Anemia

- **Definition:**
  Condition in which the concentration of Hemoglobin or the red cell mass is reduced below normal.
Table 1. Normal red blood cell values in children

<table>
<thead>
<tr>
<th>AGE</th>
<th>Hemoglobin (g/dl)</th>
<th>MCV (fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>- 2 SD</td>
</tr>
<tr>
<td>Birth (cord blood)</td>
<td>16.5</td>
<td>13.5</td>
</tr>
<tr>
<td>1-3 days (capillary)</td>
<td>18.5</td>
<td>14.5</td>
</tr>
<tr>
<td>1 week</td>
<td>17.5</td>
<td>13.5</td>
</tr>
<tr>
<td>2 weeks</td>
<td>16.5</td>
<td>12.5</td>
</tr>
<tr>
<td>1 month</td>
<td>14.0</td>
<td>10.0</td>
</tr>
<tr>
<td>2 months</td>
<td>11.5</td>
<td>9.0</td>
</tr>
<tr>
<td>3-6 months</td>
<td>11.5</td>
<td>9.5</td>
</tr>
<tr>
<td>0.5-2 years</td>
<td>12.0</td>
<td>10.5</td>
</tr>
<tr>
<td>2-6 years</td>
<td>12.5</td>
<td>11.5</td>
</tr>
<tr>
<td>6-12 years</td>
<td>13.5</td>
<td>11.5</td>
</tr>
<tr>
<td>12-18 years, female</td>
<td>14.0</td>
<td>12.0</td>
</tr>
<tr>
<td>12-18 years, male</td>
<td>14.5</td>
<td>13.0</td>
</tr>
<tr>
<td>18-49 years, female</td>
<td>14.0</td>
<td>12.0</td>
</tr>
<tr>
<td>18-49 years, male</td>
<td>15.5</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Hasting, C. Anemia, In: Hematology/oncology handbook, 2002; 3
Classification anemia in children

**ETIOLOGY**

1. Impaired red cell formation
   A. Deficiency
      - Decreased dietary intake
      - Increased demand
      - Decreased absorption
      - Increased loss
      - Impairment in red cell formation can result from one of the following deficiencies:
        1. Iron deficiency
        2. Folate deficiency
        3. Vitamin B12 deficiency
        4. Vitamin C deficiency
        5. Protein deficiency
        6. Vitamin B6 deficiency
        7. Thyroxine deficiency
   B. Bone marrow failure.
      1. Failure of single cell line
         a. Megakaryocytes
         b. Red cell precursors
         c. White cell precursors
      2. Failure of all cell line
         a. Constitutional
         b. Acquired
      3. Infiltration
         a. De novo ec Leukemia
         b. Secondary ec: Neuroblastoma, Lymphoma
         c. Dyshematopoietic anemia

II. Blood loss

III. Hemolytic anemia
   A. Corpuscular
      1. Membrane defects
      2. Enzymatic defects
      3. Hemoglobin defects
         a. Heme
         b. Globin
            - Qualitative...... Sickle cell
            - Quantitative.... Thalassemia
   B. Extracorpuscular
      1. Immune
         a. Isoimmune
         b. Autoimmune
            ( 1) Idiopathic
            ( 2) Secondary
               Immunologic disorder
               One cell line
               Multiple cell line
      2. Nonimmune( Idiopathic, secondary )

Lanzkowsky P. Manual of Pediatric Hematology and Oncology 4 th eds
Blood Smear

Hypocromic Microcytic

MCV LOW
( Red Cell Size < 70 fl)
- Iron deficiency anemia
- Thalassemia
- Sideroblastic anemia
- Chronic disease
(Infection, Cancer, inflammation, renal disease)
5. Lead toxicity
6. Hemoglobin E trait
7. Atransferrinemia
8. Inborn errors of iron metabolism
9. Copper deficiency
10. Severe malnutrition

Macrocytic

MCV HIGH
( Red Cell Size > 85 fl)
- Normal newborn
- Increased erythropoiesis
- Postsplenectomy
- Liver disease
- Obstructive jaundice
- Aplastic anemia
- Hypothyroidism
- Megaloblastic anemia
- Down syndrome
- Syndrome with elevated High F
- Myelodysplastic syndrome
- Diamond-Blackfan syndrome

Normocytic

MCV NORMAL
( Red Cell Size 72-79 fl)
- Acute blood loss
- Infection
- Renal failure
- Connective tissue disorder
- Liver disease
- Disseminated malignancy
- Early iron deficiency
- Aplastic anemia
- Bone marrow infiltration
- Dyserythropoietic anemia
- Hemolysis
- RBC enzym deficiency
- RBC membrane defects

Specific

- Fanconi anemia
- Dyskeratosis Congenital
- Pearson syndrome

Lanzkowsky P, Manual of Pediatric Hematology and Oncology 4th eds.
Laboratory Studies often Helpful in Investigation of a patient with anemia

- **Usual Initial studies**
  - Hemoglobin and hematocrit determination
  - Erythrocyte count and red cell indices, including MCV and RDW
  - Reticulocyte count
  - Study of stained blood smear
  - Leucocyte count and differential count
  - Plateled count

- **Suspected Iron deficiency**
  - Free erytrocyte protoporphyrin
  - Serum ferittin levels
  - Stool for occult blood
  - 99m Tc pertechnetate scan for Mechel’s diverticulum-if indicated
  - Endoscopy (upper and lower bowel)- if indicated

- **Suspected Vitamin B12 or folic acid**
  - Bone Marrow
  - Serum vitamin B12 level
  - Serum folate level
  - Gastric analysis after histamine injection
  - Vitamin B12 absorption test (radioactive cobalt) (Schilling test)

- **Suspected hemolytic anemia**
- Suspected hemolytic anemia
  - Evidence of red cell breakdown
    - Blood smear
    - Serum bilirubin level
    - Urinary urobilinogen
    - Hemoglobinuria
    - Serum haptoglobin
  - Evidence of red cell regeneration
    - Reticulocyte count
    - Blood smear
    - Skelatal radiographs
  - Evidence of type of hemolytic anemia: corpuscular
    - Membrane
      - Blood smear
      - Osmotic fragility test
      - Autohemolysis test
    - Hemoglobin
      - Sickle test
      - Hemoglobin electrophoresis
      - Hemoglobin F determinitation
      - Kleihauer-Betke smear
      - Heat-stability test
    - Enzymes
      - Enzyme assay
Evidence of type of hemolytic anemia: extracorporeal

Immune
  Antiglobulin test
  Acid serum lysis test
  Sucrose lysis test
  Donath-Landsteiner antibody
  ANA

Suspected aplastic or leukemia
  Bone marrow (aspiration or biopsy)-cytocentrifugation, immunologic markers, chromosome analysis
  Skeletal radiographs

Other tests often used especially to diagnose the primary disease
  Viral serology, e.g. HIV
  ANA, complement, CH50
  Blood urea, creatinine, T4, TSH, Tissue biopsy (skin, lymph node, liver)
Investigation of Anemia

- **History, physical examination, CBC**
  - Compatible with iron deficiency
  - Low: **Response to Trial of iron**
    - Yes: Iron deficiency
    - No: **Laboratory evaluation of microcytic anemia**
  - High: **Peripheral smear**
    - Low: Neutrophils, platelets
    - High: Hemolysis
      - Yes: Investigate Blood loss
      - No: **Specific tests**
        - Dictated by history, physical, & red cell morphology
          - Low: Bone marrow failure
          - Normal or high: Pure red cell aplasia or megaloblastic anemia

- **MCV**
  - Normal or high: **Reticulocyte count**
  - Low: Peripheral smear
    - No Hemolysis: Neutrophils, platelets
### Table 3. Physical examination of the anemic child

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>Severe anemia</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Hemolytic anemia, acute &amp; chronic</td>
</tr>
<tr>
<td></td>
<td>Hepatitis, aplastic anemia</td>
</tr>
<tr>
<td>Petechiae, purpura</td>
<td>Autoimmune haemolytic anemia with thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>Bone marrow aplasia or infiltration</td>
</tr>
<tr>
<td><strong>Heent</strong></td>
<td></td>
</tr>
<tr>
<td>Cavernous hemangioma</td>
<td>Microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Frontal bossing, prominent malar &amp; maxillary bones</td>
<td>Extramedullary hematopoiesis (thalassemia major, congenital hemolytic anemia)</td>
</tr>
<tr>
<td>Icteric sclerae</td>
<td>Congenital hemolytic anemia &amp; or hyperhemolytic crises</td>
</tr>
<tr>
<td></td>
<td>associated with infection</td>
</tr>
<tr>
<td>Angular stomatitis</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Glossitis</td>
<td>VIt. B12 or iron deficiency</td>
</tr>
<tr>
<td><strong>Chest</strong></td>
<td></td>
</tr>
<tr>
<td>Rales, gallop rhythm</td>
<td>Congestive heart failure, acute or severe anemia</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td><strong>Extremities</strong></td>
<td></td>
</tr>
<tr>
<td>Radial limb dysplasia</td>
<td>Fanconi’s anemia</td>
</tr>
<tr>
<td>Spoon nails</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Triphalangeal thumbs</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Red cell aplasia</td>
</tr>
<tr>
<td><strong>Spleen</strong></td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Congenital hemolytic anemia, infection, hematologic malignancies, portal hypertension with resultant hypersplenism</td>
</tr>
</tbody>
</table>

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IRON DEFICIENCY ANEMIA

- **Definition:**
  - Anemia resulting from lack of sufficient iron for synthesis of hemoglobin.

- **Prevalence:**
  - The most common cause of anemia worldwide
  - An estimated 30% of the world’s population:
    - 4.5 billion \(\Rightarrow\) anemic
    - 500 – 600 million \(\Rightarrow\) Iron def. anemia
  - North American (1970): 30 – 75% of child 1 – 2 years of age
  - Israeli: 25% females (aged 16 – 17 yrs)
  - Indonesia: 25 – 35% (aged 5 yrs)
Figure 16.3 Iron cycle.
Causes of Iron Deficiency Anemia

I. Deficient intake
   Dietary (milk, 0.5-1.5 iron/L)

II. Increased demand
   Growth (low birth weight, prematurity, low-birth-weight twins or multiple births, adolescence, pregnancy), cyanotic congenital heart disease

III. Blood loss
   A. Perinatal
      1. Placental (Transplacental bleeding into maternal circulation, Retroplacental, Intraplacental, Fetal blood loss at before birth)
      2. Umbilicus (rupture umbilical cord, Inadequate cord tying, post exchange transfusion)
   B. Postnatal
      Gastrointestinal tract, Hepatobiliary system, Pulmonary hemocidation, recurrent epistaxis

IV. Impaired absorption
   Malabsorption syndrome, celiac disease, severe prolonged diarrhea, postgastrectomy, inflammatory bowel disease, Helicobacter pylori infection associated chronic gastritis
Consequences of anemia:

- **Mild – moderate iron deficiency (Hb 6-10 g/dl):**
  - Compensatory mechanism (+)

- **Severe iron deficiency (Hb < 5 g/dl):**
  - Fatigue, listlessness, irritability, anorexia, tachycardia, cardiac dilatation & systolic murmurs.

- **Advanced iron deficiency:**
  - Pale, plump, & petulant.
CLINICAL MANIFESTATIONS

Nonhematologic consequence:

- Pica:
  - Phagophagia (compulsive eating of ice)
  - Geophagia: interest in dirt consumption $\Rightarrow$ risk for parasitic infestation & lead poisoning
- Epithelial changes: Koilonychia, atrophy of lingual papil
- Exercise intolerance
- Behavioral changes
- Abnormal thermogenesis
- Altered host response
Koilonychia
LABORATORIUM FINDINGS

- Red blood cells (RBCs)
  - Hb concentration: ↓
  - Chronic iron def. ⇒ red cell indices (MCV, MCH, MCHC): ↓ parallels with Hb concentration
  - Reticulocytes: slightly ↑
  - Red cell morphology:
    - Mild iron def. ⇒ hypochromic, anisocytosis
    - Chronic iron def. ⇒ poicylocytosis (targets cells, ovalocytes, mycrocytes & cell fragments)
  - RBCs survival: shortened
Live Blood Cell Analysis

Photos taken with a dark field microscope

Normal Red blood cell  Microcytes
Poikilocytosis

Anisocytosis
- **Platelets**: varies from thrombocytopenia to thrombocytosis

- **Iron metabolism**:
  - Serum iron: ↓
  - TIBC: ↑
  - Transferrin sat. (ratio SI: TIBC): ↓
  - Serum ferritin: < 10 - 12 µg/dl
  - FEP (Free erythrocyte porphyrin): > 100 µg/dl

- **Factor VIII activity**: ↑ 2 – 3 fold.
DIAGNOSIS

Based on:
- History
- Physical examination
- Laboratorium findings

Diagnostic criteria for iron deficiency anemia (IDA):

Criteria of IDA by WHO:
1. Hb concentration < normal (age dependent)
2. Mean Hb concentration < 31% (N: 32 - 35%)
3. Serum iron < 50 Ug/dl (N: 80-180 ug/dl)
4. Transferrin sat. < 15 (N: 20-50%)
Criteria of IDA by Cook & Monsen:

1. Microcytic hypochromic anemia
2. Transferrin sat. < 16%
3. FEP levels > 100 ug/dl eritrosit
4. Serum ferritin level < 12 u/dl

Diagnostic to established if 2 from 3 criterias (Transferrin sat. serum ferritin & FEP) are present.
Criteria of IDA by Lanzkowsky:

1. Peripheral smears:
   - Microcytic hypochromic
   - MCV, MCH, MCHC: ↓
   - RDW > 17%

2. FEP: ↑

3. Serum ferritin: ↓

4. Serum ferritin ↓, TIBC ↑, Transferrin sat. < 16%

5. Response to iron preparation

6. Bone marrow: Iron (-) / ↓
DIFFERENTIAL DIAGNOSIS

- β Thalassemia trait
- α Thalassemia trait
- Anemia of chronic diseases & infection
- Lead poisoning
Disorders Associated with Hypochromia

1. Iron deficiency
2. Hemoglobinopathies
   - Thalassemia α-β, Hemoglobin Koln-Leopore-H-E
3. Disorders of heme synthesis caused by a chemical
   - Lead, Pyrazinamide, Isoniazide
4. Sideroblastic anemias
5. Chronic infections or other inflammatory states
6. Malignancy
7. Hereditary orotic aciduria
8. Hypo- or a transferrinemia
   - Congenital
   - Acquired (e.q, hepatic disorders); malignan disease, protein malnutrition (decreased transferin synthesis), nephrotic syndrome (urinary loss)
9. Copper deficiency
10. Inborn error of iron metabolism
    - Congenital defect of iron transport to red cells
TREATMENT

- Treatment of IDA is twofold:
  - Replenishment of body iron
  - Correction of the factors responsible for the deficiency

- Iron can be administered orally, IM, or IV.
● Oral iron therapy

● Ferrous salt: adsorbed 3X better than ferric salts

● Ferrous gluconate, ferrous fumarate, & ferrous succinat: well adsorbed but >> expensive

● Dose: 4 – 6 mg/kg of elemental iron in three divided doses.

● An adequate response to iron therapy: \( \uparrow \text{Hb concentration} > 1\text{g/dl in 10 days} \) & reticulocytosis within 3 – 5 days after starting oral iron supplementation.

● Side effect: >> adults than in infants & children; temporary staining of the teeth
- **Parenteral iron therapy**
  - Indicated: for steadfast noncompliance with oral medication, iron malabsorption, ongoing iron loss exceed.
  - Preparation: iron dextran ⇒ a complex of ferric hydroxide with ↑ molecular weight dextrans.
  - 25% of the iron remains at the injection site for months ⇒ staining of the skin.
  - Dose: weight (kg) x desired increment Hb (g/dl) x 2.5
Erythropoietin

- Recombinant human erythropoietin (EPO) stimulates proliferation & differentiation of erythroid precursors in heme synthesis.

- A typical starting dose: 150 U/kg (3x a week) → IV or SQ

Transfusion therapy

- Children with very severe anemia (Hb < 5 g/dl)
- Blood is best given: packed red cells by a modified exchange transfusion → avoid expansion of the blood volume.
**Prevention**

- Encouragement of breast feeding
- Use of iron - fortified infant formulas after weaning
- The introduction of whole cow's milk to 1 year of age
- Use of iron - fortified infant cereals & ascorbic acid-rich foods at 4 – 6 months
- Supplemental iron for preterm infants after the first month.

**Treatment**