Pediatric Anemias

Oncology Fall Nursing Conference
John Stoddard Cancer Center
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Cancer and Blood Disorders Center
Objectives

• Define anemia and red blood cell (RBC) indices in pediatric patients
• Learn to categorize anemias based on RBC size and mechanism
• Understand the presentation, workup, and treatment of pediatric anemias
• Will not discuss anemia secondary to blood loss or anemia secondary to malignancy in great detail
What is anemia?

• **Physiologic Definition:**
  – Hemoglobin (Hgb) level too low to meet cellular oxygen demands

• **Statistical Definition:**
  – Hgb level <2 SD below mean for age, gender, race, and developmental stage

3 yo with cyanotic heart disease and Hgb 13 g/dL is **ANEMIC**

A 6 week-old thriving premie with Hgb 7.7 g/dL is **NOT ANEMIC**
Many factors affect baseline Hgb levels

- Age
- Gender
- Race
- Sexual Maturation
- Altitude
- Heredity
Method of blood draw affects Hgb levels in newborns

Age: Physiologic Anemia of Infancy

Physiologic nadir at ~2 mos (earlier and lower in premies)

Adapted from Saarinen, Siines, J Pediatr, 1978
Hgb and MCV increase after age 1

Dallman, J Pediatr, 1979; Nathan & Oski, 7th Ed.
African-Americans have lower Hgb

<table>
<thead>
<tr>
<th>Age 5-9</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>± 2 SD</td>
</tr>
<tr>
<td>White</td>
<td>13</td>
<td>11.6-14.3</td>
</tr>
<tr>
<td>Black</td>
<td><strong>12.6</strong></td>
<td>11.1-14.1</td>
</tr>
<tr>
<td>Age 10-14</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>White</td>
<td>13.7</td>
<td>12.3-15.5</td>
</tr>
<tr>
<td>Black</td>
<td><strong>13.1</strong></td>
<td>11.5-15.2</td>
</tr>
</tbody>
</table>

P<0.001

Dallman, Am J Clin Nutr, 1978
Tanner Stage Affects Hgb in Boys

Boys

Girls

Daniel, Pediatrics, 1973
Altitude raises hemoglobin

Merino, Blood, 1950
Hgb has a hereditary component
Rule of Thumb

• To determine lower limit of normal* for hemoglobin concentration
  – “The Eleven Plus Point One Rule”
  – 11 + 0.1 x (age in years) = lower limit of normal* for hemoglobin concentration

• To determine lower limit of normal* for MCV
  – “The Seventy Plus One Rule”
  – 70 + 1 x (age in years)

• Examples
  – 2 year old male with Hgb 11.3 gm/dl & MCV 73 fl = normal
  – 7 year old female with Hgb 11.3 gm/dl & MCV 73 fl = abnormal
    (anemic and microcytic)

* 2 S.D. below mean

Courtesy of George Buchanan, UT Southwestern
Diagnosis of anemia

- Most anemias can be diagnosed with history, physical exam, and minimal laboratory testing
- **History**: fatigue, pallor, jaundice, poor diet/feeding, blood loss, routine screening
- **PE**: pallor, jaundice, tachycardia, heart murmur, other findings with specific anemias (i.e. splenomegaly, congenital anomalies)
- **Labs**:
  - CBC, retic, peripheral blood smear
    - Norms specified by individual labs may be inaccurate
    - Sampling (cap vs. venous)
  - Ancillary studies as indicated
Anemia classification by RBC size

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Iron deficiency</td>
<td>• Anemia of inflammation</td>
<td>• DBA</td>
</tr>
<tr>
<td>• Thalassemia</td>
<td>• Acute blood loss</td>
<td>• Fanconi Anemia</td>
</tr>
<tr>
<td>• Anemia of inflammation</td>
<td>• Transient erythroblastopenia of childhood (TEC)</td>
<td>• Aplastic anemia and other bone marrow failure syndromes</td>
</tr>
<tr>
<td>• Lead poisoning</td>
<td>• Diamond-Blackfan anemia (DBA)</td>
<td>• Trisomy 21</td>
</tr>
<tr>
<td>• Other unstable hemoglobinopathy</td>
<td>• Autoimmune hemolytic anemia (AIHA)</td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Sickle cell anemia</td>
<td>• B12/Folate Deficiency</td>
</tr>
<tr>
<td></td>
<td>• Hereditary Spherocytosis (HS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• G6PD deficiency &amp; Enzymopathies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Statistical</td>
<td></td>
</tr>
</tbody>
</table>
Classification of anemia by mechanism

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Increased Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Iron deficiency</td>
<td>• AIHA</td>
</tr>
<tr>
<td>• Thalassemia</td>
<td>• Thalassemia</td>
</tr>
<tr>
<td>• Anemia of inflammation</td>
<td>• Sickle cell anemia</td>
</tr>
<tr>
<td>• Lead poisoning</td>
<td>• Hereditary Spherocytosis</td>
</tr>
<tr>
<td>• TEC</td>
<td>• Acute blood loss</td>
</tr>
<tr>
<td>• DBA</td>
<td>• G6PD, other enzymopathies</td>
</tr>
<tr>
<td>• B12/Folate deficiency</td>
<td></td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>• Bone Marrow Failure Sx</td>
<td></td>
</tr>
</tbody>
</table>
Case 1

An 18 mo old boy presents for a WCC. He has pallor and fatigue. He has also been eating paper. He is hemodynamically stable. PCP checks venous CBC.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>4.6 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>55</td>
</tr>
<tr>
<td>Retic</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

*Further history reveals he drinks 64 ounces of cow’s milk per day

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Plt</td>
<td>520 (H)</td>
</tr>
<tr>
<td>TIBC</td>
<td>510 (H)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>3 (H)</td>
</tr>
</tbody>
</table>
Case 1 – Peripheral Blood Smear

Normal Smear

Case 1

Microcytic, hypochromic, polychromasia, anisopoikilocytosis
Case 1 - Iron Deficiency

• Most common nutritional deficiency in the world
  – 1 billion people and half the world’s children
• United States
  – 12-36 mo olds (1-4% prevalence of IDA)
    • Excessive cow’s milk intake
  – Teenage girls
    • Menorrhagia

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Why is iron important?

65% of TBI is in HEMOGLOBIN

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Cow’s Milk is for Baby Cows
Causes of IDA in children

• Nutritional
  – **Excessive Cow’s Milk Intake**
    • Chronic low grade hemorrhagic enteropathy
    • Low iron content
    • Poor bioavailability of iron (50% in BM, 5-10% cow’s milk)
    • Prevention of eating iron-rich foods
  – Lead Poisoning
  – Vegan/Poor Meat Intake

• Blood Loss
  – Menorrhagia
  – GI (celiac, IBD)
  – Parasite/Worm (#1 cause of GI blood loss worldwide)
Iron Deficiency Anemia

**Presentation**
- Pallor
- Fatigue
- Pica
- Irritability
- Breath-holding spells
- Nutritional history
- Blood loss
- Developmental delay

**Labs**
- Anemia with low retic
- Microcytic, hypochromic
- ↑RDW
- ↓RBC
- ↑ or ↓ plts
- ↑ TIBC, ↓ ferritin (Iron studies NOT REQUIRED)
IDA

Treatment

• **Decrease milk intake:** 16-24 oz/day
• Promote iron rich foods
• Control/evaluate for blood loss
• If HD stable, no transfusions necessary
• Ferrous Sulfate 4-6 mg/kg elemental Fe per day (divided once or BID)
  – **MVI with iron is inadequate**
  – Take with juice, meat to enhance absorption (NOT MILK!)
  – Constipation, metallic taste, teeth staining
• IV iron if malabsorption suspected
  – Anaphylaxis, hypotension

Iron content of foods

<table>
<thead>
<tr>
<th>FOOD</th>
<th>IRON (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef liver, braised (3 oz)</td>
<td>5.8</td>
</tr>
<tr>
<td>Lean sirloin, broiled (3 oz)</td>
<td>2.9</td>
</tr>
<tr>
<td>Lean ground beef, broiled (3 oz)</td>
<td>1.8</td>
</tr>
<tr>
<td>Skinless chicken breast, roasted dark meat (3 oz)</td>
<td>1.1</td>
</tr>
<tr>
<td>Skinless chicken breast, roasted white meat (3 oz)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pork, lean, roasted (3 oz)</td>
<td>0.9</td>
</tr>
<tr>
<td>Salmon, canned with bone (3 oz)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
IDA - Prognosis

Prognosis

- Retic should ↑ in 4-6 days
- Hgb should ↑ ~1 g/dL/week
- Once CBC normalized, treat 3 more months to replete hepatic stores
- **Long-term neurocognitive deficits**

Refractory to iron therapy?

- Non-compliance
- Non-compliance
- Non-compliance – check bottle in clinic
- Underlying cause ongoing (menorrhagia, cow’s milk)
- Malabsorption (celiac, IBD, genetic mutations)
- Wrong dx (thalassemia, etc.)
Case 2

An 18 mo old boy of Laotian descent presents for a WCC. He has pallor and fatigue. He has splenomegaly and slight jaundice on exam. He has good nutrition. PCP checks venous CBC.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>7.9 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>63</td>
</tr>
<tr>
<td>Retic</td>
<td>4%</td>
</tr>
</tbody>
</table>

Numerous target cells on smear

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt</td>
<td>124 (L)</td>
</tr>
<tr>
<td>RBC</td>
<td>5.4 (H)</td>
</tr>
</tbody>
</table>
Case 2 – Normal globin synthesis varies with age
Case 2 – Normal globin synthesis
Case 2 - Thalassemia

Decreased production of $\alpha$ or $\beta$ globins

Imbalance between $\alpha$ or $\beta$ globins

Globins in excess precipitate and damage RBC membrane

Anemia
Bone Marrow Expansion
Extramedullary Hematopoiesis
Increased intestinal iron absorption
Case 2 - Thalassemia

• **β-thalassemia mutations**
  - >1% in Mediterranean basin, northern Africa, SE Asia, India, Indonesia
  - >20% in some villages in Greece
  - Rare in No. Europe, Korea, Japan, and No. China

• **α-Thalassemia**
  - Most common single gene disorder in the world?
  - Frequency: 5-10% in Mediterranean basin
  - 20-30% in West Africa
  - 68% in SW Pacific
  - <1% in Britain, Iceland, and Japan
Case 2 – Normal globin synthesis

Fetus/Newborn:
- γ
- Hgb F

Child/Adult:
- α
- β
- Hgb A

α = β
Case 2 – α-thalassemia

Fetus/Newborn

γ

α

γ

α

γ

α

γ

α

β

γ

Hgb F

Hgb Bart’s

Child/Adult

α < β

γ

γ

γ

γ

γ

γ

α

α

γ

α

β

γ

α

β

γ

α

β

Hgb A

Hgb H
**α-thalassemia**

- Mutations affecting α-globin gene
  - Differ from β-thalassemia
  - Tend to be whole gene deletions

α-globin cluster:

<table>
<thead>
<tr>
<th>chromosome 16</th>
</tr>
</thead>
</table>
## α-thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>α genes</th>
<th>Name</th>
<th>Phenotype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>αα/αα</td>
<td>4</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>αα/α-</td>
<td>3</td>
<td>Silent carrier</td>
<td>Normal, maybe slight microcytosis</td>
<td>None</td>
</tr>
<tr>
<td>αα/--</td>
<td>2</td>
<td>Thal. Trait</td>
<td>Borderline microcytic anemia, possible Bart’s on NB screen, <em>Asian</em></td>
<td>None</td>
</tr>
<tr>
<td>α-/α-</td>
<td></td>
<td>Thal. Trait</td>
<td><em>African</em></td>
<td>None</td>
</tr>
<tr>
<td>--/α-</td>
<td></td>
<td>Hgb H disease</td>
<td>Moderate microcytic anemia, Hgb Barts on NBS, Hgb 7-10, MCV-50’s, chronic hemolysis (jaundice and HSM)</td>
<td>Avoid oxidant stress, tx infections, transfuse prn, ?splenectomy</td>
</tr>
<tr>
<td>--/αcsα</td>
<td>1</td>
<td>Hgb H-Constant Spring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td>Embryonic lethal</td>
<td>Severe microcytic, hemolytic anemia, Hydrops fetalis</td>
<td>In utero transfusion then BMT</td>
</tr>
</tbody>
</table>

---

**Minor**

**Intermedia**

**Major**
β-thalassemia

Fetus/Newborn

Child/Adult

Hgb F

Unstable

Hgb A
β-thalassemia

Phenotypic variability

- Mutations affecting both the β-globin gene and its regulators/promoters
- Cause anywhere from 0% production to 99.9% of normal production
  - $\beta^0 = 0\%$ production
  - $\beta^+ = 1\text{-}99\%$ production

Common β-globin mutations

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
β-thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>β/β</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β/β&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Mild microcytic anemia</td>
<td>None</td>
</tr>
<tr>
<td>β/β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Hgb: 10-12, MCV – 60-70, RDW &lt;18, ↑Hgb A2</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β&lt;sup&gt;+&lt;/sup&gt;/β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>moderate hemolytic microcytic anemia, Hgb 6-10, picked up at 6mo-2yrs with pallor, poor growth, and HSM</td>
<td>Possible transfusion, possible splenectomy</td>
</tr>
<tr>
<td>β&lt;sup&gt;+&lt;/sup&gt;/β&lt;sup&gt;0&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β&lt;sup&gt;0&lt;/sup&gt;/β&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Severe microcytic, hemolytic anemia, marked HSM, bony expansion, growth failure</td>
<td>Lifelong transfusions, splenectomy, BMT</td>
</tr>
</tbody>
</table>
Thalassemia – Clinical Picture

• **Presentation**
  – Family History
  – NB screen
    • Bart’s (2 or 3 gene α deletion)
    • Hgb F only (β thal major)
  – Microcytic anemia, target cells, ↑ RBC
  – Elevated Hgb A₂ on electropheresis
    • β thal trait
  – Extramedullary hematopoiesis

Cunningham, Hem Onc Clin NA, 2010
Thalassemia – Treatment and Prognosis

• **Treatment**
  – Varies as above
  – Genetic counseling

• **Prognosis**
  – Excellent in mild-intermediate
  – Worse in major disease (iron overload, organ damage)

**Survival: Thalassemia Major**

Cunningham, Hem Onc Clin NA, 2010
Case 3

A 20 mo old girl presents with pallor and fatigue. She may have had a viral illness a few weeks ago. No skeletal anomalies. PCP checks venous CBC.

Peripheral blood smear is unremarkable.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>5.6 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>78</td>
</tr>
<tr>
<td>Retic</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>920</td>
</tr>
</tbody>
</table>
Case 3 – Transient Erythroblastopenia of Childhood (TEC)

• Transient red cell aplasia
• Incidence 5 per million children
• **Presentation:**
  – Antecedent viral illness, otherwise healthy child
  – Anemia can be profound
  – ↓Retic (unless recovering)
  – Neutropenia common
• **Treatment:** observation, transfusion required in about 60%
• **Prognosis:** Resolves in 1-2 months
An 11 mo old girl presents to her PCP with pallor and fatigue. She may have had a viral illness a few weeks ago. She has unusual looking thumbs and is small for her age. PCP checks venous CBC and hand x-ray.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>5.6 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>96</td>
</tr>
<tr>
<td>Retic</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
Diamond-Blackfan Anemia (DBA)

- Inherited bone marrow failure syndrome
- Pure red cell aplasia
- **Presentation:**
  - Age < 1 year
  - Physical anomalies in ~25-50%
- **Labs:**
  - Macrocytic anemia
    (sometimes normocytic)
  - ↓ retic

**Frequency of Physical Anomalies in DBA**

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>25-50%</td>
</tr>
<tr>
<td>Short stature</td>
<td>13%</td>
</tr>
<tr>
<td>Thumbs</td>
<td>8%</td>
</tr>
<tr>
<td>LBW</td>
<td>5%</td>
</tr>
<tr>
<td>Eyes</td>
<td>5%</td>
</tr>
<tr>
<td>Cleft lip/palate</td>
<td>4%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3%</td>
</tr>
<tr>
<td>GU</td>
<td>3%</td>
</tr>
<tr>
<td>Abn. facies</td>
<td>3%</td>
</tr>
<tr>
<td>Gonadal</td>
<td>3%</td>
</tr>
<tr>
<td>Neck</td>
<td>2%</td>
</tr>
<tr>
<td>Head</td>
<td>2%</td>
</tr>
<tr>
<td>Dev. Delay</td>
<td>2%</td>
</tr>
<tr>
<td>Ears, CNS</td>
<td>1%</td>
</tr>
</tbody>
</table>

Shimamura and Alter, Blood Rev, 2010
DBA – Caused by defective ribosomal biogenesis

Shimamura and Alter, Blood Rev, 2010
## DBA vs. TEC

<table>
<thead>
<tr>
<th></th>
<th><strong>DBA</strong></th>
<th><strong>TEC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>Inherited</td>
<td>Acquired</td>
</tr>
<tr>
<td><strong>Physical anomalies</strong></td>
<td>25-50%</td>
<td>None</td>
</tr>
<tr>
<td><strong>Age at dx (mos, mean)</strong></td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td><strong>Antecedent virus</strong></td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td><strong>Hgb (g/dL)</strong></td>
<td>1.2-10</td>
<td>2.4-10.6</td>
</tr>
<tr>
<td><strong>ANC &lt; 1000</strong></td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Plt &gt; 400</strong></td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>↑ Adenosine Deaminase</strong></td>
<td>90%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>↑ MCV (at dx)</strong></td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>↑ MCV (in remission)</strong></td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>↑ Hgb F (dx)</strong></td>
<td>100%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>↑ Hgb F (recovery)</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>↑ Hgb F (remission)</strong></td>
<td>85%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
DBA – Treatment and Prognosis

• **Treatment**
  – Glucocorticoids
    • 80% respond
  – Transfusional support: iron overload
  – Bone Marrow transplant

• **Prognosis**
  – 20% achieve remission by age 25
  – Mean life expectancy 11.4 y (range 0-54y)

• **Surveillance for Malignancy**
  – AML/MDS
  – Osteosarcoma
  – Soft tissue Sarcoma
  – Breast Cancer
  – Hodgkin’s
  – Liver/GI
  – Melanoma
  – NHL

Shimamura and Alter, Blood Rev, 2010
Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Case 5

A 14 yo girl presents with fatigue, joint pains, and rash. Other family members have similar problems. PCP checks venous CBC. Peripheral smear shows slight microcytosis and thrombocytosis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>9.9 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>81</td>
</tr>
<tr>
<td>Retic</td>
<td>1.3%</td>
</tr>
<tr>
<td>Plt</td>
<td>512 (H)</td>
</tr>
<tr>
<td>ESR</td>
<td>53 (H)</td>
</tr>
<tr>
<td>UA</td>
<td>+hematuria</td>
</tr>
<tr>
<td>ANA</td>
<td>Highly pos</td>
</tr>
</tbody>
</table>
Case 5 – Anemia of inflammation

• Hypoproliferative anemia due to systemic illness/inflammation

• Decreased EPO production and responsiveness, defective iron utilization

• **Presentation:**
  – Infection, autoimmune dz, cancer
  – Normochromic, normo to microcytic anemia
  – Low retic, elevated markers of inflammation (ESR, CRP, plts)

• **Treatment:** treat underlying condition
Case 6

A 4 yo boy recently immigrated from the Sudan and sees you for fever, fatigue, jaundice. He is tachycardic, spleen tip is palpable and he looks ill. PCP checks venous CBC.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>5.5 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>81</td>
</tr>
<tr>
<td>Retic</td>
<td>19%</td>
</tr>
</tbody>
</table>

Herrick, 1910
Case 6 – Sickle Cell Anemia

- **Presentation:** NB screen, but be aware of African descent and not born in USA
- **Diagnosis:** Hgb electrophoresis

<table>
<thead>
<tr>
<th></th>
<th>DNA</th>
<th>RNA</th>
<th>AA</th>
<th>Hgb</th>
<th>RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CCT</td>
<td>GAG</td>
<td>GAG</td>
<td>GAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GGA</td>
<td>CTC</td>
<td>CTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missense Mutation</td>
<td>CCT</td>
<td>GTG</td>
<td>GAG</td>
<td>GAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GGA</td>
<td>CAC</td>
<td>CTC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AA: Alanine; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; Hgb: Hemoglobin; RBC: Red blood cell.

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Complications of Sickle Cell Disease

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Treatment of SCD Complications

• General principles:
  – **Supportive measures**: opioids, NSAIDS, IVF, warm compresses, avoidance of temperature extremes, good hydration
  – **Hydroxyurea**: ↑Hgb F, ↑H₂O in RBC, ↓WBC, ↓RBC adhesion
  – **Transfusions**: simple or exchange
  – **Bone Marrow Transplant**: definitive therapy
<table>
<thead>
<tr>
<th>Complication</th>
<th>Notes</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Crisis (VOC)</td>
<td></td>
<td>Hydroxyurea</td>
<td>Hydration, opioids, NSAIDS</td>
</tr>
<tr>
<td>Acute Chest Syndrome</td>
<td>Sickling/infectious process in the lungs</td>
<td>Hydroxyurea</td>
<td>Antibiotics, O2, avoid overhydration, transfusions</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>Young children, except in SC dz</td>
<td></td>
<td>Monitoring, cautious transfusion</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Encapsulated organisms due to functional asplenia</td>
<td>PCN prophylaxis up to age 5, immunizations, fever precautions</td>
<td>Empiric antibiotics</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>Transcranial Doppler</td>
<td>Chronic transfusion, ?hydroxyurea</td>
</tr>
<tr>
<td>Aplastic Crisis</td>
<td>Parvovirus B19</td>
<td></td>
<td>Monitoring, transfusion</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Swelling of hands/feet in infants</td>
<td></td>
<td>Hydration, pain control</td>
</tr>
<tr>
<td>Priapism</td>
<td></td>
<td></td>
<td>Hydration, warm bath, pain control, sudafed, urologist</td>
</tr>
</tbody>
</table>

Other: Retinopathy, Nephropathy, Pulmonary Artery HTN, Avascular necrosis, Cognitive
Case 7

A 7 day old girl is seen by the PCP for a WCC. She has prolonged jaundice and is tiring with feeds. Several family members are intermittently jaundiced and some have had their spleens and gallbladders removed. PCP checks venous CBC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>6 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>81</td>
</tr>
<tr>
<td>Retic</td>
<td>18%</td>
</tr>
<tr>
<td>MCHC</td>
<td>36 (H)</td>
</tr>
<tr>
<td>TBili</td>
<td>16</td>
</tr>
</tbody>
</table>
Case 7 – Hereditary Spherocytosis

- Spectrin, ankyrin, or protein 4.2 deficiency
  - Reduced surface-to-volume ratio
  - Reduced cellular deformability
  - Release of microvesicles
  - Band-3 deficiency
  - Release of microvesicles

- Lipid bilayer
  - Spectrin
  - Ankyrin
  - Band 3

- Low pH
- High macrophage contact
- Low glucose concentration
- High oxidants concentration
- Erythrostasis
- Splenic trapping
- Tail of osmotic fragility curve
- Haemolysis
- Further loss of membrane
Case 7 – HS

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
**HS**

- **Epidemiology:**
  - More common pts of Northern European descent
  - Incidence: 1 per 5000
  - Family history in 75% (autosomal dominant)

- **Presentation:** jaundice, splenomegaly

- **Complications:**
  - Hemolytic/Aplastic crisis during illness
  - Cholelithiasis

- **Diagnosis:** FHx, jaundice, ↑retic, ↑MCHC, ↑ bili, DAT neg, spherocytes, osmotic fragility test, EMA

- **Treatment:** close monitoring during illness and first few mos of life, transfusions, splenectomy (PCN prophylaxis, thrombosis)

- **Prognosis:** Excellent

Nathan & Oski, Hematology of Infancy and Childhood, 7th ed.
Case 8

A 15 year old girl is seen in the ER for fatigue, pallor, fever, and easy bruising. She has no skeletal anomalies.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>6.2 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>107</td>
</tr>
</tbody>
</table>
Case 9 – Aplastic Anemia

- Bone Marrow Failure Syndrome
- Presentation:
  - Physical anomalies
  - Medication, environmental, infectious exposures
  - Sx of pancytopenia
- Labs:
  - Pancytopenia
  - MACROCYTOSIS
  - ↓ retic

**Severe AA Criteria**

<table>
<thead>
<tr>
<th></th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marrow</strong></td>
<td>&lt;25% cellularity</td>
</tr>
<tr>
<td><strong>ANC</strong></td>
<td>&lt;500</td>
</tr>
<tr>
<td><strong>Plt</strong></td>
<td>&lt;20K</td>
</tr>
<tr>
<td><strong>Abs Retic</strong></td>
<td>&lt;20 x 10⁹/l</td>
</tr>
</tbody>
</table>

**Causative Agents**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Chloramphenicol, sulphonamides, cotrimoxazole, linezolid</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Gold, Penicillamine, Phenylbutazone, Indomethacin, Diclofenac, Naproxen, Piroxicam, Sulphasalazine</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>Phenytoin, Carbamazepine</td>
</tr>
<tr>
<td>Anti-thyroid</td>
<td>Carbimazole, Thiouracil</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>Dothiepin, Phenothiazines</td>
</tr>
<tr>
<td>Anti-diabetics</td>
<td>Chlorpropamide, Tolbutamide</td>
</tr>
<tr>
<td>Anti-malarials</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>Mebendazole, Thiazides, Allopurinol</td>
</tr>
<tr>
<td>Environmental</td>
<td>Benzene, other solvents, pesticides, DDT, cutting oils, lubricating agents, fertilizer, Ecstasy</td>
</tr>
</tbody>
</table>

Marsh et al., BJH, 2011
Kurre, PB & C, 2005
Diagnostic Considerations

- Fanconi Anemia
- DKC (Dyskeratosis congenita)
- Viral (hepatitis, HIV, EBV, CMV etc)
- Lupus, other autoimmune
- Histoplasmosis
- Drugs
- HLH
- Chemicals
- Pregnancy
- B12/Folate
- PNH (paroxysmal nocturnal hemoglobinuria)
- Leukemias
- AML
- MDS
- Chromosomes 5,7
- IBMFS
- Acquired
Acquired AA: Treatment and Prognosis

• Treatment:
  – Transfusional support, infectious prophylaxis
  – Matched Sib:
    • Bone Marrow Transplant
    • >85% survival
  – No matched Sib:
    • Anti-thymocyte globulin (ATG)/Cyclosporine
    • 65-75% response

• Prognosis
  – ~10% risk of malignant transformation

Marsh et al., BJH, 2011
Kurre, PB & C, 2005
A 7m old boy is seen by in the ER for pallor, fatigue. Significant heart murmur on exam with tachycardia. History reveals that he lives on a farm and has been exclusively drinking goat milk since 2 mos of age. ER doc draws venous labs.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb</td>
<td>1.3 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>111</td>
</tr>
<tr>
<td>Retic</td>
<td>1.7%</td>
</tr>
<tr>
<td>WBC</td>
<td>16</td>
</tr>
<tr>
<td>Plt</td>
<td>42K</td>
</tr>
</tbody>
</table>
Case 10 – Folate deficiency

- Macrocytosis
- Nucleated RBC
- Hyper-segmented neutrophils
Case 10 – Folate deficiency

• Folate/B12 deficiency are **RARE** in children
  – Macrocytic anemia almost always due to marrow stress (bone marrow failure syndromes or acute leukemia)
• Concomitant iron deficiency
• Presentation
  – Goat milk
  – Macrocytic anemia, ↓retic
  – Thrombocytopenia (44-80% of cases)
• Treatment
  – Folic acid
  – Grains, leafy greens, beans
  – Discontinue goat milk
### Anemia classification by RBC size

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
</table>
| - Iron deficiency  
- Thalassemia  
- Anemia of inflammation  
- Lead poisoning  
- Other unstable hemoglobinopathy | - Anemia of inflammation  
- Acute blood loss  
- TEC  
- DBA  
- AIHA  
- Sickle cell anemia  
- Hereditary Spherocytosis  
- G6PD def. /Enzymopathies  
- Statistical | - DBA  
- Fanconi Anemia  
- Other BMF  
- Down’s  
- Hypothyroid  
- B12/Folate Deficiency |
Classification of anemia by mechanism

Decreased Production
- Iron deficiency
- Thalassemia
- Anemia of inflammation
- Lead poisoning
- TEC
- DBA
- B12/Folate def
- Hypothyroidism
- Bone Marrow Failure Sx

Increased Consumption
- AIHA
- Thalassemia
- Sickle cell anemia
- Hereditary Spherocytosis
- Acute blood loss
- G6PD, other enzymopathies
Summary

- Etiology of most anemias in pediatrics can be diagnosed with history, PE, blood smear review, and minimal additional lab testing
- History: fatigue, pallor, jaundice, nutritional, ethnic, FHx
- PE: jaundice, splenomegaly, heart murmur, congenital anomalies
- Labs:
  - Exclude spurious values
  - Characterize anemia in context of pt age, gender etc.
  - Determine etiology: decreased production, increased consumption, or both
  - Careful review of peripheral blood smear
  - Additional testing as needing: iron studies, Hgb electropheresis, EMA, etc.
Pearls

• Remember the 11 + 0.1 rule and 70 + 1 rules for determining low-normal Hgb and MCV
• The most common anemia in children is IDA
• Skeletal anomalies/congenital malformations are a red flag
• Macrocytosis is almost always due to bone marrow stress
Our Team

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- Leukemia
- Palliative Care

Carla Schwalm, MD
- Late Effects and Survivorship
- Nutritional Anemias

Christopher Rokes, MD
- Solid Tumors
- Neuro-oncology

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- Sickle Cell Disease
- Embryonal Solid Tumors

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THANK YOU!