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PEDIATRIC HEMATOLOGY, ONCOLOGY & IMMUNOLOGY

PEDIATRIC HEMATOLOGY, ONCOLOGY & IMMUNOLOGY

# Fetal & Neonatal

## Hematology, Oncology and Immunology

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SECTION 4

# Platelets, Platelet Disorders and Approach to Bleeding in Newborn


**Section Editors**

Nitin K Shah, Amita Mahajan



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  *Nitin K Shah*
- Neonatal Thrombocytopenia: Syndromic Causes
  *Manas Kalra, Amita Mahajan*
- Qualitative Platelet Disorders
  *Purvi Kadakia Kutty*
- Approach to a Bleeding Neonate
  *Gaurav Tripathi, Amita Mahajan*


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CHAPTER

22

# Approach to Neonatal Thrombocytopenia

Nitin K Shah

## NEONATAL MEGAKARYOPOIESIS AND THROMBOPOIESIS

### INTRODUCTION

After birth, the platelets are produced by megakaryocytes in the bone marrow and have a life of 9–10 days. In the fetus, they are produced predominantly in the liver. Platelets appear in the circulation in a fetus by 5–6 weeks of gestational age and platelet count steadily rises to 159 ± 34 × $10^9$/L by 10–17 weeks of gestation and 240 ± 60 × $10^9$/L by 18 weeks of gestation, remaining constant at that level, thereafter, until birth and beyond. Hence, the lower limit of the platelet count in a newborn, irrespective of the gestational age, remains at the adult level, i.e. more than 150 × $10^9$/L. Thrombocytopenia in a newborn is defined as platelet count lower than 150 × $10^9$/L, though clinical bleeding is usually seen with platelet count less than 50 × $10^9$/L or even lower. Spontaneous and severe bleeding is usually seen when the platelet count drops to less than 20 × $10^9$/L. Presence of significant bleeding at higher platelet counts should arouse suspicion of associated platelet dysfunction as is seen in cases with inherited thrombocytopenia, e.g. Bernard-Soulier syndrome.

A minimum platelet count of 7 × $10^9$/L is required for maintenance of the vascular integrity, and in that sense a normal platelet count of more than 150 × $10^9$/L provides a lot of reserve functional capacity. Similarly, 30% of the circulating platelets are stored in the spleen which can be brought into the circulation during the need or stress. Normal bone marrow contains 6 × $10^6$ megakaryocytes/kg body weight. The normal daily platelet production is approximately 35,000 ± 4,300 platelets per microliter of blood to maintain steady levels of about 250,000 ± 100,000 platelets/mL. Normal bone marrow can respond by increasing the platelet production by 7–8 folds during periods of thrombocytopenia.

Platelets are required at each stage of hemostasis. With the help of von Willebrand factor, they adhere to the exposed endothelial cells at the site of injury and help form the primary platelet plug. They secrete granules that contain the factors to help aggregate further platelets and coagulation factors that help form a clot locally. They secrete vasoactive amines that lead to vasospasm to prevent further blood loss. Platelet membrane provides the surface required for the coagulation to proceed.

There are several growth factors that are required for the formation of platelets from megakaryocytes in the bone marrow. These include interleukin (IL)-3, IL-6, IL-11, stem cell factor, leukemia inhibitory factor, erythropoietin (EPO) and the most important thrombopoietin (Tpo). Tpo, discovered in 1994, is a polypeptide glycoprotein that binds to its receptor c-mpl (named after its cell of discovery, i.e. acute myeloproliferative leukemic cell) expressed on the megakaryocytes, megakaryocytic precursors, hematopoietic precursor cells and platelets. Tpo acts to commit early precursor cells to lineage-specific differentiation and enhances production and release of platelets in the circulation. It acts via further signal conduction pathway and prevents apoptosis in the target cells. It also appears to play a role as pan-hematopoietic growth factor which explains why defects in its metabolism ultimately leads to total bone marrow failure, as seen in rare cases of congenital amegakaryocytic thrombocytopenia. Tpo levels are inversely proportional to the total megakaryocytic mass. High levels of Tpo indicate aregenerative type of thrombocytopenia.

The bone marrow in neonates is very sensitive to insults like hypoxia which leads to suppression of the megakaryocytes more than other precursor cells. This explains why thrombocytopenia is more common than other cytopenias in neonate, especially following hypoxic stress.

### INCIDENCE

There are very few prospective studies which have specifically looked at the incidence of thrombocytopenia in newborns. Recent prospective studies have shown that 0.5–4.1% of the neonates have thrombocytopenia. Around 30% of the babies admitted to the neonatal intensive care unit (NICU) have

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platelet counts less than 150 × $10^9$/L and around 10% of the babies will have counts less than 100 × $10^9$/L. Fortunately, most of the episodes of thrombocytopenia in NICU are mild to moderate but 20% of them (6% of the neonatal admissions) will have severe thrombocytopenia with counts less than 50 × $10^9$/L who are at a risk of severe bleeding including intracranial bleeds. Around 80% of these babies with severe bleeds are sick, preterms who have sepsis or necrotizing enterocolitis (NEC).

## CAUSES OF NEONATAL THROMBOCYTOPENIA

While traditionally one can classify the causes of neonatal thrombocytopenia into those caused by reduced production, increased destruction or consumption, sequestration, dilutional or a combination of these, it does not help while approaching a case of neonatal thrombocytopenia as most of the causes listed are rare. It is easy to group the cases as per their onset, the nadir of counts, the type of recovery, their mechanism of disease, their associated findings, presence of physical anomalies, presence of immunodeficiency and syndromes which helps to narrow down the differential diagnosis. The causes of neonatal thrombocytopenia are shown in **Box 22.1**.

### Patterns of Neonatal Thrombocytopenia

While there are many etiological causes of neonatal thrombocytopenia, most of the patients fall into two types of patterns. This helps us narrow down the etiology. Around 75% of the neonatal thrombocytopenia cases fall into the early onset type and the remaining into the late onset type.

#### *Early Onset Type*

This accounts for 75% of the total cases. Most babies have low platelet at birth or soon after birth in the first 72 hours of life. The causes include thrombocytopenia due to chronic or acute hypoxia like in preterm, intrauterine growth restriction (IUGR) baby risk factors like perinatal asphyxia, maternal diabetes, placental insufficiency, maternal hypertension or pre-eclampsia. The platelet counts in low normal in the first 2–3 days, falls to a nadir at 4–5 days and recovers by 7–8 days. The counts rarely drop below 50 × $10^9$/L. If the pattern of recovery does not follow this path, one has to think of other causes of early onset thrombocytopenia like chromosomal anomalies, congenital or perinatal infections, inherited causes or immune causes.

#### *Late Onset Type*

This accounts for the remaining 25% of the cases and is usually associated with late onset sepsis with or without NEC. The counts drop to a low level and there may be significant bleeding in these babies.

**Box 22.1** Causes of neonatal thrombocytopenia

- *Perinatal hypoxia*:
  - Maternal diabetes
  - Maternal hypertension, pre-eclampsia
  - IUGR
- *Immune causes*:
  - Alloimmune
  - Autoimmune
- *Infections*:
  - *Perinatal infections*: Bacterial, TORCH, HIV
  - Late onset sepsis or NEC
- *DIC*:
  - Asphyxia
  - Infections
  - Mismatched transfusions
  - Congenital TTP
- *Aneuploidy*:
  Trisomy 18, trisomy 13, trisomy 21, Turner's syndrome
- *Inherited*:
  - *Giant platelets*: Bernard-Soulier syndrome, May-Hegglin's anomaly, Sebastian syndrome, Fechtner syndrome, Epstein syndrome, Alport's syndrome, Montreal platelet syndrome, Quebec syndrome, Gray platelet syndrome
  - *Immunodeficiency*: Wiskott-Aldrich syndrome
  - X-linked thrombocytopenia
  - Hemophagocytic lymphohistiocytosis
  - *Bone marrow failure*: Fanconi's anemia, TAR syndrome, congenital amegakaryocytic thrombocytopenia
  - *Pre-malignant*: Monosomy 7
- *Others*:
  - *Consumption*: Kasabach-Merritt syndrome, vascular thrombosis, hepatic hemangioendothelioma
  - *Metabolic*: Propionic academia, methylmalonic acidemia
  - *Miscellaneous*: Congenital leukemia, exchange transfusions, Rh disease of newborn, subcutaneous fat necrosis of the neonate

*Abbreviations:* DIC, disseminated intravascular coagulation; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; Rh, Rhesus; TTP, thrombotic thrombocytopenic purpura

### Neonatal Alloimmune Thrombocytopenia

This is the platelet equivalent of the Rhesus (Rh) disease where alloantibodies are produced by the mother against the paternal platelets antigens inherited by the newborn from the father which are missing in the mother. These antibodies pass across the placenta and destroy the baby's platelets resulting in often moderate to severe thrombocytopenia. Unlike in Rh disease, in more than 50% of cases the first-born babies are also affected. In 80% of cases, the missing platelet antigen in the mother is human platelet antigen (HPA)-1a (also known as PlA1), in 10–15% it is HPA-5b and in the rest, it is HPA-3a, HPA-1b or some other unknown and rare antigen. In Asian

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communities, it is usually the HPA-4 antigen. Development of the alloantibodies in HLA-1A negative women is strongly associated with HLA DRB3 0101 (odds ratio of 140).

1:350 pregnancies are associated with maternal antiplatelet antibodies, but only 1:1000 livebirths are associated with neonatal alloimmune thrombocytopenia proving that a good number of them are silent or unnoticed. The affected neonates, who otherwise look well, present with purpura, bruising, mucosal bleeds and thrombocytopenia at birth or immediately after birth. The platelet count is usually less than $30 \times 10^9$/L. Around 20% of the affected neonates develop severe bleeding including intracranial bleeds. Around 20–50% of the intracranial bleeds start in the intrauterine life and 20% of the survivors develop long-term neurodevelopmental sequelae. The diagnosis is done by laboratory testing for the antiplatelet antibodies.

Treatment of the mildly affected babies without mucosal bleeds or with platelet count above $30 \times 10^9$/L is conservative. Those with significant mucosal bleeds, evidence of intracranial bleeds or platelet count less than $30 \times 10^9$/L need specific treatment including platelet transfusions, intravenous immunoglobulin (IVIg) and steroids. HPA compatible platelets need to be transfused. While one can use washed mother's platelets (which obviously will be negative for the missing platelets), HPA-1a negative platelets are usually stored and easily available in major centers in the West. If severe thrombocytopenia persists in spite of the platelet transfusions, one need to give IVIg in the dose of 2 g/kg body weight over 2–5 days and/or IV methyl prednisolone in the dose of 1 mg/kg 8 hourly. The treatment is required for 1–6 weeks till the platelet counts is in the safe range.

The severity depends on the maternal antibody titers. The second born neonate is usually severely affected if the first baby was symptomatic or had intracranial bleeds especially with intrauterine onset. In such cases, fetal monitoring of the platelet counts is advocated and the mother is given IVIg in the dose of 1–2 g/kg/week with prednisolone in the dose of 0.5–1 mg/kg/day. The fetus can also be given in-utero HPA compatible platelet transfusions if the maternal treatment alone dose not help. Elective lower segment cesarean section (LSCS) is also advocated to prevent trauma to head.

## Neonatal Autoimmune Thrombocytopenia

This occurs due to transplacental transfer of the antiplatelet autoantibodies. It is suspected because of the prior history of thrombocytopenia in the mother due to idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE) or some such autoimmune disease. The platelet count in the mother may be normal even when the antibodies persist, especially following splenectomy. The antibodies are formed against the common platelet antigens like gp1b/IX or gpIIb/IIIa. The disease is generally milder than the alloantibody-mediated neonatal thrombocytopenia. The newborn is usually normal at birth with even normal platelet count which drops after few days. Less than 10–15% of the babies have platelet counts less than $50 \times 10^9$/L and the bleeding is usually milder. Intracranial bleeds occur in less than 1–2% of babies. In most, the platelet counts recover in the next 2–3 weeks though rarely they may take a longer time. There is no role of antenatal treatment or LSCS. After birth, treatment is required in presence of significant bleeding or platelet counts less than $30 \times 10^9$/L. The treatment consists of IVIg and or steroids as in the case of alloimmune thrombocytopenia. Like in ITP, there is no role of platelet transfusions as the autoantibodies will react with all the platelets as the target antigens are common to all the donors. The prognosis is usually excellent.

## Thrombocytopenia Following Hypoxia

This is the most common cause of early onset pattern of thrombocytopenia. The newborn is usually a preterm or an IUGR baby who has risk factors like maternal diabetes, maternal hypertension or pre-eclampsia or perinatal asphyxia. The counts are $100 \times 10^9$/L in first few days, fall to a nadir of $50 \times 10^9$/L at 4–5 days and recover by 7–8 days. The counts often recover above the normal levels. They may also have neutropenia and polycythemia besides thrombocytopenia. Though platelet destruction is an important cause, especially in acute hypoxia where disseminated intravascular coagulation (DIC) with thrombocytopenia is seen in 50% of such babies, in most with chronic hypoxia there is decreased production too as the major contributing factor. Less than 10% of such babies have evidence of DIC and the Tpo levels are high suggestive of aregenerative type of thrombocytopenia. There is evidence of increased erythropoiesis with increased levels of EPO and circulating normoblasts. This with increased Tpo levels suggests preferential differentiation toward erythropoiesis with depressed megakaryopoiesis. This is because the megakaryocytes are sensitive to hypoxia and are suppressed with hypoxia temporarily. The bleeding is usually mild. Most do not need any specific treatment. Those who are symptomatic need platelet transfusions.

## Thrombocytopenia due to Neonatal Infections

### *Perinatal Sepsis*

Perinatal bacterial sepsis can occur in 1–2/1,000 livebirths. The common organisms include group B sepsis or *E. coli* in the West and gram-negative organisms like Klebsiella or *E. coli* in our country. Around 50% of the sepsis cases develop thrombocytopenia and DIC are important cause of low platelet counts. The platelet counts are low early in life and recover with the treatment of the primary cause.

### *Congenital Infections*

TORCH group of infection can lead to thrombocytopenia. Most, but not all, will have other signs like jaundice, anemia, congenital defects, hepatosplenomegaly, etc. Cytomegalovirus (CMV) is a common cause of such thrombocytopenia. About

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0.5–1% of all newborns develop congenital CMV infection and though only 10–15% of them are otherwise symptomatic, 75% of them have low platelet counts. There may be associated neutropenia and the thrombocytopenia may persist for several months. Similarly, 40% of those infected with toxoplasma can develop low platelet counts. Another common cause in our country is perinatal HIV infection and rubella infection as MMR (Measles, mumps and rubella) vaccine is still not a part of our national schedule.

### *Late Onset Sepsis*

A common cause of late onset of thrombocytopenia is late onset of sepsis with or without NEC. Thrombocytopenia may be the first sign of infection, though usually other signs of infection are also present. The platelet counts fall after the first 72 hours and may take around 7–8 days to recover after the treatment for sepsis is started and is effective. Less than 10% of these patients have DIC. The Tpo levels are high suggesting aregenerative type of thrombocytopenia. This is also evident by the fact that thrombocytopenia persist even after the infection is under control. This suggests that the cause of low platelet is less production due to suppression of the megakaryocytes. The counts are usually less than $30 \times 10^9$/L and 15–20% of the patients have significant bleeding. Platelet transfusions are required for the symptomatic patients.

### *Consumption of Platelets*

*Disseminated intravascular coagulation*: Consumption and destruction of platelets occur in DIC which usually occurs following perinatal asphyxia or neonatal infection. The newborn will have the signs of the primary disease and will have severe thrombocytopenia with significant bleeding. The patient may have the signs of thrombosis like gangrene. The prothrombin time and activated partial thromboplastin time will be prolonged and D-dimers or the fibrinogen split products (FDP) will be raised. The peripheral smear will show evidence of microangiopathic hemolytic anemia along with low platelet counts. Treatment will include use of platelets along with fresh frozen plasma besides treatment of the primary cause.

*Kasabach-Merritt syndrome:* Large hemangioma can occur over extremities, trunk, neck or in internal organs. Platelets can get trapped in the slow circulation within the hemangioma and can lead to local consumption or localized DIC with consumption of other coagulation factors too. There may be multiple afferent and feeders to the hemangioma. The mass may not be restricted to the defined anatomical layers and usually infiltrates deep into the tissues making it difficult to excise the hemangioma. The diagnosis is obvious when the hemangioma is seen externally, whereas it can be difficult if the hemangioma is in some organ. Very low platelet counts, evidence of microangiopathy, raised D-dimers or FDP levels and high retic count will suggest the diagnosis. Imaging and vascular studies will help define the extent of the lesion which may be actually much widespread than appearing visibly. Medical treatment includes use of FFP followed by antifibrinolytic agents hoping to induce thrombosis of the important feeding vessels. Interferon therapy and vincristine can help shrink the lesion permanently; however, they have their own side effects. Surgery often is mutilating and may land up into amputation.

## Congenital and Inherited Thrombocytopenia

This includes causes like chromosomal anomalies and rare inherited causes of low platelet count. The counts are low at or soon after the birth. In most, but not all, there are other features of the basic disease. The platelet count can be very low in some of them needing platelet transfusions and other treatment. The counts take a long to recover and may be low for months. Those with associated thrombasthenia bleed a lot at relative higher platelet counts. Some of them will have typical platelet morphology on smear examination.

## Chromosomal Anomalies

The incidence of thrombocytopenia in various aneuploidy cases varies from 86% in trisomy 18–31% in trisomy 13, 6% in trisomy 21 and 31% in Turner's syndrome. Usually the thrombocytopenia is not severe and many a times it is associated with neutropenia and polycythemia as seen in placental insufficiency. The mechanism of thrombocytopenia may also be similar to that seen in placental insufficiency.

## Inherited Thrombocytopenia

Inherited thrombocytopenias are a rare but interesting group of disorders which provided some insight into the molecular mechanisms for megakaryopoiesis. For some of these disorders, the molecular defects have been identified, like mutation of the c-mpl in congenital amegakaryocytic thrombocytopenia, defect in transduction pathway after binding of Tpo to c-mpl in TAR (thrombocytopenia with absent radius) syndrome, mutations in CBFA2 (core-binding factor subunit alpha-2) transcription factor gene *RUNX1* (*AML1*) in familial platelet syndrome with predisposition to acute myeloid leukemia (AML), mutation in GATA-1 transcription factor (xp 11) in X-linked thrombocytopenia with microcytosis, mutation in myosin heavy chain A gene (*MYH9*) in giant platelet syndromes including May-Hegglin anomaly and mutations in the WASP gene in Wiskott-Aldrich syndrome and X-linked thrombocytopenia. Most, but not all, have associated congenital anomalies to point to the possible diagnosis. Many of them have abnormal platelet morphology like giant platelet on peripheral smear examination. Some have associated platelet dysfunction leading to more bleeding than expected for the platelet count.

### *Inherited Thrombocytopenia with Giant Platelets*

This group includes the disorders like Bernard-Soulier syndrome; May-Hegglin syndrome and its variants like Sebastian syndrome, Fechtner syndrome, Epstein syndrome and Alport syndrome; Montreal platelet syndrome; Quebec syndrome and Gray platelet syndrome.

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*Bernard-Soulier Syndrome:* It is an autosomal recessive disorder. The platelet count is moderately low but the bleeding is quite significant. The platelets can be as large as 20 microns in diameter with cytoplasmic vacuoles. The defect is in the demarcation membrane system. This results in defect in gpIb-V-IX complex leading to poor adhesion. Diagnosis is made by absent response to ristocetin in platelet function study. A close differential with similar results is von Willebrand disease which can be differentiated by normal von Willebrand factor levels and pattern. Treatment includes platelet transfusions for significant bleeding. Stem cell transplant will be curative in this condition.

*May-Hegglin Anomaly:* This is an autosomal dominant condition characterized by thrombocytopenia, giant platelets, large inclusions in granulocytes and monocytes known as Dohle bodies and presence of physical defects like hearing loss, renal failure and cataract. The platelet count is moderately low in the range of 80–100,000/$mm^3$ but with significant bleeding due to associated platelet dysfunction. The defect is in the *MYH9* gene that codes for Myosin II-A, which is the only protein expressed in platelets and neutrophils, which explains the characteristic defects seen in platelets and neutrophils. Desmopressin (DDAVP), antifibrinolytic agents, helps to control bleeding. Platelet transfusions are rarely required.

*Gray platelet syndrome:* It is an autosomal recessive disorder with mild thrombocytopenia and significant bleeding. The platelets are unable to store alpha granule proteins. This leads to poor aggregation especially with thrombin, adenosine diphosphate and collagen. The platelets appear large, gray and bland with vacuolations. The treatment is platelet transfusion for significant bleeding.

### *Inherited Thrombocytopenia with Immunodeficiency*

This includes Wiskott-Aldrich syndrome and hemophagocytic lymphohistiocytosis.

*Wiskott-Aldrich syndrome:* This is an X-linked disorder characterized by thrombocytopenia, eczema and immunodeficiency. It is caused by mutations in the WASP gene located at Xp11-12 band. The Wiskott-Aldrich syndrome protein is known to be involved in the signal transduction and it regulates actin filament assembly in platelets as well as lymphocytes affecting their cytoskeleton. This explains the association of thrombocytopenia and immunodeficiency. Patients present with thrombocytopenia early in life with more bleeding than expected based on the platelet counts. The platelets are small in volume and the mean platelet volume is characteristically low (as is also seen in patients with TORCH group of infection). Patient usually has lower GI bleeding. Eczema and immunodeficiency develop as the child grows. Some patients have milder phenotype with minimal immunodeficiency as the defect is restricted only to the platelets even when they have the same WASP gene mutations (though restricted only to the exon 2 of the gene), these patients are grouped as X-linked thrombocytopenia. Often these patients are mistaken as ITP later in the life.

The treatment of Wiskott-Aldrich syndrome includes control of bleeding with platelet transfusions and treatment of infections. In those with difficulty, splenectomy will also help as also IVIg at times. Bone marrow transplantation is the only curative treatment possible at present. Around 10% of the patients can progress to develop lymphoma later in their life.

*Hemophagocytic lymphohistiocytosis:* This is a rare but interesting disease caused by mutations in the genes for perforin or granzymes involved in the killing of phagocytosed material by the phagosomes of the macrophage-monocyte series and natural killer cells. Absence of effective killing by the phagosomes leads to unnecessary stimulation of the macrophages and monocytes leading to production of cytokines by these cells leading to what is described as cytokine storm which leads to all the symptoms like hemophagocytosis, cytopenias, liver dysfunction, central nervous system (CNS) changes, fever, DIC, increased triglycerides levels, etc. It is an autosomal recessive disorder which can present even at or soon after the birth with fever, thrombocytopenia, convulsions, hyperbilirubenemia and cytopenias. The diagnosis is made by high index of suspicion and demonstrating hemophagocytes in the bone marrow or organs like liver, spleen or lymph nodes. Sometimes hemophagocytes are also seen on the peripheral blood smears. The treatment includes use of steroids and VP-16 to induce remission. Bone marrow transplant will cure those who do not respond to conservative management.

### *Inherited Thrombocytopenia with Bone Marrow Failure*

This includes three disorders, i.e. congenital amegakaryocytic thrombocytopenia, TAR syndrome and Fanconi's anemia.

*Congenital amegakaryocytic thrombocytopenia:* This is a rare autosomal recessive disorder presenting as neonatal thrombocytopenia which progresses over the time to total bone marrow failure. It presents with bleeding and thrombocytopenia in the first few days to weeks of life where it may be confused with many other common etiologies especially alloimmune thrombocytopenia. Around 20% of the patients can develop intracranial hemorrhage. 10–30% of them can have associated orthopedic or CNS anomalies. It is only when the patient dose not recover that a bone marrow is ordered which will pick up absent or grossly reduced megakaryocytes with normal granulopoietic and erythropoietic elements. It is caused by mutations in the c-mpl genes which results in marked maturation of the megakaryocytes and its precursors. As the action of Tpo via c-mpl is vital for maturation of other hemopoietic cells, even the other series will get affected with time including the stem cells due to lack of preservation of apoptosis induced by Tpo. This explains why there is total bone marrow failure with time. While platelet transfusions help controlling

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the bleeding, the only curative treatment is bone marrow transplant. 50% of them will progress to aplastic anemia over next 5 years. 5% of them can develop leukemia. IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) have limited role and Tpo has no role what-so-ever in the treatment of these patients.

*Fanconi's anemia and TAR:* Both are autosomal recessive disorders characterized by inherited bone marrow failure. Both have characteristic physical anomalies. Both are caused by known mutations. Mutations in *HOXA10, HOXA11* and *HOXD11* genes are implicated for TAR whereas more than three different types of Fanconi's anemia gene mutations are identified for Fanconi's anemia. TAR presents with thrombocytopenia, bleeding and characteristic forearm deformity due to absence of radius. Isolated absence of radii is seen in only 10% of the patients and 50% of the patients also have associated defects in ulna, knees or humorous, besides absent radii. The thumb on the affected side is always present in TAR, which differentiates it from Fanconi's anemia (which rarely can present in neonatal period) where such radial deformities are seen but the thumb is always absent from the affected side. Besides this, other anomalies seen in Fanconi's anemia seen include short stature, microcephaly, mental retardation, hyperpigmentation, hypogonadism, renal anomalies, other skeletal anomalies like rudimentary thumb, absent thumb, triphalangeal thumb, etc. Fanconi's anemia usually presents as anemia in later life though it can present in neonatal period in 10% of the cases. While TAR tends to improve after the age of 1 year, Fanconis' anemia usually progresses with time into complete bone failure and has high chances of developing malignancies. The only curative treatment is bone marrow transplant with proper conditioning regime avoiding radiation. Another syndrome of CTRUS (congenital thrombocytopenia with radio-ulnar synostosis) is described where the patient has absent pronation-supination due to fusion of radius and ulna. It behaves similar to TAR with improved platelet counts after the age of 1 year. Defect in HOX 11a is implicated in this condition.

### Miscellaneous Causes

There are some rare but important and distinct causes of neonatal thrombocytopenia like osteopetrosis which leads to thrombocytopenia and later bone marrow failure due to calcification of marrow spaces; congenital leukemia and metastatic neuroblastoma which cause thrombocytopenia due to bone marrow infiltration by the malignant cells and organic acidemias and other metabolic disorders which all can lead to bone marrow suppression.

## CONCLUSION

Neonatal thrombocytopenia is due to a complex etiology. Early onset neonatal thrombocytopenia is mainly due to perinatal events and late onset due to infections or rare chronic causes. Neonatal Alloimmune thrombocytopenia is quite common and needs prompt treatment to prevent intracranial bleeds. Look for syndromic baby which will suggest inherited causes of thrombocytopenia such as Fanconi's anemia or TAR. Systemic approach will help diagnose most of the cases. Platelet transfusions will help decrease morbidity and mortality.

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# Fetal & Neonatal
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