ANEMIA

Definition:
REDUCTION IN:
Hemoglobin concentration, hematocrit or number of red blood cells

Protocol of initial procedures concerning a child with anemia
• History
• Physical examination
• CBC
• Mean corpuscular volume (MCV)
• Reticulocyte count
• Peripheral blood smear examination for RBC morphology

Red blood cell values in children

<table>
<thead>
<tr>
<th>Age</th>
<th>Hemoglobin (g/dL) Mean</th>
<th>Hemoglobin (g/dL) Lower Limit</th>
<th>Mean Corpuscular Volume (fl) Mean</th>
<th>Mean Corpuscular Volume (fl) Lower Limit</th>
<th>Mean Corpuscular Hemoglobin (pg/cell) Mean</th>
<th>Mean Corpuscular Hemoglobin (pg/cell) Lower Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>14.0-14.5</td>
<td>13.5-14.0</td>
<td>77-96</td>
<td>74-80</td>
<td>19.5-22</td>
<td>18.0-21</td>
</tr>
<tr>
<td>Premature</td>
<td>15.0-18.0</td>
<td>14.5-17.0</td>
<td>85-108</td>
<td>81-98</td>
<td>22-25</td>
<td>20-24</td>
</tr>
<tr>
<td>2 months</td>
<td>11.5-13.5</td>
<td>11.0-13.0</td>
<td>70-85</td>
<td>67-80</td>
<td>18-20</td>
<td>16-20</td>
</tr>
<tr>
<td>3-6 months</td>
<td>11.5-13.5</td>
<td>11.0-13.0</td>
<td>70-85</td>
<td>67-80</td>
<td>18-20</td>
<td>16-20</td>
</tr>
<tr>
<td>6-12 weeks</td>
<td>11.5-13.5</td>
<td>11.0-13.0</td>
<td>70-85</td>
<td>67-80</td>
<td>18-20</td>
<td>16-20</td>
</tr>
<tr>
<td>12-18 weeks</td>
<td>11.5-13.5</td>
<td>11.0-13.0</td>
<td>70-85</td>
<td>67-80</td>
<td>18-20</td>
<td>16-20</td>
</tr>
<tr>
<td>Male</td>
<td>14.0-14.5</td>
<td>13.5-14.0</td>
<td>77-96</td>
<td>74-80</td>
<td>19.5-22</td>
<td>18.0-21</td>
</tr>
<tr>
<td>Female</td>
<td>14.0-14.5</td>
<td>13.5-14.0</td>
<td>77-96</td>
<td>74-80</td>
<td>19.5-22</td>
<td>18.0-21</td>
</tr>
</tbody>
</table>


J Pediatr 94:26, 1979

A. DEFICIENCY ANEMIAS
a. Iron deficiency
b. Vitamin B12 deficiency
c. Folic Acid deficiency

B. BONE MARROW FAILURE
a. Diamond-Blackfan anemia (congenital pure red cell aplasia)
b. Transient erythroblastopenia (TEC)
c. Fanconi Anemia (congenital aplastic anemia)
d. Acquired aplastic anemia

C. HEMOLYTIC ANEMIAS
a. Hereditary hemolytic anemias
   - Hereditary spherocytosis
   - Red cell enzyme defects
   - Hemoglobin defects
   - Sickle cell disease
   - Thalassemias
b. Acquired hemolytic anemias
   - Immune Hemolytic Anemia
   - Microangiopathic anemia

IRON DEFICIENCY

the most common cause of anemia in children

Iron demand exceeds iron supply
Peak prevalence - infancy /6-24 months/ and adolescence

Etiology:
I. Deficient intake or absorption
II. Increased demand
III. Blood loss

IRON DEFICIENCY

I. Deficient iron intake/absorption
1. Dietary / iron requirement: 1mg/kg/day
   Milk diet in infancy (0.5-1.5 mg Fe/LOF milk)
   breast-fed absorb 49% of iron
   cow-milk-fed absorb 10% of iron
   Low meat intake /adolescent girls/
2. Malabsorption syndrome, celiac disease, prolonged diarrhea

II. Increased demand
1. Growth: low birth weight, prematurity, multiple gestation,
   high growth rate /infancy-adolescence/
2. Chronic hypoxia
3. Pregnancy, lactation
III. Blood loss
1. Prenatal - fetomaternal, twin to twin transfusion
2. Perinatal – obstetric complications
3. Postnatal -
   a/ gastrointestinal
   b/ exudative enteropathy / hypersensitivity to cow’s milk,
   c/ anatomic gut lesions
   d/ parasitic infestations
   Menstrual loss
   Trauma, surgery

Clinical features and tissue effects
A. gastrointestinal: anorexia, pica, leaky gut syndrome
B. neurological: irritability, fatigue, lower mental and motor test scores, impaired educational performance
C. cardiovascular: tachycardia, systolic murmur, cardiomegaly, hepatomegaly
D. musculoskeletal: diminished physical endurance

Lab work-up
A. Hemoglobin, MCV, normal reticulocyte count,
   blood smear-small, pale red blood cells
B. MCH mean corpuscular hemoglobin,
   MCHC mean corpuscular hemoglobin concentration,
C. ferritin, STfR (serum transferrin receptor)
D. serum iron, iron-binding capacity TIBC

• Serum ferritin ↓
• Serum iron ↓
• TIBC ↑
• Hemoglobin ↓
• MCV ↓

Folic acid / vit B12 deficiency

Etiology
- Deficient intake/absorption: malnutrition, infants fed with boiled goat’s milk, malabsorption states, drugs side effects, barbiturates, phenytoin/
- Increased demands: chronic hemolysis, prematurity
- Disorders of metabolism: congenital defects, folate antagonists (methotrexate, trimethoprim), liver diseases

Clinical features
- Insidious onset, pallor, fatigue, anorexia, diarrhea
- In Cbl deficiency: developmental delay, weakness, irritability, hypothermia, loss of reflexes, paresthesias, ataxic gait

Diagnosis
A. Hemoglobin, MCV, white blood cells and platelet count
B. Bone marrow: hypercellular, megaloblastic-large cells with large nucleus and mature cytoplasm
C. Serum folate level <5ng/ml, serum vit B12 level <80pg/ml
D. Therapeutic trial – response to 50µg dose of folic acid
E. Gastrointestinal evaluation

Therapy
- Folic acid 1-5mg/day for several months
- Vit B12 100µg x week i.m., followed by 100µg monthly
- Diet improvement
Failure of single cell line - PURE RED BLOOD CELL APLASIA

Diamond-Blackfan anemia /DBA/
- Inherited /AR/
- <1 year of age
- No previous history
- Often physical defects present
- MCV
- Hb F
- Therapy: steroids, transfusions, bone marrow transplantation

Transient erythroblastopenia of childhood /TEC/
- Congenital /AR/
- Onset: 3-8 years of age
- Abnormal chromosomal breakage
- Physical anomalies common: thumbs, radii, metacarpals, kidney, eyes
- Cafè au lait spots
- Therapy: No specific therapy, sometimes transfusion, spontaneous recoveries

Bone marrow failure – APLASTIC ANEMIA /AA/
- Immune-mediated destruction of stem cells in the marrow
- Pancytopenia - Hb, reticulocytes, platelets, WBC, and platelet count
- Splenomegaly, hepatomegaly and lymphadenopathy not characteristic

Fanconi Anemia
- Congenital /AR/
- Onset: 3-8 years of age
- Abnormal chromosomal breakage
- Physical anomalies common: thumbs, radii, metacarpals, kidney, eyes
- Cafè au lait spots
- Therapy: bone marrow transplantation

Acquired aplastic anemia
- 70% idiopathic
- Secondary: drugs/toxins/chemicals, radiation, viruses /hepatitis/, preleukemia, MDS

HEMOLYTIC ANEMIAS - general features

A. Reduced red cell survival and accelerated hemoglobin catabolism
   a. extravascular hemolysis: unconjugated bilirubin, fecal and urinary urobilinogen
   b. intravascular hemolysis: hemoglobinuria, plasma hemoglobin

B. Increased erythropoiesis
   - reticulocytes, bone marrow-erythroid hyperplasia

C. Erythroblastopenic crises
   - Hb with reticulocytes

SPHEROCYTOSIS - the most common hereditary hemolytic anemia in Northern Europeans

Etiology:
- Autosomal dominant red cell membrane skeletal proteins defect

Clinical features:
- Anemia, jaundice, splenomegaly of variable severity
- Significant jaundice often in newborns /exchange transfusion/

Lab work-up:
- RDW
- MCHC
- Blood smear-microspherocytes /dense, small red cells with high volume to surface ratio/
- Increased red cell osmotic fragility
- Membrane protein analysis

Therapy:
- Folic acid supplementation 1mg/day
- Red cell transfusion when indicated
- Splenectomy in moderate and severe cases (not before 6yrs of age)

GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Etiology and pathogenesis
- Impaired red cell response to oxidant agents
- X-linked recessive
- A variant: African-American population
- B variant: Mediterranean population

Various clinical presentations:
- Variant A: self-limited hemolysis
- Variant B: severe hemolysis, may be life-threatening
  - Neonatal jaundice
  - Episodic hemolytic anemia induced by drugs /sulfonamides, salicylates, / infection
  - Chronic nonspherocytic hemolytic anemia
  - Favism /explosive intravascular hemolysis due to broad beans eating/

Lab work-up: enzyme assay

Therapy:
- Avoid the precipitating factors
- Red cell transfusion when indicated

PYRUVATE KINASE (PK) DEFICIENCY

Etiology and pathogenesis
- Autosomal recessive
- Metabolic block of glycolytic pathway - reduced ATP
- Deformed red blood cells easily destructed in splenic cords

Clinical features
- Hemolytic anemia of variable severity: not drug induced
- Common neonatal jaundice, bone changes, hemosiderosis from multiple transfusions

Lab work-up: enzyme assay

Therapy
- Folic acid
- Transfusions if indicated
- Splenectomy followed by significant rise of reticulocyte count
SICKLE CELL DISEASE

the most common hemolytic anemia in African-American population
African, Mediterranean, Middle Eastern, Indian ethnicity

Etiology and pathogenesis:
autosomal inheritance
replacement of glutamic acid with valine in the globin chain
abnormal HbS,
sickle shaped red cells in their deoxygenated state
hemolytic anemia with microvascular obstruction \( \rightarrow \) tissue ischemia / infarction

Clinical features:

- Hemolysis manifestations
  - Vaso-occlusion manifestations
    - Recurrent painful crises
      - Hand-foot syndrome - <5yrs of age painful swelling of hands and feet
      - Painful multiple bones crises with fever and spontaneous recovery
      - Abdominal crises - infarction in the liver, spleen, lymph nodes
    - Splenic sequestration
      - Pooling of large amounts of blood in the spleen, splenomegaly
    - Stroke, convulsions, blindness
    - Hepatopathy, hematuria
    - Functional asplenia - overwhelming infections; encapsulated bacteria dangerous
- Late manifestations
  - Progressive myocardial damage
  - Renal failure
  - Aseptic necrosis of long bones
  - Tissue hemosiderosis

Lab work-up

Hb, MCV normal, granulocytes, platelets, ESR !!

Therapy

- HSCT
- HbF production stimulating agents - hydroxyurea, erythropoietin
- Infection prophylaxis
- Prompt antibiotic in case of fever
- Painful crises
  - Hydration + alkalization
  - Analgesic agents
  - Red cells transfusions and partial exchange transfusions
  - Avoidance of dehydration, hypoxia, chilling, acidosis

SICKLE CELL DISEASE

Lab work-up

Hb, MCV normal, granulocytes, platelets, ESR !!

Therapy

- HSCT
- HbF production stimulating agents - hydroxyurea, erythropoietin
- Infection prophylaxis
- Prompt antibiotic in case of fever
- Painful crises
  - Hydration + alkalization
  - Analgesic agents
  - Red cells transfusions and partial exchange transfusions
  - Avoidance of dehydration, hypoxia, chilling, acidosis

THALASSEMIAS
congenital hemolytic anemias with ineffective erythropoiesis
reduced or absent synthesis of \( \alpha \) (thalassemia \( \alpha \)) or \( \beta \) (thalassemia \( \beta \)) chains of Hb

Thalassemia \( \alpha \)
- Moderate anemia
  - Deletion of 2 genes
- Significant anemia
  - Deletion of 3 genes
- Death in utero
  - Deletion of 4 genes
- Silent carrier
  - Deletion of 1 gene

Thalassemia \( \beta \)
- Major
  - Homozygous
  - Mediterranean population
    - Severe hemolytic anemia,
    - Massive hepatosplenomegaly
    - Bone marrow hyperplasia, tower skull, prominent cheekbones;
    - Iron overload, hemochromatosis,
    - Heart failure, liver cirrhosis, endocrine problems
    - Hypersplenism
- Minor
  - Heterozygous
  - Mild anemia

Lab work-up

Hb, MCV, MCH = microcytic hypochromic anemia

Thalassemia

Lab work-up

Hb, MCV, MCH = microcytic hypochromic anemia

Therapy

- HSCT
- Red cells transfusions
- Chelation therapy
- Supportive care

Autoimmune hemolytic anemia /AIHA/

Etiology and pathogenesis

- Idiopathic
- Secondary to drugs, viral infections, autoimmune diseases, malignancies
  - Immunodeficiencies
  - Warm reactive and cold reactive antibodies

Warm IgG-mediated antibodies cause the most common form of AIHA in children

Clinical features - hemolytic anemia

Lab work-up

- Direct Coombs test

Therapy

- Corticosteroids: Prednisone 2mg/kg 2-4 weeks
- Intravenous IgG
- Red cells transfusions
ANEMIA OF CHRONIC DISEASES

- Chronic inflammatory diseases
- Infections
- Malignancies

Lab work-up

- Serum iron,
- Iron-binding capacity (TIBC)
- Serum transferrin receptor
- Ferritin
- Bone marrow evaluations in malignancies