Anemias

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Definition of anemia

- Anemia is best defined in relation to H&H (hemoglobin [Hb] and hematocrit [HCT]) levels below the normal reference range, because a patient’s symptoms and physiologic consequences are the result of decreased oxygen-carrying capacity of the blood.

- According to World Health Organization (WHO) criteria, anemia is diagnosed in males when Hb is <130 g/L (13 g/dL) and HCT is <0.39 (39%); in nonpregnant females, when Hb is <120 g/L (12 g/dL) and HCT is <0.36 (36%).
Hematocrit evaluation in anemia

The diagram illustrates that a person can have a low hematocrit and not be anemic. This occurs when a patient is overhydrated, typically as a result of overenthusiastic intravenous fluid therapy.
Pathological classification of anemias

• Blood loss
  ✓ Acute
  ✓ Chronic

• Decreased production
  ✓ Deficiency anaemias
    ✓ Iron deficiency
    ✓ Vitamin B12 and Folate deficiency
  ✓ Bone marrow disease/infiltration

• Increased destruction
  ✓ Inherited (Membrane, enzyme, Hb defects)
  ✓ Acquired (immune and non-immune)
Classification of anemias by mean cell volume (MCV)

<table>
<thead>
<tr>
<th>Microcytic (MCV &lt;80 fL)</th>
<th>Macrocytic (MCV &gt;100 fL)</th>
<th>Normocytic (MCV 80–100 fL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly microcytic</td>
<td>Occasionally macrocytic</td>
<td>Occasionally normocytic</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Anemia of chronic disease</td>
<td>Early iron deficiency</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Hemoglobinopathies</td>
<td></td>
</tr>
<tr>
<td>Hereditary sideroblastic anemia</td>
<td>Hypoproliferative anemia</td>
<td></td>
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<td></td>
<td>Refractory anemia</td>
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<td></td>
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<tr>
<td>Occasionally microcytic</td>
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<tr>
<td>Anemia of chronic disease</td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobinopathies</td>
<td></td>
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</tr>
</tbody>
</table>

Classification of anemias by mean cell hemoglobin (MCH)

- MCH represents the average content of Hb in average RBC.

I. Hypochromic anemia <27 picograms/cell

II. Hyperchromic anemia >31 picograms/cell

III. Normochromic anemia 27 - 31 picograms/cell
Classification of anemia according to the degree of severity

1. Mild - hemoglobin - 120-90 g /l
2. Moderate - hemoglobin - 90-70 g /l
3. Severe - hemoglobin - less than 70 g /l
Anisocytosis and poikilocytosis

- Normally all red blood cells are relatively uniform in size and shape.
- Variation in size is referred to as “anisocytosis”
- Variation in shape is referred to as “poikilocytosis”
IRON DEFICIENCY

and

IRON DEFICIENCY ANAEMIA
Definition

- Iron deficiency will result from any condition in which dietary iron intake does not meet the body's demands.
- Iron deficiency anemia is characterized by a defect in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic).
Epidemiology

• Iron deficiency anemia (IDA) is a disease that is potentially exposed to people of all ages, both sexes, all socio-economic classes and geographic regions.

• However, the most prone to IDA are pregnant women, women of reproductive age and children under school age, and patients with low socio-economic status.

• According to the report of the World Health Organization anemia affects 1.6 billion people, accounting for 24.8% of the global population.

• The highest prevalence of IDA in the world has seen in Africa and South East Asia.

• In India, for example, up to 88% of pregnant and 74% of non-pregnant women are affected. Throughout Africa, about 50% of pregnant and 40% of non-pregnant women are anaemic. West Africa is the most affected, and southern Africa the least.
Iron deficiency is coded as:
• (E61.1) Iron deficiency

Iron deficiency anemia is coded as:
• (D50) Iron deficiency anaemia
• (D50.0) Iron deficiency anaemia secondary to blood loss (chronic)
• (D50.1) Sideropenic dysphagia
• Kelly-Paterson syndrome
• Plummer-Vinson syndrome
• (D50.8) Other iron deficiency anaemias
• (D50.9) Iron deficiency anaemia, unspecified
### Classification

**Causes of Iron Deficiency and Iron Deficiency Anaemia**

<table>
<thead>
<tr>
<th>Increased Requirements</th>
<th>Decreased Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Growing infants and children</td>
<td></td>
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<tr>
<td>• Menstruating women</td>
<td></td>
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<tr>
<td>• Pregnancy</td>
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<tr>
<td>• Lactation</td>
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<tr>
<td>• Multiparity</td>
<td></td>
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<tr>
<td>• Parturition</td>
<td></td>
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<tr>
<td>• Low socioeconomic status</td>
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<tr>
<td>• Vegetarian diet</td>
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<tr>
<td>• Lack of balanced diet or poor intake</td>
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<tr>
<td>• Alcoholism</td>
<td></td>
</tr>
<tr>
<td>• Elderly</td>
<td></td>
</tr>
<tr>
<td>• High risk ethnic groups (<em>First Nations, Indo-Canadians</em>)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased Loss</th>
<th>Decreased Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Menorrhagia</td>
<td></td>
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<tr>
<td>• GI bleeding</td>
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<td>• Regular blood donors</td>
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<tr>
<td>• Post-operative patients with significant blood loss</td>
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<tr>
<td>• Hematuria</td>
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<tr>
<td>• Intestinal parasites (travel or immigration from an endemic area)</td>
<td></td>
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<tr>
<td>• Hemolytic anemias</td>
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<tr>
<td>• Extreme physical exercise (endurance athletes)</td>
<td></td>
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<tr>
<td>• Dietary factors (<em>tannins, phytates in fibre, calcium in milk, tea, coffee, carbonated drinks</em>)</td>
<td></td>
</tr>
<tr>
<td>• Upper GI Pathology: • Chronic gastritis</td>
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<tr>
<td>• Gastric lymphoma</td>
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<tr>
<td>• Celiac disease</td>
<td></td>
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<td>• Crohn’s disease</td>
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<tr>
<td>• Medications that decrease gastric acidity or bind iron</td>
<td></td>
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<tr>
<td>• Gastrectomy or intestinal bypass</td>
<td></td>
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<tr>
<td>• Duodenal pathology</td>
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<tr>
<td>• Chronic renal failure</td>
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</tbody>
</table>
10.17 Hookworm infection is the most common cause of iron-deficiency anaemia worldwide. The worms are seen attached by their buccal capsules to the villi of the small intestine, where they feed by sucking blood (up to 0.2 ml per day per worm). In gross hookworm infection, severe iron-deficiency anaemia may result.
Iron exchange

Figure 1. Distribution of Iron in Adults. In the balanced state, 1 to 2 mg of iron enters and leaves the body each day. Dietary iron is absorbed by duodenal enterocytes. It circulates in plasma bound to transferrin. Most of the iron in the body is incorporated into hemoglobin in erythroid precursors and mature red cells. Approximately 10 to 15 percent is present in muscle fibers (in myoglobin) and other tissues (in enzymes and cytochromes). Iron is stored in parenchymal cells of the liver and reticuloendothelial macrophages. These macrophages provide most of the usable iron by degrading hemoglobin in senescent erythrocytes and reloading ferric iron onto transferrin for delivery to cells.
Iron balance

- Iron enters the body by absorption from dietary sources in the duodenum. Iron circulates bound to transferrin and is delivered primarily to the bone marrow for erythropoiesis. Senescent erythrocytes are phagocytosed by reticuloendothelial macrophages to recycle iron back into the circulation. Iron storage and release also occur in hepatocytes. Sloughing of enterocytes and bleeding are the only significant means for removing iron from the body. On average, approximately 1-2 mg of iron is provided on a daily basis by intestinal absorption, and this is balanced by an equal amount of iron loss by epithelial shedding in the gastrointestinal tract and blood loss in menstruating women. Most of the iron required for erythropoiesis, approximately 20-25 mg/d, is provided by iron recycling from senescent erythrocytes. The circulation pool of transferrin-bound iron is much smaller, approximately 3 mg, and therefore must be turned over every few hours to ensure an adequate supply of iron for erythropoiesis.
Intestinal iron absorption

- An individual enterocyte is depicted.
- Dietary non-heme iron (Fe\(^{3+}\)) must be reduced for transport across the apical brush border. DMT1 mediates proton-dependent Fe\(^{2+}\) import.
- Dietary heme iron is transported by HCP1.
- Once inside the cell, heme oxygenase releases iron from protoporphyrin, presumably allowing it to enter the same pool as non-heme iron.
- Some iron is used or stored within the enterocyte in ferritin, and is later lost when the intestinal mucosa is sloughed.
- Some iron is exported across the basolateral membrane by ferroportin and oxidized to Fe\(^{3+}\) for incorporation into serum transferrin.
The Transferrin Cycle

- The liver synthesizes transferrin and secretes it into the plasma. Transferrins are produced locally in the testes and CNS. These two sites are relatively inaccessible to proteins in the general circulation (blood:testis barrier, blood:brain barrier).
- When not bound to iron, it is known as "apotransferrin".
- Each transferrin molecule has the ability to carry two iron ions in the ferric form (Fe3+).
- A transferrin binds to a transferrin receptor on the surface of a cell (e.g., to erythroid precursors in the bone marrow). Then it is transported into the cell in a vesicle by receptor-mediated endocytosis. The pH of the vesicle is reduced by hydrogen ion pumps (H+ ATPases) to about 5.5, causing transferrin to release its iron ions. The receptor (with its ligand, transferrin, bound) is then transported through the endocytic cycle back to the cell surface, ready for another round of iron uptake.
Ferritin

- Ferritin is a globular protein complex consisting of 24 protein subunits and is the primary intracellular iron-storage protein, keeping iron in a soluble and non-toxic form.
- Ferritin that is not combined with iron is called apoferritin.
- Each ferritin complex can store about 4500 iron (Fe3+) ions.
- The heavy chain of Ferritin also possesses ferroxidase activity, this involves the conversion of iron from the ferrous (Fe2+) to ferric (Fe 3+) forms. This limits the deleterious reaction which occurs between ferrous iron and hydrogen peroxide known as the Fenton reaction which produces the highly damaging hydroxyl radical.
Protective compensatory mechanism in chronic hypoxia

There are several protective compensatory mechanism in chronic hypoxia followed by IDA:

1. Activation of the protein complex - hypoxia-inducible factor 1 (HIF-1), which provides a physiological compensatory response to hypoxic stress by regulating the synthesis of erythropoietin, transferrin, and vascular endothelial growth factor, and the optimization of oxidative phosphorylation in the mitochondria.

2. Activation of chemoreceptors and sympathetic-dependent vasoconstriction. Hypoxemia causes activation of chemoreceptors of carotid sinus, which in turn reflexively activate sympathetic-adrenal system. This leads to the release of catecholamines and arteriolar narrowing the skin, mucous membranes, muscles, abdomen and kidneys in order to reallocate tissue perfusion from "no" vital to vital organs (brain, heart).

3. Increase cardiac output by increasing stroke output and increase in heart rate. This explains the often observed in IDA tachycardia. Initial oxygen starvation and an additional increase in oxygen demand of the heart with tachycardia provoke exacerbation of chronic heart disease, up to anginal attacks.
Effects of Hypoxia

(hi-pok´se-ah)

A condition in which the body as a whole or a region of the body is deprived of adequate oxygen supply.

Low oxygen pressure at high altitude

The **carotid body**, a cluster of specialized cells in the carotid artery, detects low oxygen levels in the blood and alerts the brain.

In response, the **brain** sends signals to the rest of the body to:

- Increase breathing rate and constrict vessels in the **lung**
- Increase **heart** rate
- Dilate **peripheral blood vessels** in arms, legs, hands, and feet
Consequences of hypoxia

Variety of metabolic disorders during hypoxia reduces to the basic pathogenic mechanisms such as:

• Decrease of ATP synthesis as a result of failure of oxidative phosphorylation in the mitochondria.

• As a result of deficit of ATP violation of all energy-dependent cellular processes take place: synthesis of proteins, lipids, nucleic acids, the work of membrane ion channels, antioxidant protection.

• Hypoxia is always accompanied by acidosis (due to the accumulation of lactic acid, pyruvate, etc.), which itself aggravates hypoxia - a vicious cycle develops.
Clinical picture of ID and IDA

- Sideropenic syndrome
- Anemic syndrome
Anemic syndrome

Three pathogenetic mechanisms contribute to the anemic syndrome:

1. **Hemic hypoxia**: refers to the decrease in amount of Hb in the blood.

2. **Tissue hypoxia** which is the reduction of oxygen supply to a tissue below physiological levels despite adequate perfusion of the tissue by blood.

3. **Decreased viscosity of blood** (systolic murmur at the apex and noise in the jugular veins)
# Symptoms of anemic syndrome

<table>
<thead>
<tr>
<th>Organs and systems</th>
<th>Hemic hypoxia</th>
<th>Tissue hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory system</strong></td>
<td>• Dyspnea</td>
<td>Dyspnea</td>
</tr>
<tr>
<td><strong>Cardiovascular system</strong></td>
<td>-</td>
<td>• Heart pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Palpitations</td>
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<tr>
<td></td>
<td></td>
<td>• Heart failure</td>
</tr>
<tr>
<td><strong>Central and peripheral nervous system</strong></td>
<td>-</td>
<td>• Feeling of lack of air, especially in unventilated areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Headaches</td>
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<tr>
<td></td>
<td></td>
<td>• Daytime sleepiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>• Fainting</td>
</tr>
<tr>
<td><strong>Skin and mucous layers</strong></td>
<td>• Pallor</td>
<td>• Hypersensitivity to cold</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chilliness</td>
</tr>
<tr>
<td><strong>Skeletal muscles</strong></td>
<td>-</td>
<td>• Weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fatigue during exercise</td>
</tr>
</tbody>
</table>
Conjunctival pallor

Due to vasoconstriction of the arterioles of the skin and mucous membranes, a pallor of skin, palmar creases and conjunctiva appears.

Pale conjunctiva. Note that the color of the pale anterior rim and the posterior part of the conjunctiva are the same.

Normal conjunctiva. Note the full redness of the anterior rim and its dissimilarity to the posterior aspect of the conjunctiva.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1497067/figure/fig2/
Sideropenic syndrome

Sideropenic syndrome is caused by reduction in the synthesis of iron-containing proteins (hemoglobin, myoglobin, ferritin, hemosiderin, etc.) and decreased activity of iron-containing enzymes (cytochrome c reductase, succinate dehydrogenase, myeloperoxidase, etc.). This results in a dystrophic and atrophic processes followed in almost all cells.

The symptoms are:

• Symptoms of lesion of rapidly dividing cells: mucous membranes, skin and bone marrow
• Pica chlorotica
• Sideropenic dysphagia or Plummer-Vinson syndrome
• Sideropenic fever (some patients have long-term temperature increase to subfebrile values)
• Central and peripheral nervous systems symptoms such as irritability, poor memory, poor concentration, intolerance to areas with limited air circulation, restless leg syndrome.
• Deep iron deficiency may be accompanied by muscle atrophy, decreased muscle strength, hypotension, sphincter deficiency (frequent urge to urinate, nocturnal enuresis, urinary incontinence when laughing or coughing).
### Symptoms of sideropenic syndrome

#### Symptoms of lesion of rapidly dividing cells

<table>
<thead>
<tr>
<th>The epithelium of the skin and skin appendages</th>
<th>The epithelium of lining mucosa</th>
<th>Bone marrow cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dry, exfoliating, itchy skin • Tendency to cracked skin • Poorly healing wounds and injuries • Angular stomatitis - inflammation in the corners of the mouth • Fragility, loss, early graying of hair • Thinning, brittle, dull nails, koilonychia</td>
<td>• Sideropenic dysphagia or Plummer-Vinson syndrome • Atrophic glossitis • Atrophic gastritis • Atrophic rhinitis • Atrophy of the intestinal mucosa</td>
<td>• Decreasing the amount of hemoglobin in red blood cells • Decreasing the amount of red blood cells • Reduction of the phagocytic activity of neutrophils • Reduce the number of T-lymphocytes and/or reduction of their function</td>
</tr>
</tbody>
</table>
Symptoms of sideropenic syndrome

Pica chlorotica

- Taste perversion or pica chlorotica characterized by an overwhelming desire to eat inedible (chalk, clay, sand, ice, salt, etc.).
- Manifestations of the syndrome also include sideropenic perversion of the sense of smell - addiction to smells, which by most others are perceived as unpleasant (gasoline, kerosene, acetone, dyes, shoe polish, naphthalene, etc.).
- The term «pica» comes from the Latin «pica» - magpie - a bird known for its indiscriminate eating habits. It is believed that the term was first introduced Byzantine physician Etius of Amide in the 6th century AD, in his textbook on obstetrics. Etius said: "At about the second month of pregnancy, there is a disorder called Pica, and derived from the names of magpie ... Women want different: some spicy foods, other – salty."
- One should note that pica in most cases is a manifestation of iron deficiency, but sometimes it is a manifestation of zinc deficiency or mental disorders.
Plummer-Vinson syndrome

Sideropenic dysphagia

The syndrome is associated with:

• Dysphagia (difficulty swallowing), due to upper esophageal webs
• Iron deficiency anemia that is not associated with anemia.

The presence of mucous membranes and webs in the upper third of the esophagus.
Angular cheilitis
(synonyms: angular stomatitis, bridou)

Angular cheilitis is an inflammatory lesion at the labial commissure, or corner of the mouth, and often occurs bilaterally. The condition manifests as deep cracks or splits.

http://sdk-center.ru/lechenie_stomatita.html
Cheilitis

Cheilitis is a medical condition involving inflammation of the lip.

Sideropenic glossitis

Glossitis is inflammation of the tongue

http://flipper.diff.org/app/items/info/1626
Koilonychia

Koilonychia, also known as "spoon nails", is a nail disease that can be a sign of hypochromic anemia, especially iron-deficiency anemia. It refers to abnormally thin nails (usually of the hand) which have lost their convexity, becoming flat or even concave in shape.

http://mrishaanshareef.blogspot.com/2008/10/finger-nails-to-predict-health.html
Koilonychia
Sideropenic skin changes
Poorly healing wounds and injuries
Sideropenic skin changes
Dry, exfoliating, itchy skin
# Diagnostics

## Stages of Iron Deficiency

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Laboratory findings</th>
</tr>
</thead>
</table>
| Stage 1  
Pre-latent iron deficiency  
Depleted iron stores | There are depleted iron stores but increased iron absorption and normal serum iron and capacity to bind iron and transport in around the body. | • Low ferritin  
• Depletion of bone marrow iron |
| Stage 2  
Latent iron deficiency | There are decreased iron serum levels and there is an increase in the capacity of binding and transporting iron. | • Low transferrin saturation  
• Low serum iron  
• Raised serum transferrin  
• Normal haemoglobin |
| Stage 3  
Iron deficiency anemia  
Features of stages 1+stages 2+anemia | Features of stages 1+stages 2+anemia | • Low haemoglobin |
# Pre-latent iron deficiency laboratory markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>Quantitative, well standardized</td>
<td>Affected by inflammation, liver disease</td>
<td>45-340 ng/mL</td>
</tr>
<tr>
<td>Bone-marrow iron</td>
<td>Well established, high specificity</td>
<td>Affected by EPO treatment, invasive, expensive</td>
<td></td>
</tr>
</tbody>
</table>
Examination of bone marrow

- The examination of Prussian blue–stained bone marrow aspirate for the presence or absence of histiocytic iron granules has been considered the “gold standard”
- Iron appears as variously sized intracellular blue granules or wispy amorphous intracellular deposits. The complete absence of staining is considered to represent iron deficiency.

There is no stainable iron. The specimen is diffusely pale red/pink, which is the color of the counterstain on this slide.


Normal iron stores are seen as dark blue-staining material in the bone marrow.

# Latent iron deficiency laboratory markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Changes in ID</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble transferrin receptor (sTfR), serum</td>
<td>Increase</td>
<td>Quantitative (tissue deficiency) unaffected by inflammation</td>
<td>Patients with hemolysis or recent blood loss may have falsely elevated sTfR levels</td>
<td>1.8 – 4.6 mg/L</td>
</tr>
<tr>
<td>Transferrin, serum</td>
<td>Increase due to an increase in synthesis.</td>
<td></td>
<td>High levels can be seen in pregnancy and during estrogen administration.</td>
<td>200-400 mg/dL</td>
</tr>
<tr>
<td>Transferrin Saturation</td>
<td>Decrease less than 20%</td>
<td>Inexpensive Well established</td>
<td>Wide diurnal variation, Low specificity</td>
<td>Transferrin is 20-45% saturated with iron.</td>
</tr>
<tr>
<td>Serum iron (should always be interpreted in the context of other markers of ID)</td>
<td>Decrease</td>
<td></td>
<td>Serum iron alone is unreliable due to physiologic diurnal variations</td>
<td>50-150 ug/dL</td>
</tr>
</tbody>
</table>
## Iron deficiency anemia laboratory markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Changes in ID</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte count</td>
<td>Decrease</td>
<td>3.8-5.2 x 10¹² /liter (female)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4-5.9 x 10¹² /liter (male)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Decrease</td>
<td>12-140 g/dL (female)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>130-150 g/dL (male)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Decrease</td>
<td>36-45% (female)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42-50% (male)</td>
</tr>
<tr>
<td>Mean Cell Volume (MCV)</td>
<td>Decrease Microcytosis</td>
<td>80-100 femtoliters (fl)</td>
</tr>
<tr>
<td>Mean cell hemoglobin (MCH)</td>
<td>Decrease Hypochromic</td>
<td>27 to 31 picograms/cell</td>
</tr>
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<td>(MCH) is the average mass of</td>
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<tr>
<td>hemoglobin per red blood cell</td>
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</tbody>
</table>
Peripheral blood smear in iron-deficiency anemia

Microcytosis with hypochromasia (100× oil). Hypochromic and microcytic red blood cells are seen with occasional target cells. The small, mature lymphocyte can be used to size the red blood cells. Many of the red blood cells have increased central pallor (hypochromia).
## Hemoglobin levels

Haemoglobin levels to diagnose anaemia at sea level (g/l) (WHO 2010)

<table>
<thead>
<tr>
<th>Population</th>
<th>Non-Anaemia*</th>
<th>Anaemia*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild(^2)</td>
</tr>
<tr>
<td>Children 6 - 59 months of age</td>
<td>110 or higher</td>
<td>100-109</td>
</tr>
<tr>
<td>Children 5 - 11 years of age</td>
<td>115 or higher</td>
<td>110-114</td>
</tr>
<tr>
<td>Children 12 - 14 years of age</td>
<td>120 or higher</td>
<td>110-119</td>
</tr>
<tr>
<td>Non-pregnant women (15 years of age and above)</td>
<td>120 or higher</td>
<td>110-119</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>110 or higher</td>
<td>100-109</td>
</tr>
<tr>
<td>Men (15 years of age and above)</td>
<td>130 or higher</td>
<td>110-129</td>
</tr>
</tbody>
</table>
Revised Hemoglobin levels

In 2006, Ernest Beutler and Jill Waalen criticized existing since 1968 the lower limit of normal hemoglobin for women and men, proposed by WHO. Based on the research database the third revision of the National Register of Health, USA (NHANES-III) and its own database Scripps-Kaiser, gathered in San Diego from 1998 to 2002, they have proposed new lower limits of hemoglobin for adults of different by sex and race.

Proposed lower limits of normal for hemoglobin concentration of the blood for white and black adults

<table>
<thead>
<tr>
<th>Group</th>
<th>Hemoglobin, g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White men, y</strong></td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>137</td>
</tr>
<tr>
<td>60+</td>
<td>132</td>
</tr>
<tr>
<td><strong>White women, y</strong></td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>122</td>
</tr>
<tr>
<td>50+</td>
<td>122</td>
</tr>
<tr>
<td><strong>Black men, y</strong></td>
<td></td>
</tr>
<tr>
<td>20-59</td>
<td>129</td>
</tr>
<tr>
<td>60+</td>
<td>127</td>
</tr>
<tr>
<td><strong>Black women, y</strong></td>
<td></td>
</tr>
<tr>
<td>20-49</td>
<td>115</td>
</tr>
<tr>
<td>50+</td>
<td>115</td>
</tr>
</tbody>
</table>
Management of iron deficiency

Three main strategies can be applied in order to improve iron status in individuals and populations:

- Dietary modification
- Food fortification
- Iron supplementation
Determine and treat underlying cause

"I can't believe this! You're low in iron."
Dietary modification

- Dietary iron sources include meat, fish and poultry, lentils, dried beans, grain products, vegetables, dried fruit, and molasses.

**Dietary Factors That Enhance and Inhibit Iron Absorption**

**Enhance:**
- Gastric acid
- Ascorbic acid
- Malic acid
- Citric acid

**Inhibit:**
- Phosphate
- Calcium
- Tea (tannic acid)
- Coffee
- Colas
- Soy protein
- High doses of minerals
- Bran/fiber
Oral iron medicines representing different iron salts

Percentage and amount of iron in some commonly used oral iron preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Iron compound (mg/tab)</th>
<th>Elemental iron mg/tab (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-sulfate(hydrous)</td>
<td>300</td>
<td>60 (20%)</td>
</tr>
<tr>
<td>Fe-sulfate(dried)</td>
<td>200</td>
<td>65 (32.5%)</td>
</tr>
<tr>
<td>Fe-fumarate</td>
<td>200</td>
<td>66 (33%)</td>
</tr>
<tr>
<td>Fe-gluconate</td>
<td>300</td>
<td>36 (12%)</td>
</tr>
<tr>
<td>Fe-succinate</td>
<td>100</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>Fe-bisglycinate</td>
<td>300</td>
<td>60 (20%)</td>
</tr>
<tr>
<td>Carbonyl iron</td>
<td>100</td>
<td>98 (98%)</td>
</tr>
<tr>
<td>Na-feredetate</td>
<td>231</td>
<td>33 (14%)</td>
</tr>
</tbody>
</table>
Side-effects after oral iron intake

• The oral administration of iron can cause gastrointestinal side-effects in some individuals such as epigastric discomfort, nausea, vomiting, constipation, and diarrhea.
• The frequency of these side-effects is directly related to the dose of iron or % of elemental iron in tablet.
• In addition, iron consumed with a meal is better tolerated than when it is taken on an empty stomach, although the amount of iron absorbed is reduced.
• Also blackening of teeth and faeces may occur due to formation of iron sulfide and metallic taste.
## Doses of oral iron supplements for the treatment of IDA (WHO)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment (daily dose, mg)</th>
<th>Prophylaxis (daily dose, mg)</th>
<th>Duration /months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>120</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>Pregnant</td>
<td>120</td>
<td>60</td>
<td>3</td>
</tr>
</tbody>
</table>
Iron poisoning

• After aspirin, the second commonest cause of accidental poisoning among small children is iron.

• Most deaths occur in children, particularly 12 to 14 months. As little as 1 to 2 gm of iron may cause death.

• The colored sugar coating of many commercially available tablets may attract the child and he may consume them.

http://www.ijmps.com/files/documents/2.3.2.pdf
Parenteral iron therapy

• Parenteral medicines contain only trivalent iron.
• Indication for parenteral iron medicines are:
  1. intolerance to oral iron preparations
  2. severe iron deficiency where a rapid therapeutic effect is needed
  3. functional iron deficiency where the iron demand for haemoglobin synthesis exceeds the amount that can be mobilised from filled iron stores, e.g.
  4. anaemia of inflammation
  5. iron deficiency, where oral iron therapy is insufficient because of chronic blood loss
  6. malabsorption of iron due to intestinal disorders
  7. poor compliance to oral iron treatment
  8. risk of drug-drug interactions between
  9. oral iron and concomitant medication.
There are three parenteral iron products:

1. Iron dextran (Cosmofer, DexFerrum, Infed). A notable side effect is allergic reaction, which occurs in less than 1 on 100 treated patients, but may cause severe, sometimes fatal, complications, including loss of consciousness, collapse, difficulty breathing, hives, swelling, convulsions and severe low blood pressure (hypotension).

2. Iron sucrose (Venofer) has an occurrence of allergic reactions of less than 1 in 1000. A common side effect is taste changes, especially a metallic taste. Doses can be given up to 3 times a week.

3. Iron carboxymaltose (trade name Ferinject) is a newer formulation of parenteral iron which is dextran free with the shell being fully metabolised in the body to simple sugars. The most common side effect are headaches which occur in 3.3%. It can be given over 15 minutes in doses up to 1,000 mg and has been adopted in many hospitals due to the increased number of patients that can be treated as no test dose is required and the patient does not need to be monitored after a dose has been administered.

• Parenteral iron causes the same therapeutic response as oral iron but can cause adverse effects, such as anaphylactoid reactions, serum sickness, thrombophlebitis and pain.
Transfusion

• Blood transfusions are helpful in the context of life threatening anaemia with haemoglobin level less than 50 g/dl.

• The repeated use of blood transfusions needs a careful appraisal. Iron overload, immune modulation and sensitization to HLA antigens may occur. 6
Prognosis

• Prediction of iron deficiency and IDA depends on the cause. If iron deficiency and IDA are caused by alimentary deficiency - the prognosis is favorable, ie with adequate compensation for iron, a complete recovery.

• However, the prognosis is poor, if the IDA is due to an untreated disease such as gastrointestinal tumors.

• When iron deficiency and IDA occur in the fetus and young children then the prognosis is poor - there are intrauterine growth retardation, delayed neuro-psychological and physical development in young children.

• Chronic IDA is rarely the cause of death, but severe hypoxia may aggravate concomitant pulmonary or cardiac disease.

• Very rarely severe anemia causes anemic coma, when patients refuse from blood transfusions for religious reasons.
Prevention

• Prevention of IDA is divided into primary and secondary.
• **Primary prevention** - is iron intake by persons at risk in order to prevent the development of IDA.
• **Secondary prevention** - is iron intake by persons with IDA and persons with irremovable cause of IDA, in order to prevent recurrence of IDA.
Anemia of chronic disease
Definition

• Anaemia of chronic disease (ACD) is the second most prevalent after anaemia by iron deficiency.
• It is characterized by inadequate erythrocyte production in the setting of low serum iron, low iron binding capacity, low transferrin, but normal or high serum ferritin with a preserved or even increased macrophage iron stores in the bone marrow.
• The erythrocytes are usually normocytic and normochromic, but long standing anaemia can give rise to microcytic and hypochromic blood picture.
Causes of anaemia of chronic disease

**Infections:**
- Tuberculosis
- Viral infections including human immunodeficiency
- viruses infection
- Bacterial
- Parasitic
- Fungal

**Cancer**
- Haematologic
- Solid tumours

**Autoimmune**
- Rheumatoid arthritis
- Systemic lupus erythematosus
- and connective tissue disorders
- Vasculitis
- Sarcoidosis
- Inflammatory bowel disease

**Chronic renal disease and inflammation**

**Miscellaneous**
- Chronic rejection after solid – organ transplantation
Pathogenesis

• A hallmark of anaemia of chronic disorder is an increased uptake and retention of iron within cells of the reticuloendothelial system.

• This leads to subsequent limitation of the availability of iron for erythroid cells, and iron-restricted erythropoiesis.
Cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels: (A) Induction of hepcidin synthesis in the liver (especially by interleukin-6 [IL-6]). (B) Inhibition of erythropoietin release from the kidney (especially by interleukin-1β [IL-1β] and tumour necrosis factor α [TNFα]). (C) Direct inhibition of the proliferation of erythroid progenitors. (D) Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNFα).
Pathogenesis

A proposed mechanism for the anemia of chronic disease (ACD) is shown here. In the presence of infection, inflammation, or malignancy, the macrophage is stimulated to produce Interleukin-6 (IL-6), which induces the production of hepcidin by the liver. Hepcidin, in turn, through its interaction with the iron export protein ferroportin, inhibits iron absorption from the gastrointestinal tract and decreases release of iron from macrophages. Both effects lead to the reduced plasma iron levels (hypoferremia) characteristic of ACD.
Protective mechanism of ACD

• Iron is an essential nutrient for proliferating microorganisms, and the sequestration of iron from microorganisms or tumour cells into the reticuloendothelial system is believed to be a potentially effective defense strategy to inhibit the growth of pathogen.
Clinical manifestation

• Most often the sign and symptoms seen in patients with ACD are referable to the underlying disease.

• Common symptoms elicited from the history include weight loss, anorexia, fever, chills, myalgias and arthralgias.

• The anaemia usually occurs insidiously over a period of approximately 3 to 4 weeks and thereafter remains stable or unchanged.
Laboratory Evaluation

- ACD is a normochromic, normocytic anaemia that is characteristically mild (haemoglobin level, 9.5 g per deciliter) to moderate (haemoglobin level, 8 g per deciliter). Hematocrit: 28 ~ 32%.
- ↓ Iron (hypoferremia)
- ↓ Iron-binding capacity
- ↓ Transferrin saturation
- ↑ Ferritin
- ↓ soluble transferrin receptor conc.
- ↑ Hemosiderin within macrophages
Table 1: Differentiation Between Anemia of Chronic Disease and Iron-Deficiency Anemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anemia of Chronic Disease</th>
<th>Iron Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Transferrin</td>
<td>Reduced to normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Normal to increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>Soluble transferrin receptor</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Ratio of soluble transferrin receptor to log ferritin</td>
<td>Low (&lt;1)</td>
<td>High (&gt;2)</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Treatment

- Iron therapy: does not correct the anemia!
- Recognition and correction of underlying disorders!
- Erythropoietin administration. Purified recombinant erythropoietin (epoetin alfa) is effective for treatment of the anemia of renal failure and other secondary anemias such as anemia related to cancer or inflammatory disorders (eg, rheumatoid arthritis).
Vitamin B 12 deficiency anemia
Epidemiology

• The prevalence of pernicious anemia ranges from 50 to 4000 cases per 100,000 persons, depending on the diagnostic criteria.

• All age groups are affected, but the median age range in large series is 70 to 80 years.

• Pernicious anemia is more common in persons of African or European ancestry.
Pernicious anemia

• Pernicious anemia is an autoimmune gastritis resulting from the destruction of gastric parietal cells and the associated lack of intrinsic factor to bind ingested vitamin B12. The immune response is directed against the gastric H/K–ATPase, which accounts for associated achlorhydria.
Causes B12 deficiency

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malabsorption</td>
</tr>
<tr>
<td>Pernicious anemia (autoimmune gastritis)</td>
</tr>
<tr>
<td>Total or partial gastrectomy</td>
</tr>
<tr>
<td>Gastric bypass or other bariatric surgery</td>
</tr>
<tr>
<td>Ileal resection or organ reconstructive surgery (ileal conduit diversion and ileocystoplasty)</td>
</tr>
<tr>
<td>Inflammatory bowel disease, tropical sprue</td>
</tr>
<tr>
<td>Imerslund–Gräsbeck and other syndromes‡</td>
</tr>
</tbody>
</table>

| Mild malabsorption                         |
| Protein-bound vitamin B₁₂ malabsorption   |
| Mild atrophic gastritis                    |
| Use of metformin¹⁴                         |
| Use of drugs that block stomach acid      |

| Dietary deficiency                        |
| Adults                                    |
| Vegan or vegetarian diet, or diet low in meat and dairy products |
| Infants                                   |
| Breast-feeding in infants with vitamin B₁₂—deficient mothers¹⁵,¹⁶ |
Sources of vitamin B12

- Vitamin B12 is produced by soil microbes that live in symbiotic relationships with plant roots.
- Vitamin B12 is found only in foods of animal origin in meat, liver, kidney, eggs, cheese, milk.
- B12 in human milk is contained in the form of methylcobalamin (the main form of the vitamin in the body).

Vitamin B12 contains cobalt in its structure and a cyano group, each together forming a cyanocobalamin. The human body does not synthesize B12.
Body`s demands for vitamin B

• The daily requirement of vitamin B12 has been set at 2.4 μg
• Total stores of B12 in the adult human body is about 2-5 mg.
• Stores B12 in the body are large, so that the deficit occurs only after 5-6 years after decrease of intake
• The daily intake is about 9.6 mg
• The daily output is about 2.5 mg with urine and feces.
• Principal place of deposit of vitamin B12 is the liver. Large amount is absorbed as the spleen and kidney, somewhat less - muscles.
**Actions of cobalamin**  Role of cobalamin in homocysteine and methylmalonic acid metabolism. Panel A – Methylcobalamin is a cofactor in the synthesis of methionine from homocysteine. Panel B – Adenosylcobalamin is a cofactor in the synthesis of succinyl-CoA from methylmalonyl-CoA. Tetrahydrofolate (THF) participates in homocysteine but not methylmalonic acid (MMA) metabolism. Thus, cobalamin deficiency is characterized by elevations in the serum levels of both homocysteine and MMA, while only homocysteine levels are elevated in folate deficiency.

Methylmalonic acid

• Patients with cobalamin deficiency have increased concentrations of MMA in their serum (S-MMA) because 5’-deoxyadenosylcobalamin is required for the enzymatic conversion of L-methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase.

• An increased concentration of MMA in serum and its excessive urinary excretion are believed to be direct measures of tissue stores of cobalamin and thus provide an indication of functional cobalamin deficiency.
Absorption of Vitamin B12

– Dietary B-12 binds to haptocorrin (HC) (R factor) in saliva and gastric juices.
– Haptocorrin is produced by the salivary glands of the oral cavity, in response to ingestion of food.
– The essential function of haptocorrin is protection of the acid-sensitive vitamin B12 while it moves through the stomach.
– In duodenum, pancreatic enzymes promote dissociation from HC to bind to Intrinsic Factor (IF).
– IF-B12 complex taken up by ileal receptor cubilin.
– Released into plasma bound to transcobalamines TC I, II, III and haptocorrin.
– Haptocorrin binds approximately 80% of circulating B12, rendering it unavailable for cellular delivery by Transcobalamin II.
Absorption of Vitamin B12
Clinical signs

The Triad:

1. Blood disturbances
2. Gastrointestinal lesions
3. Damage of CNS and PNS
Optic atrophy, anosmia, loss of taste, glossitis

Abnormalities in infants and children
- Developmental delay or regression, permanent disability
- Does not smile
- Feeding difficulties
- Hypotonia, lethargy, coma
- Hyperirritability, convulsions, tremors, myoclonus
- Microcephaly
- Choreoathetoid movements

Infertility

Peripheral blood
- Macrocytic red cells, macroovalocytes
- Anisocytosis, fragmented forms
- Hypersegmented neutrophils, 1% with six lobes or 5% with 5 lobes
- Leukopenia, possible immature white cells
- Thrombocytopenia
- Pancytopenia
- Elevated lactate dehydrogenase level (extremes possible)
- Elevated indirect bilirubin and aspartate aminotransferase levels
- Decreased haptoglobin level
- Elevated levels of methylmalonic acid, homocysteine, or both

Spinal cord
- Myelopathy
- Spongy degeneration

Paresthesias
- Loss of proprioception: vibration, position, ataxic gait, limb weakness; spasticity (hyperreflexia); positive Romberg sign; Lhermitte's sign; segmental cutaneous sensory level

Autonomic nervous system
- Postural hypotension
- Incontinence
- Impotence

Peripheral nervous system
- Cutaneous sensory loss
- Hyporeflexia
- Symmetric weakness
- Paresthesias

Bone marrow
- Hypercellular, increased erythroid precursors
- Open, immature nuclear chromatin
- Dyssynchrony between maturation of cytoplasm and nuclei
- Giant bands, metamethylocytes
- Karyorrhexis, dysplasia
- Abnormal results on flow cytometry and cytogenetic analysis

Brain
- Altered mental status
- Cognitive defects
- "Megaloblastic madness": depression, mania, irritability, paranoia, delusions, lability
Diagnostics
Changes in blood

1. Reduction in the number of erythrocytes and decrease of hemoglobin level
2. Prevalence of macrocytes (diameter $> 8$ mcm, MCV $> 100$ fl) and megalocytes (diameter of 10 to 12 mcm) in blood smear
3. The increase in color index greater than 1.0 (hyperchromic RBC, MCH $> 34$ pg).
4. Cabot rings and Howell–Jolly bodies
5. Anisocytosis, poikilocytosis
6. Large number of makroovalocytes.
7. Reduced number of reticulocytes
8. Leukopenia
9. Neutropenia with a shift to the right (presence of overmature hypersegmented neutrophils $> 5\%$)
10. Eosinopenia
11. Monotsitopeniya and relative lymphocytosis
12. Thrombocytopenia
Cabot rings and Howell–Jolly bodies

• **Cabot rings** are thin, red-violet staining, threadlike strands in the shape of a loop or figure-8 that are found on rare occasions in erythrocytes.
• **Howell–Jolly bodies** are histopathological findings of basophilic nuclear remnants (clusters of DNA) in circulating erythrocytes.
Hypersegmented neutrophil
Hypersegmented neutrophil

**Megaloblastic blood picture**  Peripheral blood smear showing a hypersegmented neutrophil (7 lobes) and macroovalocytes, a pattern that can be seen with cobalamin or folate deficiency. Courtesy of Stanley L Schrier, MD.
Macro-ovalocytes, basophilic stippling, and bizarre-shaped red cell forms

Vitamin B12 deficiency. (Peripheral blood, 100 x.) Shown are several hallmark features of vitamin B12 deficiency, including macro-ovalocytes, basophilic stippling, and bizarre-shaped red cell forms. (Courtesy of L Damon.)
Macroovalocytosis

Peripheral smear shows marked macroovalocytosis in a patient with vitamin B12 deficiency. Courtesy of Stanley L Schrier, MD.
Megaloblastic erythropoiesis

Comparison of normal and megaloblastic erythropoiesis with respect to erythroid precursors in the bone marrow. Left panel: Normal erythropoiesis. Right panel: Megaloblastic erythropoiesis. Courtesy of Stanley L Schrier, MD.
## Laboratory confirmation of diagnosis

<table>
<thead>
<tr>
<th>Marker</th>
<th>B12-anemia</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vitamin B12</td>
<td>&lt; 200 pg/ml</td>
<td>200-900 pg/ml</td>
</tr>
<tr>
<td>Serum methylmalonic acid</td>
<td>&gt;0.75 µmol/l</td>
<td>0.07 - 0.27 µmol/l</td>
</tr>
<tr>
<td>Serum or plasma total homocysteine</td>
<td>&gt;21 µmol/liter</td>
<td>2.2 - 13.2 µmol/l</td>
</tr>
</tbody>
</table>
### Tests to determine cause of deficiency

<table>
<thead>
<tr>
<th>Marker</th>
<th>B12-anemia</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti–intrinsic factor antibodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Anti–parietal-cell antibodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Fasting high serum gastrin level</td>
<td>&gt;100 pmol/liter</td>
<td></td>
</tr>
<tr>
<td>Low level of serum pepsinogen I</td>
<td>&lt;30 µg/liter</td>
<td></td>
</tr>
</tbody>
</table>
**Treatment**

- **Saturation phase**: 4-6 weeks
- **Fixating phase**: 6 month
- **Maintenance phase**: lifelong

- Vitamin B12 is administered orally, intramuscularly, intravenously and intralumbarly.
- Different forms of vitamin B12 can be used, including cyano,-hydroxy,- and methylcobalamin.
Injected Vitamin B12

• About 10% of the injected dose (100 of 1000 μg) is retained.
• Patients with severe abnormalities should receive injections of 1000 μg at least several times per week for 1 to 2 weeks, then weekly until clear improvement is shown, followed by monthly injections.
High-Dose Oral Treatment

• High-dose oral treatment is effective and is increasingly popular.

• 0.5 to 4% of radioactively labeled oral vitamin B12 can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia.

• Thus, oral doses of 1000 μg deliver 5 to 40 μg, even if taken with food.
Response to treatment

• Hematologic response is rapid, with an increase in the reticulo-cyte count in 1 week and correction of megaloblastic anemia in 6 to 8 weeks.
The end