

Little Babies Born with Little Numbers

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Overview

- Consults
- Congenital Anemias
- Congenital Thrombocytopenias

Anemia in the newborn

- Polycythemic and macrocytic at birth
- D1 of life:
 - Mean hemoglobin (Hgb) 19.0 ± 2.2 g/dL
 - Mean hematocrit (Hct) $61 \pm 7.4\%$
 - Mean reticulocyte count (Retic) $3.2 \pm 1.4\%$

Gestation (weeks)	Hct (%)	Hgb (g/dL)	Retic (%)
37-40	53	16.8	3-7
32	47	15.0	3-10
28	45	14.5	5-10
26-30	41	13.4	—

- Red cell production ceases shortly after birth with the abrupt fall in erythropoietin level
 - Retic on D7 0.5%
 - Physiologic nadir of Hgb at 7-9wks, 10.7 ± 0.9 g/dL

Primary causes of newborn anemia

- Blood loss
- Increased destruction
- Decreased production

- ...but the etiologies differ...

➤ **Blood loss**

- Increased destruction
- Decreased production

Blood Loss

- Result of obstetrical accident
- Acute or chronic fetal-maternal hemorrhage
- Internal hemorrhage

Obstetrical Accidents

- Placenta previa or abruptio
- Umbilical cord rupture
 - Precipitous deliveries, short cord, entangled
- Umbilical cord abnormalities
 - Venous tortuosity, arterial aneurysms
- Velamentous insertion of the cord – inserts into chorion vs. placenta
- Inadvertantly incised during a c-section

Fetal to Maternal Hemorrhage

- ~ 50% of all pregnancies, fetal cells can be demonstrated in the maternal circulation
- More common following traumatic diagnostic amniocentesis or external cephalic version prior to delivery

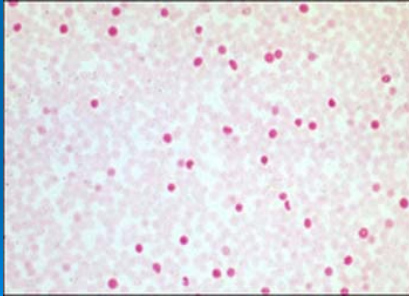
Clinical Presentation

- **Chronic:**
 - pallor disproportionate to distress, CHF, hepatomegaly
 - Low Hgb, microcytic, hypochromic, low iron
 - Clinical course usually uneventful
 - Fe therapy
- **Acute:**
 - Circulatory shock, distress
 - Normal hgb initially, quickly drops in first 24h
 - Normochromic, macrocytic, normal iron
 - IVF, pRBC, Fe therapy later

➤ **Diagnosis:**

- Blood smear
- Coombs' test is negative
- Not jaundiced
- Kleihauer-Betke technique – relies on resistance by fetal hgb to elution from the intact cell in an acid medium

Kleihauer-Betke technique:



Twin-to-twin Transfusion Syndrome

- 6-33% of pregnancies with a monochorial placenta (70% of monozygotic twin pregnancies)
 - each fetus uses its own portion of the placenta, but the connecting blood vessels allow blood to pass from one twin to the other
 - donor is anemic, recipient is polycythemic
- ≥ 5 g/dL difference in hemoglobin between twins
 - Max 3.3 g/dL in cord blood hgb in dizygotic twins

Internal Hemorrhage

- Anemia that appears in first 24-72h of age and not associated with jaundice
- Scalp bleeds
 - Cephalohematomas
 - Subaponeurotic/subgaleal hemorrhage
 - More common after difficult deliveries or vacuum extractions, vit K deficiency
 - Traumatic deliveries → subdural/subarachnoid hemorrhages

- Intraventricular Hemorrhage
 - May occur in half of all infants with BW < 1500g
 - Many without neurologic symptoms
- Breech deliveries – hemorrhage into adrenals, kidneys, spleen, retroperitoneal area

- Blood loss
- **Increased destruction**
- Decreased production

Increased Destruction

- Hemolytic anemia: pathologic process resulting in a shortening of the normal RBC life span of 120 days
 - Term: 60-80 days
 - Preterm: 20-30 days

- Usually a combination of clinical and laboratory findings:
- 1. Persistent increase in retic count with/without abnormally low hgb in the absence of current of previous hemorrhage
- 2. Rapidly declining hgb without an increase in the retic count in the absence of hemorrhage
- 3. Frequently jaundiced

Hemolytic Anemia of the Newborn

- **Intrinsic causes:**
 - RBC Enzyme defects
 - RBC membrane defects
 - Hemoglobinopathies
- **Extrinsic causes:**
 - Immune hemolysis
 - Rh incompatibility
 - ABO incompatibility
 - Minor blood group incompatibility (e.g., Kell, Duffy)
 - Acquired hemolysis:
 - Infection

RBC Enzyme Deficiencies

- Glucose-6-phosphate dehydrogenase (G6PD) Deficiency
 - Majority of pts have no anemia and almost no hemolysis; they develop both only as a result of oxidative challenge by exogenous agents
- Pyruvate Kinase (PK) Deficiency
 - Most frequent glycolytic enzymopathy associated with anemia
 - Hyperbilirubinemia, mild to profound anemia

RBC Membrane Defects

- Hereditary spherocytosis, elliptocytosis, stomatocytosis, xerocytosis...
- All may manifest in the newborn period
- Diagnosis usually established at a later age
 - Except HS: morphologic abnormality, anemia, positive family history

Hereditary Spherocytosis

- Most common hemolytic anemia in people of Northern European descent, 1:5000
- 75% positive family history
- Commonly symptomatic in the newborn period
- Jaundice in the first 48h
 - 20% after the first week
- Severe anemia is rare
- Splenomegaly uncommon
- Symptomatic neonates is not correlated with a more severe form of HS

- **Diagnosis:**
 - Osmotic Fragility Test – Incubated is the most useful and reliable
 - Glycerol Lysis Test is not useful, but *acidified* version is more sensitive
 - Pink Test is a adaptation of the GLT and more accurate and reliable
 - Easy screening test due to small sample needed

Diagnostic confusion

- HS and ABO incompatibility
 - Severe anemia and jaundice
 - Direct antiglobulin test positive, OF test positive (microspherocytes may be present)
- Bacterial sepsis
 - Provoke spherocytosis, hemolysis, jaundice, increases OF

ABO Incompatibility

- Most common in an A infant and O mother
 - Maternal isohemagglutinin titres are usually higher for A than for B
 - A antigen expression on neonatal red cells is usually higher than that of B antigen
- DAT (direct antiglobulin test) or Coombs' test may be negative in such settings
 - A antigen density is low enough that the "cross-linking" for the test does not occur

- Blood loss
- Increased destruction
- **Decreased production**

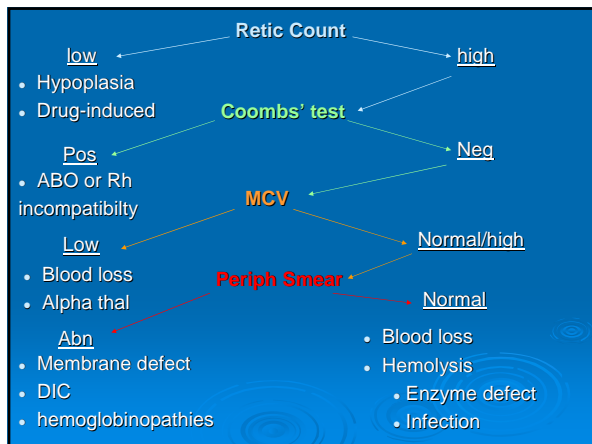
Diamond-Blackfan Anemia

- Isolated anemia with inappropriately low retic count
- Up to 25% are anemic at birth
 - Hgb can be <10
 - 5-10% are SGA
 - 25% have at least one congenital anomaly
 - Head, face, palate, limb, kidney
- Bone marrow is normocellular with remarkable paucity of erythroid precursors

- Can be differentiated from **Fanconi's Anemia** by normal chromosomal breakage study in DBA
 - Uncommon to present in neonatal period
 - Defect in DNA repair
- Treatment: corticosteroids

Let's narrow this down...

- History, physical, review of lab data, smear, family history, obstetric history, placenta...



Thrombocytopenia

- Healthy infants have the same platelet count as adults 150-450 x 10⁹/L
- Premature infants have a slightly lower platelet count, but still within normal range
- **Thrombocytopenia:** platelet count < 150,000

Neonatal thrombocytopenia

- Common abnormality in neonates admitted to a NICU
- ~22% of infants develop thrombocytopenia in tertiary-care NICU
 - >50% with platelets < 100,000
 - 20% < 50,000

Thrombocytopenia in the sick infant

- Thrombocytopenia present by **D2** in 76%
- Nadir by **D4** in 75%
- Recovers to > 150,000 by **D10** in 86%

Causes of thrombocytopenia

- Increased platelet destruction – **most common**
- Decreased platelet production
- Platelet pooling in an enlarged spleen
- Combination of these mechanisms

Platelet Destruction (Consumption)

- Immune vs. nonimmune
- **Immune** thrombocytopenia = increased rate of platelet clearance caused by platelet-associated IgG (PAIgG) or complement
- **Nonimmune** thrombocytopenia = most frequent cause is disseminated intravascular coagulation

Nonimmune events

- **Birth asphyxia** – consistently associated with evidence of DIC and thrombocytopenia in sick infants
 - Animal studies have linked hypoxia with thrombocytopenia
- **IUGR** – also associated with thrombocytopenia
 - May reflect accelerated platelet consumption associated with chronic hypoxia and placental dysfunction

- **Infections** – TORCH infections acquired either *in utero* or postnatally
 - Thrombocytopenia is frequently severe, <50,000
- **Bacterial sepsis** – multifactorial:
 - Consumption secondary to DIC
 - Endothelial damage by bacteria or bacterial products leading to platelet adhesion and aggregation
 - Bone marrow suppression
 - Immune-mediated thrombocytopenia

- **Congenital viral infection** – may present with many clinical problems (jaundice, purpura, hepatosplenomegaly, neurologic symptoms, intracranial calcifications, congenital heart disease)
 - Viral neuramidase induces loss of sialic acid from the platelet membrane, causes platelet destruction
 - Viral particles and degenerative morphologic changes have been demonstrated in the megakaryocytes of mice and in a patient with CMV infection

Kasabach-Merritt Syndrome

- **Hemangiomas** – can cause consumptive coagulopathy
 - Hypofibrinogenemia, elevated fibrinogen-fibrin degradation (FDP), microangiopathic hemolysis, thrombocytopenia
 - Can occur anywhere on the body surface or in the viscera
- **Severe thrombocytopenia (<50,000)**
 - 50% experience severe systemic bleeding
- **Thrombocytopenia and coagulopathy disappear as tumor regresses**
- **Treatment:** corticosteroids, tumor excision, local irradiation, tumor embolization

Premature Infants

- Infants who have suffered acute processes may have thrombocytopenia:
 - 1. Respiratory distress syndrome**
 - One study shows mechanical ventilation as an independent factor for thrombocytopenia
 - 2. Persistent pulmonary hypertension of the newborn**
 - Intrapulmonary platelet aggregation; autopsy shows pulmonary microthrombi

3. Necrotizing enterocolitis

- ~50% thrombocytopenic, ~20% DIC

4. Hyperbilirubinemia and phototherapy

- Mild thrombocytopenia; rabbit model showed that PT shortened measures of platelet survival time

5. Polycythemia

- Hcts >70% may be thrombocytopenic; usually born to preeclampsia mothers

Decreased Platelet Production

- Rare, <5% of neonatal thrombocytopenia
- Disorders of bone marrow production
 - Congenital leukemia, Congenital leukemoid reactions in Down's syndrome, Neuroblastoma, Histiocytosis, Viral infections (CMV), Osteopetrosis
- Bone marrow aplasia
 - TAR: thrombocytopenia with absence of radius syndrome
 - Amegakaryocytic thrombocytopenia



- Aplastic disorders are at greatest risk of serious bleeding
 - Splenectomy or steroids of no benefit for TAR syndrome
 - Platelet transfusions highly effective but should be reserved for symptomatic infants to reduce risk of alloimmunization
- Megakaryocytes usually appear in the bone marrow in several months
- TAR syndrome patients may also have platelet dysfunction

How to treat these patients

- < 30,000 - 50,000 places newborns at risk of serious bleeding
- > 50,000 in otherwise well full-term infants represents very little risk for bleeding
- 50,000 – 100,000 in sick premature infants may have an impact
 - 60% have prolonged bleeding time that shortens following a platelet transfusion with count increased to > 100,000

- Irradiated platelets help prevent graft-versus-host disease in the neonate recipient
- 10-15 mL/kg may be clinically effective

Immune Events

- Immune neonatal thrombocytopenia should always be suspected in otherwise healthy infants with isolated thrombocytopenia
- Caused by:
 - IgG antiplatelet autoantibody
 - Alloantibody, which is produced in mothers, crosses the placenta, and causes thrombocytopenia in neonates
- These events are usually short-lived, but can cause serious bleeding

Neonatal Alloimmune Thrombocytopenia

- Frequency: 1:1000 to 2000 newborns
- Maternal IgG alloantibodies are directed against specific paternally derived antigens on the infant's platelets
- Most frequent alloantigens:
 - HPA-1a (PLA-1) - >75%
 - HPA-5b - 15%
 - HPA-15b - 4%
- One or more immune response genes determine the formation of maternal alloantibodies

- Thrombocytopenia persists as long as the maternal IgG antibody remains in the infant's circulation
 - IgG $\frac{1}{2}$ life is ~ 21 days, but life span is dependent upon the life span of sensitized platelets

Clinical Presentation

- Severe (< 50,000), isolated thrombocytopenia in a healthy, full-term infant
- Minor bleeding is frequent
 - Petechiae, GI hemorrhage, hematuria, hemoptysis
- Intracranial hemorrhage in up to 15%
 - Prenatal or postnatal
- Severity of bleeding not only reflects low platelets, but also platelet dysfunction
 - Binding to glycoproteins IIb-IIIa

- Mothers will have normal platelet counts, no bleeding history
- May have previously delivered thrombocytopenic newborns
- High probability that previous newborns were affected

Diagnosis

- Parental tests to determine which antigens are present in the parents
- Maternal serum for alloantibodies – but these may not be detected in some cases

- **Rx: Neonatal Alloimmune Thrombocytopenia Test**
 - Send-out to Blood Center of Wisconsin
 - Includes: Platelet Antigen Genotyping - Panel of Mother and Father, Platelet Antibody Identification Panel of Mother
 - 30 ml ACD-A whole blood from mother and father and 10 ml serum from mother, refrigerated
 - Turnaround time is 10d

Treatment

- Platelet transfusion:
 - Preferred is washed and irradiated maternal platelets (compatibility, safety, availability)
 - Usually if it known ahead of time
 - Donor platelets
 - Intravenous IgG may be effective

Neonatal Autoimmune Thrombocytopenia

- Secondary to maternal autoimmune disorders
- Usually milder than alloimmune
- Most common is ITP
 - SLE
 - Lymphoproliferative disorders
 - Hyperthyroidism

- Platelet count nadir occurs several days subsequent to birth
- Cord platelet count is rarely < 50,000
- Intracranial hemorrhage rarely, if ever, occurs prenatally

- Pregnant mother should be treated according to her own platelet count
- No reliable predictors of severe thrombocytopenia in the infant
- Maternal count not predictive of infant's risk
- Delivery may be vaginal
 - Evidence lacking that c-section is safer

Diagnosis

- Clinical presentation of the mother and infant
- Do not have clinical or laboratory evidence of any other neonatal problems

Treatment

- IVIg after delivery is safe and effective
 - 80% response rate in infants
 - Unclear whether addition of steroids to IVIg is beneficial
- 1 g/kg on 2 consecutive days
- If bleeding, platelet transfusion
- If no response, methylprednisolone 3 mg/kg) + IVIg

Conclusion

- Differential diagnoses for neonatal anemias and thrombocytopenias are vast
- Common things are common
- Don't treat just numbers
- A good history is key