Anemia in children
Anemia may be defined as a reduction in red blood cell (RBC) mass or blood hemoglobin concentration. In practice, anemia most commonly is defined by reductions in one or both of the following:

- **Hematocrit (HCT)** – The hematocrit is the fractional volume of a whole blood sample occupied by RBCs, expressed as a percentage. As an example, the normal HCT in a child age 6 to 12 years is approximately 40 percent.

- **Hemoglobin (HGB)** – This is a measure of the concentration of the RBC pigment hemoglobin in whole blood, expressed as grams per 100 mL (dL) of whole blood. The normal value for HGB in a child age 6 to 12 years is approximately 13.5 g/dL (135 g/L)

Normal ranges for HGB and HCT **vary substantially with age, race, and sex.** The threshold for defining anemia is a HCT or HGB at or below the 2.5th percentile for age, race, and sex.
<table>
<thead>
<tr>
<th>Age</th>
<th>Hemoglobin (g/dL)</th>
<th>Hematocrit (%)</th>
<th>MCV (fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th percentile</td>
<td>Lower limit*</td>
<td>50th percentile</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.5</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>African American</td>
<td>12</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>2 to 3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.6</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>African American</td>
<td>12</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>4 to 6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.9</td>
<td>11.7</td>
<td>38</td>
</tr>
<tr>
<td>African American</td>
<td>12.5</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>7 to 10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13.5</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>African American</td>
<td>12.7</td>
<td>11.2</td>
<td>38</td>
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<tr>
<td>11 to 14 years</td>
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<tr>
<td>Caucasian</td>
<td>13.7</td>
<td>12.3</td>
<td>40</td>
</tr>
<tr>
<td>Male</td>
<td>14.3</td>
<td>12.6</td>
<td>42</td>
</tr>
<tr>
<td>Female</td>
<td>12.9</td>
<td>10.6</td>
<td>38</td>
</tr>
<tr>
<td>Male</td>
<td>13.6</td>
<td>11.8</td>
<td>40</td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13.7</td>
<td>11.5</td>
<td>40</td>
</tr>
<tr>
<td>Male</td>
<td>15.4</td>
<td>13.7</td>
<td>46</td>
</tr>
<tr>
<td>15 to 18 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13.7</td>
<td>11.5</td>
<td>40</td>
</tr>
<tr>
<td>Male</td>
<td>15.4</td>
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<td>46</td>
</tr>
<tr>
<td>African American</td>
<td>12.8</td>
<td>10.7</td>
<td>38</td>
</tr>
<tr>
<td>Male</td>
<td>14.9</td>
<td>12.9</td>
<td>44</td>
</tr>
</tbody>
</table>
Common etiology according to the age

Age of patient
Birth to three months

"physiologic anemia" - approximately six to nine weeks of age (healthy term infants!)

To distinguish pathologic anemia:
Anemia (HGB <13.5 g/dL) within the first month of life
Anemia with lower HGB level than is typically seen with physiologic anemia (ie, <9 g/dL)
Signs of hemolysis (eg, jaundice, scleral icterus, or dark urine) or symptoms of anemia (eg, irritability or poor feeding)

Other causes: blood loss, immune hemolytic disease (ie, Rh or ABO incompatibility), congenital infection and congenital hemolytic anemia (eg, hereditary spherocytosis, glucose-6-phosphate dehydrogenase [G6PD] deficiency)
Age of patient

**Infants three to six months**
- hemoglobinopathy
- nutritional iron deficiency is an unlikely cause of anemia before the age of six months in term infants

**Toddlers, children, and adolescents**
- acquired causes of anemia are more likely, particularly iron deficiency anemia.
- screening for iron deficiency anemia is recommended in all children at 9 to 12 months of age
Classification of the anemias

Mean corpuscular volume (MCV 75-100 fl) classifies anemias

1. **microcytic** (iron deficiency, thalassemia minor, Pb poisoning, chronic infection)

2. **normocytic**: according to reticulocyte count

   - reticulocyte count high:
     - bilirubin: norm.
     - leuko, platelets: high
   - reticulocyte count low:
     - leuko, platelets: normal
     - increased

Hemorrhage /hemolysis // AA, neopl. /PRCA/ infection

3. **macrocytic** (folate+B12 defic., immune hemolytic anemia, liver disease, also AA, preleukemia)
Anemias

Anemia in infants and children

- Inadequate production (deficiency)
- Increased blood loss
- Hemolysis
- Other causes
Inadequate production

- Normal red cell precursors (reticulocyte count normal)
  (red cell life span decreased, inadequate BM response, erythropoietin, inadequate iron uptake by reticuloendothelium)
  - hemolysis, deficient food supply of Fe, B12, folate, malabsorption, inflammation (IBD, JCA), chronic infection (pyogenic)

- Decreased red cell precursors (reticulocyte count low)
  - Bone marrow failure syndromes (single or all lines):
    - Congenital: Fanconi, Diamond-Blackfan, dyskeratosis congenita
    - Acquired: aplastic anemia, pure red cell aplasia (PRCA)
    - Infiltration: de novo – leukemia, secondary – neuroblastoma, lymphoma, connective tissue disease
Iron deficiency

Iron deficiency is the most common nutritional deficiency in children, if iron deficiency is unrecognized, it can result in iron deficiency anemia (IDA)

- Typical presentation of nutritional IDA: Age six months to three year
- The most common presentation of IDA is an otherwise asymptomatic, well-nourished infant or child who has a mild to moderate microcytic, hypochromic anemia

Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

- Much less frequent are infants with severe anemia, who present with lethargy, pallor, irritability, cardiomegaly, poor feeding, and tachypnea
- IDA is typically caused by insufficient dietary iron, it is sometimes caused by an underlying medical problem-malabsorption syndrome- celiac disease, helicobacter pylori infection (H. pylori), IBD
Iron deficiency

- **HOW to prevent iron deficiency** and IDA:
  - introducing iron-rich complementary foods (eg, iron-fortified cereals) at 4 to 6 months of age.
  - Avoiding unmodified (nonformula) cow's milk until age 12 months.
  - After 12 months of age, milk intake should be limited to no more than 600 mL daily

- For children **with presumed IDA**, an empiric trial of oral iron therapy and dietary changes rather than either intervention alone is preferred - 3 mg/kg of elemental iron, once daily between meals

- The dg of iron deficiency is confirmed if there is **an appropriate response to empiric iron therapy** (defined as a rise in hemoglobin of >1 g/dL within four weeks for children with mild anemia or within two weeks for those with moderate or severe anemia)
Iron deficiency
PREVENTION OF IRON DEFICIENCY

• **Recommended intake**
  
  **Infants**
  
  • Full-term – 1 mg/kg daily (maximum 15 mg)
  
  • Premature – 2 to 4 mg/kg daily (maximum 15 mg)

  **Children**
  
  • 1 to 3 years old – 7 mg daily
  
  • 4 to 8 years old – 10 mg daily
  
  • 9 to 13 years old – 8 mg daily

• Because only a fraction of dietary iron is absorbed, the dietary requirement is considerably higher than the net absorbed iron requirement, which is dependent on the bioavailability of the iron in the food.
Anemia of chronic disease/anemia of inflammation

- After iron deficiency, this is the second most common cause of anemia worldwide
- Pathogenesis
- Reduced iron availability — ACD/AI is thought to result from an evolutionary defense strategy of the body in order to limit the availability of iron for invading microbes

In the presence of infection, inflammation, or malignancy, the macrophage is stimulated to produce IL-6 and IL-1β, which induce the production of hepcidin by the liver. Hepcidin inhibits iron absorption from the GIT and decreases release of iron from macrophages. Inflammatory cytokines such as IL-1β and TNF-α reduce erythropoietin production and the efficiency of erythropoiesis, which are also components of ACD.
Anemia of chronic disease/anemia of inflammation

- normochromic, normocytic RBCs and a low reticulocyte count
- low circulating iron levels, low transferrin saturation, normal or high concentration of the iron storage protein ferritin

Treatment

- the goal is to reduce symptoms and improve clinical outcomes, not to normalize the hemoglobin level.
- The preferred initial therapy is treatment of the underlying disorder, RBC transfusions should be reserved for those with severe, life-threatening, and symptomatic anemia
## Causes and differential diagnosis of anemia of chronic disease/anemia of inflammation (ACD/AI)

<table>
<thead>
<tr>
<th>Causes of ACD/AI</th>
<th>Alternative diagnosis of ACD/AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory conditions in which cytokine production leads to altered iron trafficking and decreased production of RBCs.</td>
<td>Anemia caused by mechanisms other than inflammation.</td>
</tr>
<tr>
<td>Anemia is expected to improve with treatment of the underlying disorder.</td>
<td>Anemia is expected to improve with supplementation of the deficient vitamin, mineral, or hormone, or therapy directed at an abnormally functioning bone marrow.</td>
</tr>
</tbody>
</table>

- Autoimmune and autoinflammatory diseases
  - Castleman disease
  - Inflammatory bowel disease
  - Rheumatoid arthritis
  - Sarcoidosis
  - SLE
  - Vasculitis
- Congestive heart failure
- COPD and pulmonary arterial hypertension
- Hematologic malignancies and other cancers
- Infection
  - Complicated urinary tract, skin, or skin structure infections
  - Endocarditis
  - HIV Infection
  - Other systemic bacterial, parasitic, viral, and fungal infections
  - Osteomyelitis
  - Pneumonia
  - Septicemia
  - Tuberculosis
- Obesity

- Aplastic anemia
- Chronic kidney disease with low EPO
- Endocrine disorders
  - Adrenal insufficiency
  - Hyperthyroidism
  - Hyperparathyroidism
  - Hypothyroidism
  - Panhypopituitarism
- Lymphoproliferative disorders
- Myelodysplastic syndromes
- Vitamin/mineral deficiencies
  - Copper
  - Folate
  - Iron
  - Vitamin B12
  - Vitamin D
Fanconi anemia

inherited bone marrow failure syndrome characterized by pancytopenia, predisposition to malignancy, and physical abnormalities including short stature, microcephaly, developmental delay, café-au-lait skin lesions, and malformations belonging to the VACTERL-H association

some individuals may not be diagnosed with FA until adulthood

cells cannot properly repair a particularly deleterious type of DNA damage

increased sensitivity to cytotoxic therapies and a predisposition to certain malignancies, loss of hematopoietic stem cells – bone marrow failure

Genetics — FA is caused by mutations in one of at least 17 different FA genes (FANCA to FANCQ)

Ar, Ad, X linked

Epidemiology - approximately 1 in 100,000 to 250,000 births
But one of the most common inherited bone marrow failure syndromes
Fanconi anemia - clinical features

- Malformations have been reported to occur in 60 to 75% of patients
- Despite the high frequency of malformations, only a small percentage of patients with FA (<5 percent) are diagnosed within the first year of life
- An important clue to the diagnosis, their absence does not eliminate the possibility of FA!

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any physical abnormality</td>
<td>60 to 75%</td>
</tr>
<tr>
<td>Skin - Generalized hyperpigmentation; hypopigmented areas; large freckles, café-au-lait spots</td>
<td>40 to 60%</td>
</tr>
<tr>
<td>Short stature, delicate features</td>
<td>40 to 60%</td>
</tr>
<tr>
<td>Upper limbs – Absent or hypoplastic thumb, supernumerary, bifid, clinodactyly</td>
<td>35 to 50%</td>
</tr>
<tr>
<td>Gonads – Hypogenitalia, undescended/absent testes, hypospadias; bicornuate or malpositioned uterus</td>
<td>25% (males) &lt;5% (females)</td>
</tr>
<tr>
<td>Head – Microcephaly or hydrocephaly; birdlike face, mid-face hypoplasia, Sprengel’s deformity of neck</td>
<td>20 to 25%</td>
</tr>
<tr>
<td>Eyes – Microphthalmia, ptosis, epicanthal folds, strabismus</td>
<td>20 to 40%</td>
</tr>
<tr>
<td>Kidney – Abnormal, ectopic, horseshoe, hypoplastic, or absent kidney; hydronephrosis</td>
<td>20 to 30%</td>
</tr>
<tr>
<td>Ears – Deafness (usually conductive); low set ears, abnormal shape, narrow canal</td>
<td>10 to 20%</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>10%</td>
</tr>
<tr>
<td>Cardiopulmonary anomalies – Congenital heart disease (patent ductus arteriosus, atrial or ventricular septal defects, coarctation, situs inversus)</td>
<td>6%</td>
</tr>
<tr>
<td>Gastrointestinal anomalies – Atresias, imperforate anus, tracheoesophageal fistula, malrotation</td>
<td>5%</td>
</tr>
</tbody>
</table>
Fanconi anemia
Fanconi anemia
Fanconi anemia

**Cytopenias** - include thrombocytopenia, macrocytic anemia, or pancytopenia

- may only be mild upon presentation or may develop later in the disease course
- **thrombocytopenia** may be misdiagnosed as ITP
- **anemia** is typically macrocytic, often the last severe cytopenia to develop
- **neutropenia** (absolute neutrophil count [ANC] < 500/microL)

**Bone marrow failure**

- in the small percentage of patients BMF does not develop
- may be indistinguishable from findings seen in other causes of BMF - AA or MDS
- Dg in infancy due to congenital anomalies- screening bone marrow biopsies are often normocellular
- By the onset of cytopenias, the marrow may reveal **severe hypocellularity**, but it can be **normocellular before**
Fanconi anemia

**MDS/Leukemia** — common in FA; in many cases (MDS or AML, ALL and Burkitt lymphoma are also seen, although they are much less common)

**Solid tumors** — these appear at a much younger age than the age at which these tumors are seen in unaffected individuals
- HCT may increase the risk of solid tumors
- Head and neck squamous cell carcinoma (HNSCC)

**Endocrine manifestations**
Short stature, Primary hypothyroidism, Adrenal dysfunction, Adrenal dysfunction, Infertility and delayed or abnormal progression of puberty are also very frequent
Fanconi anemia – management

- according to the severity of BMF
- HSCT is the only established curative therapy for FA-BMF, MDS, leukemia
  - Best option- MSD- Flu, low dose Cy + ATG , BM (better than PBSC)
  - Although HCT is curative for bone marrow failure and potentially for hematopoietic neoplasms, it does not cure other manifestations of FA
- New- gene therapy
- Androgen therapy - is not curative, pts awaiting HCT /who cannot undergo
- Transfusion and growth factor support -judicious approach
- Routine cancer screenings and preventive interventions (eg, human papilloma virus [HPV] vaccination)
Diamondova-Blackfan anemia

congenital erythroid aplasia that usually presents in infancy
Progressive normochromic, usually macrocytic anemia in infancy or early childhood
● Reticulocytopenia
● Normal cellularity of the bone marrow with markedly decreased or absent erythroid precursors
● White blood cell count is generally normal; platelet counts are generally normal but can be increased or decreased
● Congenital malformations (50 percent of patients)
● Increased risk of malignancies AML, MDS, solid- colon cancer, female genital cancers, osteogenic sarcoma

● Increased risk of endocrine dysfunction

From DKMS website
Diamondova-Blackfanova anémia

- 90% are diagnosed within the first year of life, with 35% diagnosed within the first month (severe anemia)
- Anemia - generally macrocytic, with a mean Hgb of 6.5 in infants younger than two months of age and 4 g/dL in infants older than two months
- **ribosomopathy**, caused by genetic mutations affecting ribosome synthesis

- stabilization and activation of the **TP53** (tumor protein p53) tumor suppressor pathway, which is thought to be the main cause of the clinical manifestations, including impaired erythropoiesis

- **RPS19** is mutated in 25 percent of patients with DBA

- Erythropoietin production is normal in children with DBA
Diamondova-Blackfanova anemia

- Craniofacial abnormalities
- Ophthalmologic anomalies
- Neck anomalies
- Cardiac anomalies
- Thumb abnormalities
- Genitourinary malformations
- Pre- and postnatal growth failure
- Growth retardation (30%)
Diamondova-Blackfanova anémia
The diagnosis of classic DBA is made if all of the following diagnostic criteria are met:
● Age <1 year
● Macrocytic anemia with no other significant cytopenias
● Reticulocytopenia
● Normal marrow cellularity with a paucity of erythroid precursors

In patients who do not meet all of the above criteria, supportive criteria, which are divided into major and minor findings, can be added to make a "probable diagnosis":
● Major - presence of a gene mutation associated with DBA and a positive family history.
● Minor - elevated eADA (erythrocyte adenosine deaminase activity), congenital anomalies associated with DBA, an elevated Hgb F, and no evidence of another inherited bone marrow failure syndrome.
Diamondova-Blackfanova anémia- treatment

- **Steroid therapy** - after the age of 6 to 12 months !!! response rate 50-75%, A four-week trial

- **Transfusion therapy** - blood should be leukoreduced, to maintain Hgb levels ≥8 g/dL, which typically requires transfusion every 4-6 weeks

- **HCT** in steroid-refractory patients
  - Long-term survival is achieved in 65 to 75 percent
  - The optimum timing- a patient refractory to glucocorticoids but before excessive red cell transfusion (>20 to 25 transfusions)
  - Conditioning- myeloablative – BuFluThio (SR)

- **Other therapies** – amino acid L-leucine, Gene therapy
Schwachman -Diamond syndrome

bone marrow failure, particularly **neutropenia**, and **exocrine pancreatic dysfunction**

90% mutation of *(SBDS)* gene, *Ar* heritance

frequent infections, hepatic or cardiac abnormalities, growth failure, feeding difficulties neurocognitive deficits, other congenital anomalies, and an increased risk of MDS or AML / Or subtle presentations- isolated cytopenias

periodic bone marrow evaluation- if cytopenia, G-CSF, MDS

Clinically significant pancreatic dysfunction (eg, symptomatic steatorrhea, fat malabsorption) is treated with oral pancreatic enzyme supplementation, Fat soluble vitamins (A, D, E, and K) as needed.

**HSCT** - with severe persistent or symptomatic cytopenias, high-grade MDS, or AML

Genetic and/or other testing in family members
Hemolysis – high indirect bilirubin

**Coombs test**

**negative**
- **Corpuscular**
  - Hemoglobinopathies:
    - (Hb electrophoresis)
    - Thalassemia β (Cooley anemia)
    - Sickle cell disease
  - Enzymopathies
    - (Enzyme assays)
    - Glucose 6 phosphate deficiency
    - Pyruvate kinase deficiency.....
  - Membrane defects
    - (morphology, osmotic fragility)
    - Hereditary spherocytosis, elliptocytosis....

**positive**
- **Extracorpuscular**
  - autoimmune hemolytic anemia
    - (primary/sec.)

**Hemolysis**

Anemia in infants and children

**Hemolysis**

Anemia in infants and children

**Coombs test**

**negative**

**positive**

**Hemolysis**

**Anemia in infants and children**
Thalassemia

Hemoglobin: 4 polypeptide chains:

$\alpha$(16. ch), $\beta$, $\gamma$, $\delta$(11. ch)

at birth: Hb F ($2\alpha$, $2\gamma$) 74%, after 6 mo 2%, Hb A1 25%, Hb A2 1%

adults: Hb A1: 97% ($2\alpha$, $2\beta$), Hb A2: 3% ($2\alpha$, $2\delta$)

Thalassemia: $\beta$ is missing—very high HbF, low Hb A2

from 6 mo severe anemia, jaundice, failure to thrive, extramedullary hemopoiesis—maxillar overgrowth, frontal bossing, hepatosplenomegaly, hemochromatosis

(transfusion, splenectomy, chelation—deferoxamin, BMT)

(Middle East, Mediterranean area)
Increased blood loss

- GIT bleeding:
  - GER, Meckel div, M. Crohn, ulcerative colitis, cow’s milk intolerance,
- Menstruation – adolescence
- Parasite related blood loss
  - Ancylostomiasis
- Epistaxis, bleeding disorders
- Iatrogenic (blood samples – examination)
Other causes

- Malabsorption
- Chronic inflammatory disorders
- Renal failure – chronic (EP low)
- Chronic infection
- Malignant diseases
- Metabolic disorders:
  - Lesh-Nyhan, chronic liver disease, hypothyroidism,
  - Excess tea (tanin)
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