

Neonatal Thrombocytopenia

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Definition

- Thrombocytopenia is defined as a platelet count less than 150,000 per microliter of blood
- Platelet count less than 100,000/uL is considered as definitely abnormal at any gestational age and deserves further evaluation

Definition

- Thrombocytopenia is one of the common hematological problem encountered in the neonatal period particularly in sick newborns and premature babies.
- In general, the thrombocytopenia seen in a sick infant is likely related to the primary disease process and will resolve as the primary process improves.

Incidence

- Reported incidence of thrombocytopenia less than 100,000/ul in cord blood is around 0.7 to 0.9% and thrombocytopenia less than 50,000 count is around 0.12 to 0.14%
- Severe thrombocytopenia - platelet count less than 20,000 were seen in 0.01 to 0.08%.

Incidence

- Of the 4 million birth annually occurring in United States, about 36,000 can be expected to have congenital thrombocytopenia and 11,000 of these can be expected to have severe thrombocytopenia

Incidence

- Approximately 20-50% of infants admitted to tertiary Neonatal Intensive Care Units develop thrombocytopenia , 38% of affected infants have platelet count < 100,000/uL and 20% of infants have platelet count < 50,000/uL

Platelet physiology

- Platelets are produced by megakaryocytes in the bone marrow, and have an average lifespan of 9 to 10 days.
- Normal bone marrow contains 6×10^6 megakaryocytes per kilogram body weight
- Each megakaryocyte release up to 1000 platelets
- The normal daily rate of platelet production is equivalent to about $35,000 \pm 4,300$ platelets per microliter of blood, to maintain steady levels of about $250,000 \pm 100,000$

Platelet function

- Adhesion – after damage of the endothelial lining, platelets adhere to the exposed subendothelium. Neonatal platelet adhesion is similar to that in adults.
- Aggregation – Adenosine diphosphate (ADP), epinephrine, thromboxane A₂, platelet activating factor (PAF), thrombin, and collagen activate platelets, causing them to degranulate and aggregate.

Mechanisms that are responsible for thrombocytopenia in newborn and premature infant

1. Fetal and neonatal megakaryocytes are smaller and have lower ploidy than megakaryocytes of adult and hence may produce fewer platelets.
2. Inadequate production of thrombopoietin in response to thrombocytopenia in neonates as compared to adult leading to limited ability to increase platelet production in response to increased platelet consumption.
3. Thrombocytopenic premature neonates have fewer circulating megakaryocytes progenitors

Thrombocytopenia causes

- Immune
- Infectious
- Genetic
- Drug-induced
- Increased peripheral consumption (DIC, NEC, hypersplenism)
- Placental insufficiency
- Miscellaneous

Thrombocytopenia causes

- Commonest cause of low platelet count is **improper collection** of blood or inadequate anticoagulants and hence it is wise to confirm the laboratory reports of low platelet count with peripheral blood smear

Neonatal Alloimmune Thrombocytopenia (NAIT)

- Incompatibility between parental platelet antigens leading to maternal antibodies to antigens expressed by fetal platelets. Mother has a normal platelet count.
- First pregnancy can have affected child (unlike neonatal Rh disease)
- Human platelet antigen 1 (HPA-1 or PLA-1) incompatibility accounts for 80% to 90% of cases of NAIT.
- Incidence of NAIT is 0.05% to 0.1%
- Severe thrombocytopenia, $< 50,000$ in 87% of cases
- Petechiae in 80% of cases
- Intracranial hemorrhage in 11% of cases

Neonatal Alloimmune Thrombocytopenia (NAIT)

- Clinical manifestations:
 - severe, generalized petechiae
 - rash or purpura
 - or normal at birth and may develop symptoms and signs during 2-3 day post-partum.
 - severe complication is intracranial hemorrhage which is seen in approximately 10-15% cases and half of these occurs in utero with neuro-developmental sequelae

Neonatal Alloimmune Thrombocytopenia (NAIT)

- Diagnosis requires demonstration of maternal and fetal platelet incompatibility and absence of antigen in mother's serum, which is present in the child.

Autoimmune Thrombocytopenia

- Maternal autoimmunity leads to passive immunization with antibodies that bind both fetal and maternal platelets
- Most commonly with: incidental or gestational thrombocytopenia of pregnancy (74%) hypertensive diseases of pregnancy (21%) immune thrombocytopenic disorders during pregnancy like ITP and SLE (4%)
- ITP: 13% to 56% of infants born to mothers with ITP develop thrombocytopenia, with only 5% to 20% having platelets < 50,000 Intracranial hemorrhage rate of 3%

Infectious Causes of Thrombocytopenia

- 80% of patients with proven infections are thrombocytopenic
- When associated with disseminated intravascular coagulation (DIC) platelet counts tend to be lower, frequently $< 20,000$
- Commonly associated with fungal infection (VLBW & ELBW infants) and viral infections (TORCH, HIV, parvovirus B19 EBV)
- Mechanism is most likely a combination of accelerated destruction and decreased production.

Genetic Associations with Thrombocytopenia

Genetic causes of thrombocytopenia in neonates

- Thrombocytopenia with absent radii (TAR)
- Fanconi's anemia
- Congenital amegakaryocytic thrombocytopenic purpura
- Congenital hypoplastic thrombocytopenia with microcephaly.

Familial thrombocytopenia's

- Bernard Soulier syndrome
- May-Hogglin anomaly
- Paris-Trousseau thrombocytopenia
- X-linked recessive thrombocytopenia

Genetic Associations with Thrombocytopenia

Chromosomal anomalies

- Trisomy 13
- Trisomy 18
- Trisomy 21 (Mongol)
- Turner's syndrome

Associated with genetic disorders

- Wiskott-Aldrich syndrome (WAS)
- Noonan syndrome
- Alpert's syndrome

Inherited metabolic disorders

- Methylmalonic acidemia
- Ketotic glycinemia
- Isovaleric acidemia
- Holocarboxylase synthetase deficiency

Drugs that produce thrombocytopenia in mother, fetus and neonate

- Mechanisms by which drug produce idiosyncratic thrombocytopenia in mother and fetus are unknown but maybe related with immune reaction.
- The drugs that have been implicated are:
 - quinine
 - Thiazides
 - diuretics
 - Hydralazine
 - Tolbutamide
 - indomethacin
 - Heparin
 - vancomycin
 - intravenous lipid infusion

Drugs that produce thrombocytopenia in mother, fetus and neonate

- Drugs given to neonate like aspirin, phenylbutazine, promethazine, indomethacin, carbenicillin etc. have all been shown to produce platelet dysfunction presumably by inhibiting cyclo-oxygenase enzyme

Miscellaneous Causes of Thrombocytopenia

- As many as 60% of cases with neonatal thrombocytopenia fall in this group of idiopathic variety with platelet count varying from 50,000 to 100,000 and may persist for many weeks.

Miscellaneous Causes of Thrombocytopenia

- Thrombosis – associated with an indwelling catheter, extracorporeal membrane oxygenation (ECMO), valvular cardiac disease, renal vein thrombosis.
- Necrotizing enterocolitis (NEC) – 80% to 90% of infants with necrotizing enterocolitis due to platelet destruction, most without DIC

Miscellaneous Causes of Thrombocytopenia

- Intrauterine Growth Retardation/Infants of women with pregnancy induced hypertension (PIH) – associated with PIH, most often in premature infants, associated with decreased platelet production and usually resolves by 10 days of age.
- Asphyxia – Thrombocytopenia is seen commonly in asphyxiated infants.
- Idiopathic

Thrombocytopenia classification

- Fetal
- Early onset (first 72 hours of life)
- Late onset (after 72 hours of life)

Causes of fetal thrombocytopenia

- Alloimmune
- Congenital infection (e.g. CMV, toxoplasma, rubella)
- Aneuploidy (e.g. trisomies 18, 13, 21, or triploidy)
- Autoimmune (e.g. ITP, SLE)
- Severe rhesus disease
- Congenital/inherited (e.g. Wiskott-Aldrich syndrome)

Causes of early onset thrombocytopenia

- Placental insufficiency (e.g. GPH, IUGR, diabetes)
- Perinatal asphyxia
- DIC
- Alloimmune
- Autoimmune
- Congenital infection (e.g. CMV, toxoplasma, rubella)
- Thrombosis (e.g. aortic, renal vein)
- Bone marrow replacement (e.g. congenital leukaemia)
- Kasabach-Merritt syndrome
- Metabolic disease (e.g. propionic and methylmalonic acidaemia)
- Congenital/inherited (e.g. TAR, Congenital Amegakaryocytic Thrombocytopenia [CAMT])

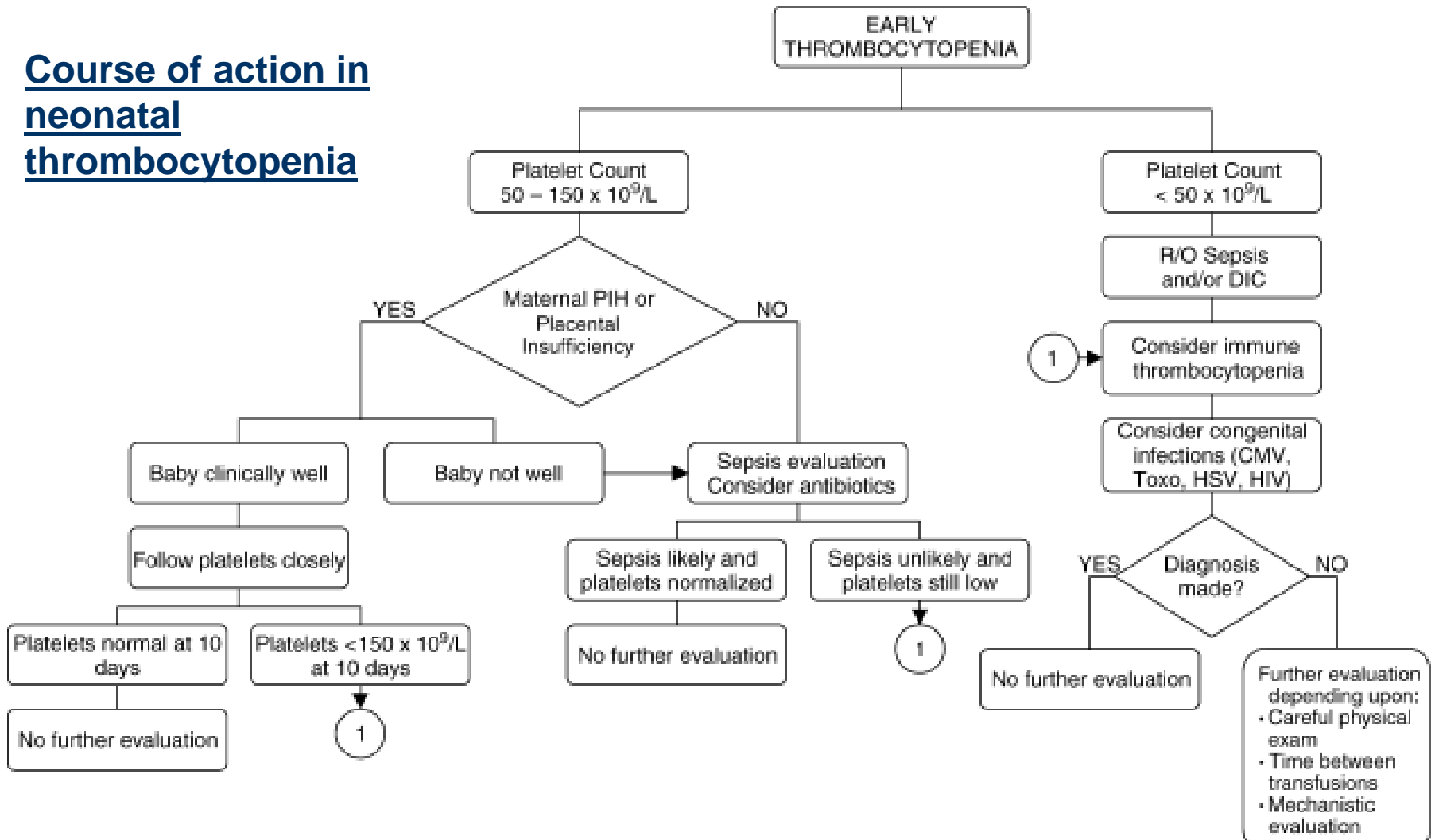
Causes of late onset thrombocytopenia

- Late-onset sepsis
- NEC
- Congenital infection (e.g. CMV, toxoplasma, rubella)
- Autoimmune
- Kasabach-Merritt Phenomenon
- Metabolic disease (e.g. propionic and methylmalonic acidemia)
- Congenital/inherited (eg TAR, CAMT)

Physical exam

- A careful physical examination of the neonate with thrombocytopenia, besides the purpura or petechiae can provide important clues for the diagnosis.
- Emphasis should be placed on:
 - dysmorphic features suggestive of chromosomal disorders
 - hepatosplenomegaly
 - abdominal masses
 - forearm or thumb abnormalities
 - Decreased ability to pronate and supinate the forearm (as in congenital amegakaryocytic thrombocytopenia)

Course of action in neonatal thrombocytopenia



Management of Thrombocytopenia

- In the absence of active bleeding treat thrombocytopenia if platelet count is less than 20,000 – 50,000. (Use the higher platelet value threshold, i.e. 50,000 in preterm and/or sick infants.)
- Platelet transfusions – usually give irradiated platelets from CMV-negative donors, 1 unit (or 2 units in large term infants or in cases of platelet destruction), reduced volume to about 10 to 20 mL/kg, over 30 – 60 minutes.
- Alloimmune thrombocytopenia (NAIT) – Treat with washed maternal platelets if Available. In utero transfusion of platelets to the fetus before delivery has been effective. Treatment of the newborn with intravenous immune globulin (IVIG), 1 gm/kg, may also be helpful.
- Autoimmune thrombocytopenia – Platelet transfusions usually not needed as thrombocytopenia is usually less severe, i.e. >50,000. Treatment with IVIG, 1 gm/kg, can be effective. Transfuse in addition to treatment with IVIG in cases of active bleeding.

Platelet Count (x10⁹)

Action

<30

Transfuse if bleeding
Consider transfusion in all other cases

30-49

Transfuse if bleeding
Consider transfusion if:

- <1000g and <7 days
- Clinically unstable (e.g. fluctuating BP)
- Previous major bleeding (e.g. Grade 3-4 IVH, pulmonary haemorrhage)
- Current minor bleeding
- Concurrent coagulopathy
- Requiring surgery or exchange transfusion

50-99

Transfuse only if bleeding

> 99

Do not transfuse

References

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Questions

- Define neonatal thrombocytopenia
- What are the platelets function?
- Which disease has the highest incidence of IVH; neonatal alloimmune thrombocytopenia or autoimmune thrombocytopenia ?
- What are the most common viral infections associated with thrombocytopenia?
- List 5 genetic causes of neonatal thrombocytopenia
- Characteristics required for the platelet transfusion in the newborn