure to fetal platelet count.
- The platelet count should be repeated for 3-4 days.
- The maternal platelet count is sometimes a useful indicator of the probability that the infant will be affected.

e) Neonatal Intensive Care Unit Patients → It can be divided into Early Onset and Late Onset Thrombocytopenia. Most cases of thrombocytopenia in neonates are actually discovered "accidentally". The table below contrasts Early from Late Onset Thrombocytopenia:

	Early Onset (< 72 hours after birth)	**Late Onset (> 72 hours after birth)**
Degree of Thrombocytopenia	Mild to moderate (rarely < 150 x 10^9/l)	Severe (frequently < 50 x 10^9/l)
Onset and Progression	Evolves slowly over several days	Rapid onset and progression over 24-28 hours
Associated with	Complicated pregnancies (Pre-eclampsia, IUGR, maternal diabetes)	Sepsis and NEC
Management	Rarely requires specific treatment	Muliple platelet transfusions often required
Mechanisms	Impaired platelet production	Combined platelet consumption and impaired production

Table 1: Comparison of early and late onset thrombocytopenia in neonates. Adapted from *Roberts and Murray, 2003* (IUGR = intrauterine growth restriction; NEC = necrotizing enterocolitis)

Procedural Investigations:

Screening lab tests for bleeding newborns include a platelet count, a blood smear, CBC, prothrombin time, partial thromboplastin time, fibrinogen, fibrin degradation products and bleeding time. No single lab test can screen for all bleeding disorders. In thrombocytopenia, the peripheral smear and platelet count are very important. Large platelets suggest peripheral destruction while small platelets are more indicative of a problem with platelet production.

Differential Diagnosis of Neonatal Thrombocytopenia:

- The Well Newborn:
  - Large platelets, normal hemoglobin and white blood cells → think consumption (Maternal ITP, NIAT)
  - Small platelets, congenital anomalies, increased mean corpuscular volume → think decreased production of platelets (TAR, Wiscott-Aldrich syndrome, CAMT)
- The Ill Newborn:
  - Large platelets, decreased fibrinogen, increased fibrin degradation products → think consumption of platelets (DIC, NEC, sepsis, thrombosis)

Supplementary Information - Management of Neonatal Thrombocytopenia:

There are no widely accepted guidelines for platelet transfusion in newborns with non-immunologically mediated thrombocytopenia. Recent guidelines are more conservative considering the lack of evidence supporting improved outcomes with platelet transfusion. In general, thrombocytopenic neonates should receive platelets when the degree of thrombocytopenia is such that there is an unacceptable risk of hemorrhage. The following table gives a summary of when it is appropriate to administer platelets to bleeding and non-bleeding neonates:

Platelet count (x 10^9/l)	**Non-Bleeding Neonate**	**Bleeding Neonate**	**NAITP (proven or suspected)**
<30	Consider transfusion in all patients	Transfuse	Transfuse (with HPA compatible platelets)
30-49	Do no transfuse if clinically stable; Consider transfusion if: - < 1000g and < 1 week of age - clinically unstable (ie fluctuating blood pressure) - previous major bleeding - current minor bleeding	Transfuse	Transfuse (with HPA compatible platelets if any bleeding)

	(ie petechiae, puncture site oozing) - concurrent coagulopathy - requires surgery or exchange transfusion		
50-99	Do not transfuse	Transfuse	Transfuse (with HPA compatible platelets if major bleeding) present
>99	Do not transfuse	Do not transfuse	Do not transfuse

Table 2: Guidelines for platelet transfusion in the newborn. Adapted from *Roberts and Murray 2003*.

Additionally, it has been shown that the administration of intravenous immunoglobulin (IVIG) before delivery results in increasing fetal platelet counts and may help to reduce thrombocytopenia in cases of NAIT and ITP. Caesarian section delivery is recommended in these neonates to prevent intracranial hemorrhage. There is a high rate of recurrence of NAIT in successive pregnancies and thus antenatal therapy should be offered.

References:

1. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. *Archives of Diseases in Childhood. Fetal and Neonatal Edition* 2003; 88: 359-364.
2. Kleigman RM, Marcdante KJ, Jensen HB, Behrman RE. Nelson Essentials of Pediatrics 5th Edition. Elselvier Saunders, 2006.
3. Kaplan C. Foetal and neonatal alloimmune thrombocytopaenia. *Orphanet Journal of Rare Diseases* 2006; 1:39.

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