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 ± 7.4%
  - Mean reticulocyte count (Retic) 3.2 ± 1.4%

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Hct (%)</th>
<th>Hgb (g/dL)</th>
<th>Retic (%)</th>
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<tbody>
<tr>
<td>37-40</td>
<td>53</td>
<td>16.8</td>
<td>3-7</td>
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<td>32</td>
<td>47</td>
<td>15.0</td>
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<td>28</td>
<td>45</td>
<td>14.5</td>
<td>5-10</td>
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<td>26-30</td>
<td>41</td>
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- 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 ± 0.9g/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 cort, 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 polycytemic
- > 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

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

Blood loss
- Increased destruction
- Decreased production
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

**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 10^9/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

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- May reflect accelerated platelet consumption associated with chronic hypoxia and placental dysfunction

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 viscerum

- 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

Immune Events

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

**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

**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

**Thrombocytopenia persists as long as the maternal IgG antibody remains in the infant’s circulation**

- IgG ½ life is ~ 21 days, but life span is dependent upon the life span of sensitized platelets
**Treatment**

- **Platelet transfusion:**
  - Preferred is washed and irradiated maternal platelets (compatibility, safety, availability)
  - Usually if 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

**Diagnosis**

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

**Treatment**

- 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

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

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