Anemia

- Anaemia is defined as an Hb level below the normal range. The normal range varies with age, so anaemia can be defined as:
  - Neonate: Hb < 14 g/dl
  - 1–12 months: Hb < 10 g/dl
  - 1–12 years: Hb < 11 g/dl.
Physiologic Anemia of the Newborn

At one week postnatal all RBC indices begin declining to a minimum value reached at about 2 months of age.

- decreased RBC production
- plasma dilution associated with increasing blood volume
- shorter life span on neonatal RBCs (50-70 days)
- more fragile RBCs
- switch from HbF to HbA
  - HbF decreases about 3% per week
  - at 6 mo. HbF represents only 2% of total Hb
  - switch to HbA provides for greater unloading of oxygen to tissues d/t lower oxygen affinity of HbA relative to HbF.

- seldom produces symptoms
- not altered by nutritional supplements
Anemia of Prematurity

- Occurs in low birth weight infants w/ poor erythropoietin response
  - Protein content of breast milk may not be sufficient for hematopoiesis in the premature infant.
  - Hb level rapidly declines after birth to a low of 7-10 g/dl at 6 weeks of age.
- Signs and Symptoms
  - apnea
  - poor weight gain
  - pallor
  - decreased activity
  - tachycardia
Anemia

Decrease Production
- Deficiency
  - Iron
  - Folic acid
  - B12
- Infiltration
  - Leukemia, lymphoma
- Failure or toxins

Increase Destruction
- Defective hemoglobin
  - Thalassemia
- Membrane defect
  - Spherocytosis
- Enzyme deficiency
  - G6PD
- Autoimmune
ANEMIA

- Size of red cells (MCV)
  - Microcytic (MCV < 70 + age)
  - Normocytic (MCV > 70 + age and < 100)
  - Macrocytic (MCV > 100)

Normal MCV:
- < 2 Y: 95-121
- 6 mo-2 years: 70-85
Microcytic Anemia

- Hemoglobin = Heme + Globin

- Iron
- Protoporphyrin

- Iron deficiency anemia
- Anemia of chronic disease
- Thalassemia
- Sideroblastic anemia
IRON DEFICIENCY ANEMIA

- **Etiology**
  - **Nutritional**
    - Exclusive breast feeding
    - Lack of iron-rich foods
    - Consumption of large amount of cow’s milk (> 32oz whole cow’s milk/day) → direct injury to intestine
  - **Impaired absorption**
    - Malabsorption syndrome (*iron absorbed from duodenum*)
      - Celiac disease
IRON DEFICIENCY ANEMIA

• Blood Loss

  – Gastrointestinal
    • Cow’s milk allergy or exudative enteropathy
    • Lesions: Meckel’s, vascular malformations
    • Parasites-Hookworms

  – Genitourinary
    • Menstrual
    • Hemoglobinuria

  – Pulmonary
    • Goodpasture’s Syndrome
    • Pulmonary hemosiderosis
IRON DEFICIENCY ANEMIA

- Clinical Presentation
  - Pallor
  - Koilonychia (spooning of nails)
  - PICA
    - Desire to eat unusual substance as ice, dirt, etc
  - Headache
  - Irritability
  - Anorexia
  - Tachycardia
  - Systolic murmur
IRON DEFICIENCY ANEMIA

• Laboratory
  - Low mean corpuscular volume (MCV)
  - Low mean corpuscular hemoglobin concentration (MCHC)
  - Elevated platelet count (>450,000/μL) in many cases
  - Normal or elevated white blood cell count
  - RBCs become more microcytic, hypochromic and increased poikilocytosis as the disease progress.
  - Target cells are usually not present

IDA can be normocytic in the beginning
IRON DEFICIENCY ANEMIA

- **Laboratory**
  - Low serum iron
  - **Low Ferritin levels**
  - Elevated TIBC
  - Low reticulocyte count
  - Mentzer index >13 (MCV/RBCs)

  A normal serum ferritin can be seen in patients who are deficient in iron and have coexistent diseases (e.g., hepatitis or anemia of chronic disorders)

  **Example:**
  - MCV = 64, RBCs = 5.3
  - 64/5.3 = 12, < 13 = Thal.

  - MCV = 72, RBCs = 4.8
  - 72/4.8 = 15, > 13 = IDA
Peripheral blood smear example of hypochromic/microcytic anemia. Notice the variability in the sizes of red blood cells. The arrows point to hypochromic erythrocytes with large central hallow (Courtesy of Dr. Nawar Hakim)
IRON DEFICIENCY ANEMIA

Treatment

- Oral administration of Ferrous salts at dose of 3-6mg/kg of elemental iron per day
- Common problem with iron
  - Taste, GI irritability and constipation
  - More water and fibers is recommended
- Response to iron therapy is diagnostic and therapeutic

To enhance the absorption:

- Ferrous sulfate or F. gluconate should be taken on an empty stomach
- Give with orange juice or lemonade
Fe^{++} deficiency

- **Tx-**
  - Fe^{++} replacement gives dramatic response
    - reticulocytosis in 72 hr, Hgb responds at ~1g/L per wk, iron stores us. replenished by 3 mo
IRON DEFICIENCY ANEMIA

- Prevention
  - Breast feeding infants
    - Preterm infants: 2 mg/kg per day of oral iron by 1 month of age
    - Full-term: 1 mg/kg per day of oral iron from 4 months of age until iron-rich foods
  - Formula-fed infants will receive adequate iron from formula and complementary foods
  - Whole milk should not be used before 12 months.
  - Limit cow’s milk to less than 500cc/day
  - Iron supplementation in populations living on a largely vegetarian diet
ANEMIA OF CHRONIC DISEASE

• Associations
  – Chronic systemic diseases
  – Chronic inflammatory process; e.g. SLE
  – Chronic pyogenic infection

• Etiology
  – Releases of inflammatory cytokines: IL-6, IL-1, TNF
  – Hepcidin released from the liver decreases intestinal iron absorption, also block release of iron from the macrophages
ANEMIA OF CHRONIC DISEASE

- **Laboratory**
  - Low Hemoglobin concentration (usually 6-9g/dL)
  - Low MCV (can be normocytic in the beginning)
  - Often normochromic anemia with progression hypochromia
  - Low serum iron
  - Elevated serum ferritin
  - Low TIBC

- **Treatment**
  - Treatment of the cause
  - Recombinant EPO may increase the hemoglobin level and improve well-being in patients with cancer

\[ \text{↑ Ferritin} \quad \text{↓ TIBC} \]

\[ \text{↓ Serum iron} \]
THALASSEMIAS

Decrease production of alpha or beta globin

Alpha Thalassemia
Beta Thalassemia

Source: Pediatric Board Study Guide A Last Minute Review, springer 2013
<table>
<thead>
<tr>
<th>Haemoglobin type</th>
<th>α-gene cluster</th>
<th>β-gene cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb Gower 1</td>
<td>$\xi_2$</td>
<td>$\varepsilon_2$</td>
</tr>
<tr>
<td>Hb Gower 2</td>
<td>$\alpha_2$</td>
<td>$\varepsilon_2$</td>
</tr>
<tr>
<td>Hb Portland</td>
<td>$\xi_2$</td>
<td>$\gamma_2$</td>
</tr>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbF</td>
<td>$\alpha_2$</td>
<td>$\gamma_4$</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA</td>
<td>$\alpha_2$</td>
<td>$\beta_2$</td>
</tr>
<tr>
<td>HbA$_2$</td>
<td>$\alpha_2$</td>
<td>$\delta_2$</td>
</tr>
</tbody>
</table>

**Haemoglobin types in newborns and adults**

- **Newborn**
  - HbF 74%, HbA 25%, HbA$_2$ 1%

- **Children >1 year old and adults**
  - HbA 97%, HbA$_2$ 2%
Normal Types of Hemoglobin

HbF (α2 γ2)  HbA (α2 β2)  HbA2 (α2 δ2)

Tetramer

(α and non-α) pair 1:1 ratio

Excess of normally produced type → cell destruction

α2 γ2, α2 γ2 = γ4
Alpha Thalassemia
**ALPHA THALASSEMIA**

- **Characteristics**
  - Healthy individuals have 4 alpha-globin genes, 2 on each chromosome 16
  - Alpha globin production is reduced to absent
  - Seen more frequently in southeast Asian and African ancestry
  - Diagnosis-clinically or with alpha globin chain analysis
  - Excess beta chains leads to beta 4 chains (Hemoglobin H)
  - Excess gamma chains leads to gamma 4 chains (Hemoglobin Barts)
Alpha Thalassemia

- Silent trait
  - Deletion or dysfunction of one gene
  - Asymptomatic
  - 1-2% Hgb Barts on neonatal electrophoresis
  - Normal Hgb electrophoresis
Alpha Thalassemia

- Alpha thalassemia trait
  - Deletion or dysfunction of two genes
  - Mild hypochromic microcytic anemia
  - 3-10% Hgb Barts on neonatal electrophoresis
- Laboratory
  - Mentzer Index <13 (MCV/RBCs).
  - Hgb > 9g/dl
  - Normal Hgb electrophoresis
  - Often misdiagnosed as iron deficiency anemia

<table>
<thead>
<tr>
<th>MCV</th>
<th>RBCs</th>
<th>8 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>64</td>
<td>5.3</td>
<td>12</td>
</tr>
<tr>
<td>72</td>
<td>4.8</td>
<td>15</td>
</tr>
</tbody>
</table>

<13 = Thal.
> 13 = IDA
Alpha Thalassemia

- Hemoglobin H disease
  - Deletion of three genes
  - Mild to moderate hypochromic microcytic anemia
  - Splenomegaly
  - Jaundice
  - Cholelithiasis (pigment stones)
  - Anemia exaggerated by infection, pregnancy, exposure to oxidizing drugs
  - > 25% Hgb Barts on neonatal electrophoresis
Alpha Thalassemia

- **Alpha thalassemia Major**
  - Deletion of four genes
  - Fetal hydrops
  - Fatal disease
  - Predominant Hgb Barts

\[ \alpha^2 \gamma^2 = \gamma_4 \]
\[ \gamma_4 = \text{Hgb Barts} \]
Beta Thalassemia
**β-thalassemia**

Chromosome 11

- **β** due to gene mutation
- **β+**
- “absent” **β0**

- **β/β+**
  - Beta thalassemia minor
    - Slightly decreased in HbA
    - Increase HbA2 > 3.5% (N. 2.5%)
    - Increases HbF to 2% (N. 1%)

- **β0/β0**
  - Beta thalassemia major
    - Little or no HbA
    - Increased HbA2 and HbF

*Pediatric Board Study Guide A Last Minute Review, springer 2015*
BETA THALASSEMIA

• Characteristics
  – Healthy individuals have 2 beta globin genes, 1 on each chromosome
  – Beta globin production is reduced to absent
  – Multiple possible genetic mutations
  – Seen more frequently in Mediterranean, southeast Asian ancestry
  – Also seen in African-Americans but generally have a milder course
  – Relative alpha chain excess leads to shortened red cell survival and variable splenic sequestration (alpha tetramers)
BETA THALASSEMIAS

• Diagnosis
  - Diagnosed by hemoglobin electrophoresis
  - Elevated HgbA2 4-6% (confirm the diagnosis of T. minor)
  - Increased HgbF
  - Beta globin chain analysis
  - Cannot be diagnosed by electrophoresis in the neonate
  - Iron, folate and B12 must be repleted to have an accurate hemoglobin electrophoresis

Alpha thalassemia Hgb Electrophoresis:
  - Normal “children and adults”
  - Neonatal EP: HgbH, Hgb Barts
BETA THALASSEMIA

Hemoglobin = Heme + Globin

Iron

Protoporphyrin

Free Erythrocyte Protoporphyrin (FEP)
Elevated in iron deficiency anemia or lead poisoning

Free Erythrocyte Protoporphyrin (FEP)
Normal in cases of thalassemia
BETA THALASSEMIA

- Thalassemia Major (Cooley's anemia)
  - Variable reduction of beta globin gene production
  - Excess alpha globin chains result in increased destruction of RBCs and ineffective erythropoiesis
  - Shortened red cell life span and splenic trapping
Clinical features and complications of β-thalassaemia major:

- Pallor
- Jaundice
- Bossing of the skull
- Maxillary overgrowth
- Splenomegaly and hepatomegaly
- Need for repeated blood transfusions

Complications shown in Box 22.3

**Box 22.3 Complications of long-term blood transfusion in children**

**Iron deposition – the most important (all patients)**
- Heart – cardiomyopathy
- Liver – cirrhosis
- Pancreas – diabetes
- Pituitary gland – delayed growth and sexual maturation
- Skin – hyperpigmentation

**Antibody formation (10% of children)**
- Allo-antibodies to transfused red cells in the patient make finding compatible blood very difficult

**Infection – now uncommon (<10% of children)**
- Hepatitis A, B, C
- HIV
- Malaria
- Prions (e.g. new variant CJD)

**Venous access (common problem)**
- Often traumatic in young children
- Central venous access device (e.g. Portacath) may be required; these predispose to infection.

**Figure 22.13** Facies in β-thalassaemia showing maxillary overgrowth and skull bossing in a child who has not been adequately transfused. This is now very rare in the UK and developed countries.
Beta Thalassemia Major

- No production of Beta chains - Chromosome 11
- Autosomal recessive
- 25% chance with each pregnancy
- Pre-natal testing for carriers
- Chorionic villous sampling for diagnosis
- Transfusion dependent - allows for normal development
- Pen Prophylaxis, Anti oxidants
- Splenectomy after age 5
- Iron overload - inherent and transfusion
- Need chelators
- BMT is a cure
BETA THALASSEMIA

- Thalassemia Major (Cooley's anemia)
  - Laboratory
    - Severe anemia
    - Few reticulocytes < 8% compared to degree of anemia
    - Microcytosis with no normal appearing RBCs on the smear
    - Numerous nucleated RBCs
    - Target cells
    - Mentzer index (MCV/RBCs) is < 9
    - Indirect (unconjugated) bilirubin is elevated

Mentzer index:
< 13  T. trait
< 9   T. major
BETA THALASSEMIA

• Treatment

• Beta thalassemia major
  – Chronic transfusion therapy
  – Before chronic transfusion is initiated, diagnosis of beta thalassemia must be confirmed first
  – Deferoxamine for iron chelation

Beta thalassemia trait
No treatment is required
Iron will not improve the anemia
iron ONLY if iron deficiency occurs.
Management

**Blood transfusion**
lifelong monthly transfusions of red blood cells. Keep Hb above 10 g/dl.

**Iron chelation**
with subcutaneous desferrioxamine, or with an oral iron chelator drug, such as deferasirox, starting from 2 to 3 years of age.

Patients who comply well with transfusion and chelation have a 90% chance of living into their forties.

**Bone marrow transplantation**, which is currently the only cure. It is generally reserved for children with an HLA-identical sibling as there is then a 90–95% chance of success (i.e. transfusion independence and long-term cure) but a 5% chance of transplant-related mortality.