Haematology

Iron Deficiency Anaemia:

Haematological features
Iron studies
Further investigation
Prescription of iron therapy

Anaemia: defined as a Hb concentration below the reference range for the age and sex of the individual.

Age	Hb Concentration (g/dL)
Cord blood	13.5 – 20.5
1st day of life	15.0 – 23.5
Children: 6 months – 6 years	11.0 – 14.5
Children: 6 – 14 years	12.0 – 15.5
Adult males	13.0 – 17.0
Adult females (non-pregnant)	12.0 – 15.5
Adult females (pregnant)	11.0 – 14.0

Symptoms and signs of anaemia

- If anaemia develops slowly, associated symptoms are often very mild, the body has time to adapt:
  - Increase in red cell 2,3-disphophoglycerate (2,3-DPG) = shifts the oxygen dissociation curve to the right and permits enhanced delivery of O2 in the tissues
  - Cardiovascular: increase SV and HR
- Acute-onset anaemia – symptoms:
  - Lassitude (physical or mental weariness, lack of energy)
  - Fatigue
  - Dyspnoea on exertion
  - Palpitations
  - Headaches
  - Older patients – impaired CV reserves – may develop angina and intermittent claudication
- Signs:
  - Pallor
  - Tachycardia
  - Wide pulse pressure
  - Flow murmurs
  - Congestive cardiac failure (in severe cases)

Normal control of red cell production:

- Usually there is equilibrium between the rate of release of new RBCs from the bone marrow into the circulation and the removal of senescent red cells from the circulation by macrophages.
- Renal EPO is responsible for translating tissue hypoxia into increased RBC production.
- Anaemia arises when:
  - Failure of adequate production of RBCs
  - Increased rate of loss of RBCs
- Reticulocyte count can enable differentiation of anaemia due to failure of production from that due to accelerated destruction:
  - Sufficient bone marrow to mount a response = reticulocyte count will be high
  - Bone marrow failure = reticulocyte count will be low

Mechanisms leading to anaemia:

1. Blood loss
2. Decreased red cell lifespan (haemolytic anaemia)
   a. Congenital defects e.g. sickle cell disease, hereditary spherocytosis
   b. Acquired defects e.g. malaria, drugs
3. Impairment of red cell formation
   a. Insufficient erythropoiesis
   b. Ineffective erythropoiesis
4. Pooling and destruction of red cells in an enlarged spleen
5. Increased plasma volume e.g. splenomegaly, pregnancy

        - Binds to ferroportin and induces it's internalisation
        - Prevents efflux of iron from the cell and thus the iron is lost when the cell is desquamated form the lumen of the gut
        - Hepcidin expression is regulated by mechanisms related to assessment of iron stores:
            - When transferrin is carrying iron, it enhances hepcidin expression and thus reduces iron absorption in the gut
            - HIF and increased erythropoietic activity can do the opposite and cause a decrease in hepcidin

- **How does iron deficiency arise?**
- Diet contains too little to meet physiological needs
    - Reduced iron stores at birth due to prematurity
    - Inadequate intake
        - Infants given unsupplemented milk or breast fed exclusively for >6/12
        - Vegan diets where iron is principally found in non-haem form (not so readily absorbed)
        - Poverty
    - Increased requirement
        - Pregnancy
        - Lactation
- Malabsorption of iron from the duodenum
    - Need gastric HCl to reduce ferric (Fe3+) to ferrous iron (Fe2+)
    - Partial or complete gastrectomy can cause deficiency through lack of acid
    - Coeliac disease
    - Atrophic gastritis
- Increased loss of iron
    - Chronic haemorrhage
        - Uterine – menorrhagia
        - GI – peptic ulceration, Meckel's diverticulum, colonic diverticulosis, ulcerative colitis, carcinoma of the stomach, colon or rectum, haemorrhoids, hookworm infestation
    - Chronic intravascular haemolysis – leading to haemoglobinuria and haemosiderinuria
- **Manifestations of iron deficiency:**
    - If mild, there will be depletion of stores in the reticuloendothelial system
    - As supply diminishes the red cells will develop hypochromic, microcytic features
    - As the deficiency progresses and Hb falls – normo or hypochromic, microcytic anaemia
    - Can affect other tissues:
        - Angular stomatitis
        - Brittle nails
        - Misshapen nails e.g. spoon-shaped nails = koilonychias
        - Dysphagia associated with pharyngeal strictures or webbing
    - On blood film:
        - Hypochromic, microcytic RBCs
        - Misshapen red cells – poikilocytes – including pencil cells and target cells
        - Bone marrow is unable to respond to the anaemia due to lack of iron, so reticulocyte count will be lower than expected for the degree of anaemia.
- **How can we confirm the diagnosis of iron deficiency?**
- Serum ferritin (how much in the stores)
- Serum iron (how much going around in the blood)
- Transferrin (how hard your body/liver is trying to work to transport iron around)
    - Ferritin:
        - The main storage protein for iron
        - For concentrations <4000microg/L it roughly correlates with the amount of tissue-storage iron
        - Ferritin levels are therefore low in iron deficiency anaemia
            - *Ferritin is also an acute phase reactant, therefore it can be raised in infection and inflammation
            - May therefore get normal serum ferritin levels in the presence of reduced iron stores in patients with acute and chronic infections and in malignancy.
    - Serum iron:
        - Falls in iron deficiency anaemia
        - However there are diurnal and day-to-day changes in the concentration, so is an unreliable indicator when looked at alone
    - Transferrin:
        - Increased in states of iron deficiency
        - Can calculate transferrin saturation: iron/transferrin x 100
        - In states of iron deficiency, the serum iron will be low and the transferrin high, so saturation is low

- Splenectomy if recurrent attacks

- Aplastic crises
  - Due to parvovirus B19 infection
  - Turns of RBC production for 2-3 days
  - As the RBC lifespan is abnormally short in these patients, this leads to life-threatening fall in Hb
  - Severe anaemia
  - Absence of reticulocytes
  - Treatment = blood transfusion
- Strokes
  - Common in patients with sickle cell disease – commonest cause of stroke in children
  - Treatment:
    - Treat as for stroke
    - Blood transfusions to maintain HbS concentration <20% should be given for at least the first 1-2 years after a stroke
    - Monitor cerebral blood flow in children when initiating an exchange transfusion programme in those at high risk of stroke
- Other infarctive crises
  - Penis = priapism
  - Kidneys = haematuria
  - Spleen = pain
- Pulmonary hypertension (not strictly a crisis)
  - Factor in early death in sickle cell disease
  - Echo monitoring
  - Exchange transfusion in those affected

- Treatment:
  - Conservative mainly
  - Specific treatments for crises
  - Hyposplenism is common (from infarction) – immunize and prophylaxis with penicillin
    - Against encapsulated bacteria e.g. Strep pneumonia, Neisseria meningitidis, Hib
  - Folic acid for anaemia
  - Hydroxycarbamide – can be used in severe disease to increase HbF concentration and decrease painful crises
  - BM transplantation

Genetic variants that protect against Malaria:

Haemoglobin abnormalities	Other erythrocyte mutations
1. Sickle cell disease 2. Thalassaemia 3. HbC and HbE erythroids	1. G6PD deficiency 2. Pyruvate kinase deficiency 3. Elliptocytosis

Haematology

Thrombophilia

Congenital and acquired factors predisposing to thrombosis.

Two natural anticoagulant pathways exist to prevent excess thrombus forming in vivo.

1. Antithrombin
    a. Serine protease inhibitor (serpin)
    b. Many of the coagulation proteins are serine protease enzymes
    c. Antithrombin forms 1:1 complexes with them and thus inhibits their activity
    d. Main effect:
        i. Neutralizes thrombin
        ii. Inhibitory activity against factor Xa
2. Protein C pathway
    a. Activation:
        i. Protein C is activated by thrombin in the presence of an endothelial cell cofactor, thrombomodulin.
    b. Action:
        i. Once activated, APC is a serine protease that acts as a natural anticoagulant by cleaving the two cofactors, factor Va and VIIIa
        ii. To do this, protein C needs it's own cofactor, protein S
        iii. Both proteins C and S are vitamin-K dependent.

Inherited thrombophilia

- Common, affect 5-7% of the population overall.
- Inherited abnormalities or deficiencies include:
    - Factor V Leiden = 1 in 20 heterozygotes, 1 in 1600 homozygotes
    - Prothrombin G20210A = 1 in 50-100
    - Protein C = 1 in 300
    - Protein S = 1 in 300
    - Antithrombin = 1 in 3000
- These inherited thrombophilias are associated with venous thrombosis only, not arterial.
- Heterzygous protein C, protein S or antithrombin deficiency:
    - 50% of normal levels of activity
    - At risk of thrombosis
- Homozygous protein C or S deficiency:
    - Neonatal purpura fulminans
- Homozygous antithrombin deficiency:
    - Fatal in utero
- Investigations:
    - Any patients with unprovoked VTE, positive FHx, or young with children/siblings
    - Relatives of a patient with proven VTE and identified heritable thrombophilia

Factor V Leiden:

- Point mutation in factor V at the site where protein C inactivates it = leads to resistance to activated protein C (APC)
- Discovered in Leiden, in the Netherlands.
- Heterozygotes = increases risk of venous thrombosis 7x
- Homozygotes = increases risk 50-100x

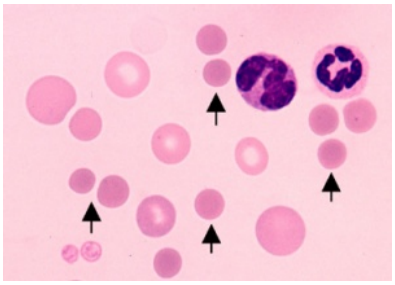
Prothrombin G20210A mutation:

- Polymorphism in the prothrombin gene.
- This leads to higher levels of prothrombin
- Associated with a 4x increased risk of VTE

Hereditary Haemolytic Anaemias

Hereditary spherocytosis:

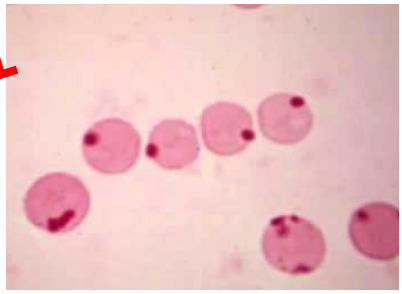
- Autosomal dominant
- Inherited cytoskeletal defect – leads to membrane defects and increased RBC fragility and premature cell death
- Clinical features
  - Often presents in childhood, FHx
  - Pallor, attacks of jaundice
  - Splenomegaly
  - Leg ulcers
- Lab features
  - Features of haemolysis
  - Spherocytes – small, spherical, darkly staining RBCs, with no central area of pallor. These are cells under haemolytic attack.



- Treatment
  - Often not required
  - Severe symptomatic anaemia – splenectomy
    - Need immunization against Pneumococcus, Hib and meningococcus.
    - Need prophylactic penicillin.
    - Annual influenza vaccine.

G6PD Deficiency:

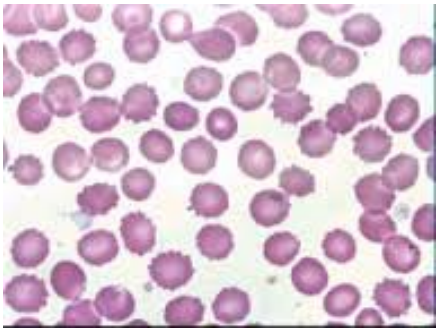
- G6PD acts to catalyse glucose-6-phosphate to generate NADPH – this is essential for the maintenance of functional Hb and prevention of oxidative attack.
- G6PD deficiency therefore leads to haemolytic anaemia.
- Occurs due to a variety of mutant alleles of the G6PD structural gene.
- Very common in subtropic and tropical region – becoming more so in Europe due to migration.
- Gene is X-linked = G6PD deficiency more common in males
- Can have mild (African type) or severe (Mediterranean type)
- Clinical features
  - Most are asymptomatic until an acute haemolytic episode occurs
  - Triggers = infection, drugs e.g. sulphonamides, primaquine, ingestion of fava beans.
- Diagnosis
  - Bloods: general features of haemolysis
  - Blood film:
    - Heinz bodies = caused by denaturation of unstable Hb
    - 'bite cells' = when the denatured Hb is removed by macrophages in the spleen
  - Red cell G6PD activity is low = <20% of normal



- Treatment
  - Usually self-limiting
  - Supportive
  - Transfusion if needed
  - Avoidance of triggers

Pyruvate Kinase Deficiency:

- Autosomal recessive, prevalence 1:10,000
- Clinical features
  - Presentation in childhood
  - Anaemia
  - Jaundice
  - Mild splenomegaly
  - Exercise tolerance that is better than expected for the degree of anaemia – this is because PK deficiency increases red cell 2,3-diphosphoglycerate concentrations, thus lowering Hb oxygen affinity, thus enhancing tissue oxygen delivery.
- Diagnosis
  - Bloods: Hb 4.5-10, features of haemolytic anaemia, reticulocytosis
  - Blood film:
    - 'Prickle cells'
  - Reduced PK activity



- Treatment
  - Conservative, folic acid supplementation
  - Blood transfusion when needed
  - Splenectomy