Pediatric Hematology: Final Review

1. Hematopoiesis & Hemoglobin Development

Hematopoiesis locations shift continuously from conception to infancy. In infants, virtually all marrow cavities are active; as the child grows, it restricts to central bones (vertebrae, sternum, ribs, pelvis) and is replaced by fat.

> **MNEMONIC: TIMELINE OF HEMATOPOIESIS**
>
> **Y**oung **L**iver **S**ynthesizes **B**lood
>
> - **Y**olk Sac: Begins at 3 weeks gestation.
> - **L**iver: Primary site by 2 months gestation.
> - **S**pleen: Active during mid-gestation.
> - **B**one Marrow: Takes over by 5-6 months gestation.

Hemoglobin Chains and Genetics

- Hemoglobin is a tetramer of 4 globin chains + 4 heme rings.
- **Alpha-globin cluster:** Chromosome **16** (4 genes).
- **Beta-globin cluster:** Chromosome **11** (2 genes).

> **MNEMONIC: GLOBIN GENES**
>
> Alpha has 5 letters, but remember it's sweet **16** (Chromosome 16). Beta is on Chromosome **11**.

Hemoglobin Types by Stage

- **Embryonic:** Gower 1, Gower 2, Portland (Gone by 3 months gestation).
- **Fetal (HbF):** $\alpha_2\gamma_2$. Predominant by 6-8 weeks gestation (90% at 24 weeks). Has a higher affinity for oxygen. Declines rapidly postnatally, reaching adult levels (<2%) by 6-12 months.
- **Adult (HbA):** $\alpha_2\beta_2$. Reaches adult levels (96%) by 6-12 months of age.
- **HbA2:** $\alpha_2\delta_2$. Normal adult level is 2.0-3.4% by 12 months. Normal HbA:HbA2 ratio is 30:1.

> **MCQ PEARL: RBC LIFE SPAN & NADIR**
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> **RBC Life span:** Normal adult is 120 days. Neonatal/Fetal is much shorter: **60-90 days**.
> **Physiologic Nadir:** Due to rapid growth and shortened RBC survival, Hemoglobin hits its lowest point at **8-10 weeks of life** in term infants (earlier and more accentuated in premature infants).

2. Evaluating Anemia in Pediatrics

Definition: Reduction in RBC number or Hemoglobin > 2 Standard Deviations below the mean for age.

Diagnostic Clues in History & Physical Exam

Clue	Possible Diagnosis
Cow's milk introduced < 1 yr, or >24 oz/day	Iron Deficiency Anemia (IDA)
Goat's milk exclusive feeding, strict vegan	Folate deficiency (Goat), Vitamin B12 deficiency (Vegan)
Neonatal Jaundice / Gallstones in family	Hereditary Spherocytosis, G6PD, PK deficiency
Triphalangeal thumbs	Diamond-Blackfan Anemia (DBA)
Hypoplastic thenar eminence / Absent radius	Fanconi Anemia
Frontal bossing / Maxillary hyperplasia	Thalassemia Major, Severe Chronic Hemolytic Anemias

3. Microcytic Anemias (MCV < 80)

Classified primarily using Iron Studies and the Mentzer Index.

> **MNEMONIC: CAUSES OF MICROCYTIC ANEMIA**
>
> **TAILS**
>
> - **T**halassemia
> - **A**nemia of Chronic Disease
> - **I**ron Deficiency Anemia (IDA)
> - **L**ead Poisoning
> - **S**ideroblastic Anemia

Iron Deficiency Anemia (IDA)

- Most common blood disease in infancy.
- Peaks at **9-24 months** (due to cow's milk and depleted iron stores) and in **adolescent girls** (menses, rapid growth).
- **Labs:** Low Ferritin (earliest sign), High TIBC, High RDW, Low RBC count, Reactive Thrombocytosis.
- **Treatment:** Oral elemental iron (4-6 mg/kg/day) for 3-4 months. An increase of Hb by ≥1 g/dL after 1 month confirms the diagnosis.

Thalassemia Minor (α or β)

- Mild, asymptomatic hypochromic microcytic anemia.

- **Labs:** Normal/High RBC count, Normal RDW, Normal Iron studies.
- In β-Thalassemia minor, **HbA2 is elevated (>3.5%)**.

> **MCQ PEARL: MENTZER INDEX**
>
> Used to differentiate IDA from Thalassemia Minor.
> Formula: **MCV** / **RBC count**
>
> - **< 13: Thalassemia Trait** (Small cells, but marrow can make PLENTY of them → High RBC count → Low ratio).
> - **> 13: Iron Deficiency** (Small cells, and marrow lacks building blocks to make them → Low RBC count → High ratio).

α-Thalassemia Syndromes

- **Silent Carrier (1 gene deleted):** Normal CBC.
- **Trait (2 genes deleted):** Mild microcytic anemia.
- **HbH Disease (3 genes deleted):** Moderate/severe anemia at birth, hemolysis.
- **Hydrops Fetalis (4 genes deleted):** Hb Barts only. Intrauterine heart failure/death.

β-Thalassemia Syndromes

- **Major (Cooley Anemia):** Profound hemolysis at 6 months (as HbF drops). "Chipmunk facies" (extramedullary hematopoiesis), hepatosplenomegaly, target cells, 'hair-on-end' skull X-ray. Needs lifelong transfusions + iron chelation (deferoxamine) to prevent hemochromatosis.
- **Intermedia:** Moderate hemolysis, usually not transfusion-dependent.

Other Microcytic Causes

- **Lead Poisoning:** Look for *basophilic stippling* on blood smear. Exposure to old paint/ceramics.
- **Sideroblastic Anemia:** Ring sideroblasts in marrow (iron stuck in mitochondria). Can be inherited or acquired (Isoniazid, alcohol, lead).

4. Normocytic Anemias (MCV 80-100)

Classified based on Reticulocyte count (Normal = ~2%). High reticulocytes = Destruction/Blood loss. Low reticulocytes = Production failure.

Intrinsic RBC Defects (Hemolytic)

- **Hereditary Spherocytosis:** Autosomal dominant defect in spectrin. Spherocytes trapped in spleen. High MCHC, increased osmotic fragility, abnormal EMA binding test. High risk for Parvovirus B19 aplastic crisis and pigmentary gallstones. Tx: Splenectomy > 5 yrs, Folic acid.
- **Hereditary Elliptocytosis:** AD spectrin defect. Often asymptomatic.
- **G6PD Deficiency:** X-linked. Oxidative damage triggers acute hemolysis. Bite cells, Heinz bodies.
  Triggers: Fava beans, Sulfa drugs, Antimalarials, Naphthalene (mothballs), Henna, Infections.

- **Pyruvate Kinase (PK) Deficiency:** Autosomal recessive. ATP depletion. Polychromatic RBCs.

Sickle Cell Disease (SS)

- Glutamic acid replaced by Valine at position 6 of the β-globin chain. Polymerizes under low O2/acidosis.
- Hb profile in SS: **HbS 85-95%, HbF 5-15%, HbA 0%**.
- **Crises:**
    - *Dactylitis:* Hand-foot swelling in infancy (often first sign).
    - *Vaso-occlusive:* Painful microvascular infarcts (bone, lung, brain).
    - *Aplastic:* Parvovirus B19 induced reticulocytopenia.
    - *Sequestration:* Massive splenomegaly, shock (medical emergency).
- **Complications:** Functional asplenia (high risk for encapsulated bacteria like *S. pneumo*, Salmonella osteomyelitis), Acute Chest Syndrome, Stroke, Priapism, Avascular necrosis of femoral head.
- **Management:** Daily prophylactic Penicillin until age 5, Pneumococcal/Meningococcal vaccines, Hydroxyurea (increases HbF), transfusions for stroke/acute chest.

> **MCQ PEARL: FEVER IN SICKLE CELL**
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> Fever in any SS patient requires URGENT assessment, blood cultures, and prompt parenteral antibiotics because of functional asplenia and high risk for rapid pneumococcal sepsis.

Extrinsic Hemolytic Processes

- **Autoimmune Hemolytic Anemia (AIHA):** Positive Direct Coombs test.
    - *Warm (IgG):* Often secondary to lymphoma, SLE, or immunodeficiency. Spherocytes present.
    - *Cold (IgM):* Associated with Mycoplasma pneumoniae and EBV.
- **Alloimmune:** Rh incompatibility (causes hydrops, strong Coombs+) or ABO incompatibility (mild, weak Coombs+, can happen in 1st pregnancy).
- **MAHA (Microangiopathic):** Mechanical damage yielding *Schistocytes (Burr cells)*. Seen in HUS, TTP, DIC, severe HTN, Kasabach-Merritt.

5. Macrocytic Anemias (MCV > 100) & RBC Aplasias

Megaloblastic Anemias

- Show hypersegmented neutrophils and pancytopenia.
- **Folate Deficiency:** Goats milk diet, celiac, phenytoin. No neuro symptoms.
- **Vitamin B12 Deficiency:** Vegan diet, pernicious anemia, Crohn's, short gut. **Neurologic symptoms** (ataxia, hyporeflexia, Babinski). Tx: IM B12.

Red Cell Aplasias (Normal or High MCV, Low Reticulocytes)

Failure of the marrow to produce ONLY Red Blood Cells.

Diamond-Blackfan Anemia (DBA)	Transient Erythroblastopenia of Childhood (TEC)
Congenital, presents < 1 year of age (often 2-6 mo).	Acquired (post-viral), presents at 6 mo - 3 years.
Macrocytic anemia.	Normocytic anemia.
Elevated HbF and eADA activity.	Normal HbF and eADA.
Associated anomalies: Triphalangeal thumbs, craniofacial, short stature.	No physical anomalies. Previously healthy child.
Cancer predisposition. Requires Steroids / Transfusions.	Resolves spontaneously in 1-2 months. No steroids needed.

6. Pancytopenia & Bone Marrow Failure

Low RBCs, Low WBCs, Low Platelets. Implies general marrow pathology.

Fanconi Anemia (Congenital Aplastic Anemia)

- Autosomal recessive DNA repair defect. Mean onset of failure is 7 years.
- **Physical signs:** Short stature, absent/hypoplastic thumbs and radius, horseshoe kidney, cafe-au-lait spots, microcephaly.
- **Labs:** Macrocytosis, high HbF, marrow hypocellularity (<30%).
- **Diagnosis:** Chromosome breakage test (DEB or Mitomycin C).
- High risk for AML, squamous cell carcinoma, Wilms tumor.

Acquired Aplastic Anemia

- Drugs (chloramphenicol, sulfa, anticonvulsants), Toxins, Viruses (HIV, EBV, CMV, Hepatitis). Often idiopathic.
- Marrow hypocellularity. Presents with bruising, petechiae, serious infections.

> **MCQ PEARL: DISTINGUISHING DESTRUCTION VS PRODUCTION**
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> **Anemia:** Use Reticulocyte count. Low = Marrow failure. High = Peripheral destruction/loss.
> **Thrombocytopenia:** Use Mean Platelet Volume (MPV). Low MPV = Marrow failure. High MPV = Peripheral destruction (e.g., ITP, large active platelets).

7. High-Yield Peripheral Smear Findings

- **Target Cells:** Thalassemia, Hemoglobin C, Asplenia, Liver disease.
- **Spherocytes:** Hereditary Spherocytosis, Autoimmune Hemolytic Anemia (AIHA).
- **Schistocytes:** Microangiopathic Hemolytic Anemia (HUS, TTP, DIC).

- **Bite Cells** / **Heinz Bodies:** G6PD Deficiency.
- **Basophilic Stippling:** Lead Poisoning.
- **Howell-Jolly Bodies:** Functional asplenia (Sickle Cell Disease) or post-splenectomy.
- **Hypersegmented Neutrophils:** Megaloblastic anemia (B12 or Folate deficiency).