Anaemia
Learning Objectives

• After this session you should..

• Be able to define anaemia
• Know the signs and symptoms of anaemia
• Be able to classify anaemia
• Know a little about the main types of anaemia
• Know which first line investigations to order for an anaemic patient
Agenda

- Red blood cells and haemoglobin
- Definition of anaemia
- Terminology
- Causes and signs and symptoms
- Classification
- Some common anaemias
Red blood cells and haemoglobin

- Biconcave disc
- Flexible (as must be able to go through blood vessels)
- Large surface area for maximum exchange
- Life span of 120 days
- After that is phagocytosed by Reticuloendothelial System
- Haem is re-used
Haemoglobin

- Carries Oxygen and delivers it to tissues from lungs
- Made of two pairs of globin polypeptide chains
  - one pair of alpha chains
  - one pair of beta chains

- Normal adult has 97% HbA (alpha and beta), 2.5% HbA2 (alpha and delta) and 0.5% HbF (alpha and gamma)

- Contains a heme group which has an iron atom
- Oxygenation and deoxygenation of Hb occurs at the haem iron
Definition

• Reduction in Hb in the blood below the reference range for age and sex
Normal values (g/dL)

**Adult**
- Male: 13.5 – 17.7
- Female: 11.5 – 16.5
- 6 months – 6 years: < 11
- 6-14 years: < 12
Terminology

- Haemolysis
- Microcytic
- Macrocytic
- Normocytic
- Hypochromic
- Megaloblastic
## Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Haemolysis</td>
<td>accelerated red cell breakdown</td>
</tr>
<tr>
<td>Microcytic</td>
<td>small red cells, low MCV (&lt;76)</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>large red cells, high MCV (&gt;96)</td>
</tr>
<tr>
<td>Normocytic</td>
<td>normal sized red cells, normal MCV</td>
</tr>
<tr>
<td>Hypochromic</td>
<td>pale red cells</td>
</tr>
<tr>
<td>Megaloblastic</td>
<td>large red cells and white cells in bone marrow</td>
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</table>
Causes of anaemia

↓ Production of red cells
- Iron deficiency
- B12 or folate deficiency
- Marrow infiltration e.g. cancer
- Any chronic disease e.g. rheumatoid, cancer

↑ Destruction of red cells
  Haemolytic anaemia
  - Disorders of RBC membrane/enzyme/haemoglobin
  - Immune destruction

Loss of red cells (bleeding)
Signs and symptoms

- Can be asymptomatic if Hb loss is slow

Symptoms
- SoB
- Fatigue
- Faintness
- Chest pains (esp if atherosclerosis)
- Intermittent Claudication

Signs
- Tachycardia
- Flow murmur
- Pale mucous membranes
- Jaundice
- Koilonychia
## Classification

- Numerous ways e.g. acquired vs. inherited
- Probably most common is by MCV

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<thead>
<tr>
<th>Microcytic (&lt;76)</th>
<th>Normocytic</th>
<th>Macrocytic (&gt;96)</th>
</tr>
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<tbody>
<tr>
<td>Iron deficiency</td>
<td>Fresh bleed</td>
<td>B12/Folate def</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(MEGALOBLASTIC)</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Pregnancy</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>Chronic Disease</td>
<td>Liver Disease</td>
</tr>
<tr>
<td>Sideroblastic</td>
<td>Myelodysplasia</td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Haemolysis</td>
<td>Haemolysis (Reticulocytes)</td>
</tr>
<tr>
<td></td>
<td>Renal Failure</td>
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</table>
Iron deficiency anaemia

• Most common cause of anaemia in the world
• Affects 500m people worldwide
• Body finds it difficult to absorb iron
• Iron lost in haemorrhage

MAJOR CAUSES
• Blood loss (uterus or GI tract)
• Increased demand (growth/pregnancy)
• Decreased absorption
• Poor intake

• Lack of Iron leads to defective Hb synthesis
• This results in red blood cells that are small (microcytic) and have reduced Hb (hypochromic)
Iron deficiency anaemia continued

Clinical features:
• Brittle nails and hair
• Koilonychia
• Angular stomatitis
• Can be seen as part of Plummer-Vinson Syndrome: oesophageal web, iron deficiency anaemia, glossitis and angular stomatitis

Investigations
• FBC
• Blood film
• Serum Ferritin – confirms the diagnosis

Treatment
• Iron deficiency is not a diagnosis!! – need to find the cause (GI bleed?/menorrhagia?)
• Oral iron
**Anaemia of chronic disease**

**Occurs in patients with chronic disease**
- Endocarditis
- TB
- Osteomyelitis
- Crohn’s disease
- RA

- There is decreased release of iron to rbc precursors in the bone marrow, decreased erythropoiesis and decreased red blood cell survival
- Caused by inflammatory cytokines

**Bloods**
- Raised ESR (inflammation)
- Serum iron is low (amount of iron bound to transferrin)
- Ferritin is high/normal
- Total Iron Binding Capacity is low (measures blood’s capacity to bind transferrin to iron – TIBC is high in iron deficiency)
- Hepsiderin
Sideroblastic anaemia

- Can be inherited or acquired
- X-linked inheritance
- Acquired via Myeloid Leukaemia/Alcohol abuse/drugs – Isoniazid, chloramphenicol, copper deficiency
- Ineffective erythropoiesis - Deranged biosynthesis of haem within red cell precursors leading to impaired Hb production

Investigations

- **FBC:** ↓Hb, ↓ MCV
- **Blood film:** Often dimorphic: hypochromic microcytic and normochromic normocytic
- **Bone Marrow:** Excess iron and ring sideroblasts,
  - Accumulation of iron in mitochondria of erythroblasts,
  - Forming a ring of iron granules around the nucleus

Treatment

- Where cause is alcohol or drugs – withdraw these
- Pyridoxine (Vitamin B6)
- Blood transfusions (with chelation therapy) – try to keep to a minimum
Haemoglobinopathy

**Thalassemia**
- **alpha thalassemia** = \(\downarrow\) alpha globin chain production
- **beta thalassemia** = \(\downarrow\) beta globin chain production
- Results in excess of other chains being produced
- Imbalance of chains leads to ineffective erythropoiesis and haemolysis
- Can be trait (heterozygous) or major (homozygous)

**Signs & Symptoms**
- Anaemia
- Failure to thrive
- Deformities of skull and long bones (anaemia leads to increased EPO causing expansion of bone marrow)
- Splenomegaly

- Diagnosed via electrophoresis: Low HbA\(_1\), (alpha and beta chains) Increased HbA\(_2\) (alpha and delta chains) and increased fetal Hb (alpha and gamma chains)
Thalassemia cont’d

Trait
• Mild/absent anaemia (as still making some beta globin chains)
• Low MCV
• Increased HbA2 on electrophoresis
• Often asymptomatic

Thalassemia major
• Severe anaemia
• Low MCV
• No HbA on electrophoresis, only HbA2 and HbF

Treatment
• Blood transfusions for life (+chelation therapy)
• Splenectomy
• Bone marrow transplant
# Microcytic anaemias

<table>
<thead>
<tr>
<th></th>
<th>Iron</th>
<th>Ferritin</th>
<th>TIBC</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron defn</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>ESR ↑</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic</td>
<td>High</td>
<td>High</td>
<td>Normal</td>
<td></td>
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Sickle Cell Disease

Pathophysiology
- Single base mutation of a valine for glutamic acid → abnormal beta globin chains
- RBC polymerises on de-oxygenation and takes on a sickle shape
- This leads to increased haemolysis of rbc and infarction (as rbc is less flexible)
- Asymptomatic carrier status (40% HbS)

Clinical signs and symptoms
- Anaemia. Chronically:, Hb of 6-8g/dL, can fall further acutely
- Vaso-occlusive crises esp pain in hands and feet, bone pain
- Splenic sequestration/ splenomegaly
- Infection (due to splenic infarcts)
- Stroke and infarcts...
- Diagnosed via electrophoresis (presence of HbS) and blood film (sickle cells/target cells) – also high reticulocyte count
- Treatment with analgesia for crises, vaccinations versus infection, hydroxyurea and Bone Marrow Transplant
Megaloblastic vs. Macrocytic Anaemia

Megaloblastic

- Defective RBC maturation in bone marrow
- e.g. B12 or Folate deficiency
- Folate and B12 necessary for DNA metabolism; Low B12 or Folate leads to defective DNA synthesis
- RNA and protein synthesis continue but mitotic division is blocked
- Nucleus becomes larger – hence large MCV
- Anaemia due to decreased survival time of rbc and ineffective erythropoiesis
- Can get pancytopenia since deficiency interferes with production of wbc and platelets also
- On bone marrow aspirate – will see megaloblasts – large cells with large immature nuclei
- On blood film – macrocytes and hypersegmented neutrophils

Macrocytic

- High MCV
- Marrow not necessarily megaloblastic
- No defect in DNA synthesis
- e.g. Chronic alcoholism, hypothyroidism
B12/Folate deficiency

B12 deficiency
• Pernicious anaemia – autoimmune gastric atrophy
• Gastrectomy – reduced IF production
• Ileal disease/resection – e.g. Crohn’s (majority B12 absorbed in ileum)
• Malabsorption – e.g. Coeliac

Folate deficiency
• Poor intake – poverty/old age
• Antifolate drugs – methotrexate
• Malabsorption – coeliac
• Pregnancy
• Haemolysis
Pernicious Anaemia

- Autoimmune – watch for other autoimmune conditions (Addison’s disease/ Grave’s disease)
- Occurs mostly >60 and Females more than males
- Associated with fair hair, blue eyes and blood group A

Pathophysiology

- Autoimmune destruction of parietal cells in gastric mucosa
- This leads to reduced Intrinsic Factor release and so decreased B12 absorption

Signs and Symptoms

- Insidious anaemia
- Lemon complexion
- Glossitis
- Neurological changes: peripheral neuropathy (glove and stocking parasthesiae)/ataxia/dementia

Investigations

- **FBC:** Macrocytic anaemia, +/- low wbc and platelets, LFT: high BR
- **Blood film:** hypersegmented neutrophils
- **Low serum B12**
- **Serum antibodies** – parietal cell (90% cases but not specific) l or intrinsic factor (50% cases, more specific)
- **Schilling test**
Haemolytic anaemia

Increased destruction of rbc with defective rbcs removed by Reticuloendothelial system (marrow, liver, spleen)
- Hereditary Spherocytosis
- G6PD deficiency
- Sickle Cell
- Transfusion reactions
- Autoimmune
- Infection (e.g. malaria)
- Drugs...

Consequences
- Reticulocytes (immature rbc)
- Elevated serum bilirubin
- Elevated urine urobilinogen
- Raised Lactate Dehydrogenase
- Raised MCV (reticulocytes)
- Reduced haptoglobin
- Jaundice
- Hepatosplenomegaly

JARS:
- Jaundice
- Anaemia
- Reticulocytes
Haemolytic anaemia

**Hereditary Spherocytosis**
- Autosomal Dominant
- Defect in membrane of rbc means cell becomes spherocytic (reduced surface to volume ratio)
- Destroyed as travels through spleen
- Can cause neonatal jaundice

**Investigations**
- Mild anaemia
- Spherocytes and Reticulocytes on blood film
- Osmotic fragility – when put in hypotonic solution, cells will explode quicker than normal cells
- Coomb’s test negative – important as can see spherocytes in autoimmune haemolysis

**Treatment**
- Splenectomy
- Need lifelong abx prophylaxis
- Spherocytes remain but anaemia normalizes
Haemolytic anaemia

G6PD deficiency

- X-linked inheritance (more males than females)
- Lack of enzyme means rbc cannot combat oxidative stress in body. Leads to rigidity and increased destruction of rbc’s.
- Most people asymptomatic but attacks can be triggered:
  - Infection
  - Drugs (aspirin/ antimalarials)
  - Fava (broad beans)

- Blood count usually normal between attacks
- Symptoms in attack: Malaise and weakness, anaemia (haemolytic), jaundice
- Blood film: Bite cells (indentation in membrane), Heinz bodies (signature of oxidative damage)
- Low levels of G6PD enzyme

- Treatment is by avoiding precipitating factors and blood transfusions if attacks are life-threatening
- Note splenectomy is not useful since haemolysis is intravascular

- Pyruvate Kinase deficiency
Haemolytic anaemia

Autoimmune haemolytic anaemia

• IgG attaches to red blood cell leading to increased destruction of rbc
• Coombs test positive
• Divided into hot and cold depending on whether antibodies attach better at 37 degrees or below
• Can be intravascular or extravascular

Causes

• Idiopathic
• Drugs (penicillin)
• Blood transfusions
• Autoimmune disorders (e.g. SLE)
• Lymphomas

Treatment

• Remove underlying cause
• Steroids
• Folic acid
• Splenectomy?
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