Haematology

Anaemia

- Erythrocytes have an average lifespan of 120 days
  - EPO stimulates erythropoiesis in hypoxia - 90% from renal cortex, 10% from liver
  - normoblasts (nucleated precursors) develop into reticulocytes (measure of production)
  - contain carbonic anhydrase - inward diffusion of CO2 converted to carbonic acid
  - bicarbonate then diffuses out; remaining H+ is buffered intracellularly
- 1mg of iron absorbed into the bloodstream each day; 70% in haem, 25% in stores
  - ferritin (protein + iron) is water-soluble; haemosiderin (fragmented ferritin) is insoluble
- Adult haemoglobin (HbA) comprises two alpha and two beta chains
  - degrades to release LDH, amino acids, iron, unconjugated bilirubin

Iron deficiency

- Due to blood loss (GI, menstrual, malignancy), malabsorption (e.g. coeliac), high demand
- Symptoms - fatigue, dyspnoea / angina, palpitations, glossitis, pruritis, tinnitus, headache
- Investigations - FBC (microcytic hypochromic), ferritin (low), transferrin / TIBC (high)
  - also screen for coeliac; consider OGD / colonoscopy
- Management - ferrous sulphate 200mg bd. / tds. (causes black stools, reflux, nausea)

Sideroblastic anaemia

- Reduced haemoglobin synthesis leading to iron accumulation in nucleated precursors
  - congenital - X-linked sideroblastic anaemia (XLSA), Wolfram’s syndrome
  - acquired - myelodysplasia, myeloma, polycythaemia, leukaemia, RA, alcohol, pregnancy
- Investigations - bone marrow (ring sideroblasts), MCV (low / normal / high), TIBC (high)
- Management - consider desferrioxamine chelation; pyridoxine (vitamin B6) if congenital

Macrocytic anaemia

- High MCV without anaemia may indicate myeloma (paraproteins), hyperglycaemia
- Macrocytic anaemia may be:
  - megaloblastic - impaired DNA synthesis due to B12 / folate deficiency
    - degradation of megaloblasts may increase unconjugated bilirubin causing jaundice
    - non-megaloblastic - RBC fatty deposits due to liver disease (alcohol), hypothyroidism
- Vitamin B12 (cobalamin) - found only in animal sources but fortified in foods e.g. cereals
  - combines with gastric IF to be absorbed in terminal ileum
  - significant hepatic stores take years to empty - deficiency is substantially delayed
  - deficiency caused by pernicious anaemia (80%), IBD, GI surgery, H. pylori, dietary
• Subacute spinal cord degeneration is a complication of severe B12 deficiency
  • symmetrical dorsal column loss primarily affecting proprioception / vibration sense
  • lower limbs more affected - initially peripheral neuropathy, hyporeflexia, weakness
  • later UMN signs - spasticity, Babinski sign, ataxia; eventually optic atrophy, dementia
• Vitamin B9 (folate) - found in green vegetables, wholegrain cereals; destroyed by cooking
  • absorbed in duodenum / jejunum; smaller liver stores - deficiency manifests in months
  • dependent on B12 for activation - deficiencies may occur concurrently
  • deficiency caused by dietary, alcohol (not beer), malabsorption (e.g. coeliac), drugs
• Investigations - FBC (macrocytic), LFTs / GGT, blood film; consider bone marrow aspirate
  • also serum B12 (unreliable), serum folate (immediate), red cell folate (storage)
  • in B12 deficiency - red cell folate may be low but serum folate normal
  • in folate deficiency - red cell folate and serum folate are both low

Pernicious anaemia
• Rare autoimmune chronic atrophic gastritis typically affecting women aged > 60
  • reduced IF production causes B12 deficiency; reduced HCl causes achlorhydria
  • associated with vitiligo, hypothyroidism, hypoparathyroidism, Addison’s, type I DM
• Symptoms - those of anaemia; anorexia, diarrhoea, weight loss, dyspepsia, jaundice
• Investigations - serum B12 (low) / folate (normal), anti-IF, anti-parietal cell (less specific)
  • consider Schilling test (radioactive B12 with IF), bone marrow aspirate
• Management - B12 injections (not folate - may cause fulminant neuropathy)
  • Complications - gastric carcinoma, gastric polyps, neuropathy, iron deficiency

Haemolytic anaemia
• Uncontrolled RBC breakdown - may be extravascular or intravascular
• Causes may be membrane (spherocytosis), enzyme (G6PD), haemoglobin (sickle cell)
  • also autoimmune, transfusions, drugs, malaria, DIC, HUS, ITP, myelofibrosis
• Symptoms - those of anaemia; jaundice, pigment gallstones, splenomegaly
• Paroxysmal nocturnal haemoglobinuria (PNH) - rare acquired stem cell disorder
  • triad of haemolytic anaemia, large venous thrombosis, pancytopenia
  • presents with dark urine (morning), abdominal pain, fatigue, symptomatic thrombosis
  • thrombi - hepatic (Budd-Chiari), mesenteric (ischaemia), dermal (painful red nodules)
  • risk of aplastic anaemia
  • consider life-long VTE prophylaxis; eculizumab limits C5 action, effective
• Investigations - platelets (normal unless DIC, HUS, ITP), Coombs’ test (for autoimmune)
  • if intravascular - Hb in serum / urine, low serum haptoglobins (bind Hb)
• Management - folate (rapidly deficient), consider transfusion, steroids, splenectomy
Aplastic anaemia

- Failure of erythropoiesis leading to pancytopenia and hypocellular bone marrow
  - majority idiopathic but may be caused by EBV, hepatitis, toxins, sickle cell anaemia
  - Fanconi's - congenital; dysmorphia, AML, SCCs - requires bone marrow transplant
  - acquired usually presents aged 15 - 25 years; strongly associated with PNH
- Presents with symptoms of anaemia / thrombocytopenia; no hepatosplenomegaly
- Investigations - bone marrow aspirate, cytogenetics
- Management - supportive includes transfusions, G-CSF, prophylactic antibiotics
  - bone marrow transplant - treatment of choice if severe and young
  - immunosuppression - ciclosporin with antithymocyte globulin if less severe or older

Coagulopathies

- PT - extrinsic pathway - prolonged in warfarin, liver disease, DIC
- APTT - intrinsic pathway - prolonged in heparin, haemophilia, von Willebrand's disease

Von Willebrand's disease

- Commonest inherited coagulopathy - vWF deficiency causing bleeding diathesis
  - mostly autosomal dominant inheritance causing variable degrees of bleeding risk
  - may also be acquired in malignancy, myeloproliferation, aortic stenosis, hypothyroidism
  - vWF facilitates platelet plug formation and perpetuates factor VIII in the serum
- Symptoms - epistaxis, menorrhagia, bruising, GI bleeding (only if severe)
- Investigations - platelets (normal), vWF / factor VIII (low), APTT (prolonged), PT (normal)
- Management - avoid NSAIDs; consider desmopressin if mild, vWF-factor VIII if severe

Haemophilia

- A: X-linked inherited factor VIII deficiency affecting intrinsic clotting pathway
  - Commoner, more severe; presents in neonates esp. spontaneous haemarthrosis
  - also haematuria (cf. vWF), haematomas, intracranial haemorrhage; GI less common
- B: X-linked inherited factor IX deficiency affecting intrinsic clotting pathway
  - Management - prophylactic transfusions and factor VIII / IX (though risk of inhibitors)
    - acutely in type A - factor VIII, consider desmopressin; in type B - factor IX

Thrombotic thrombocytopenic purpura (TTP)

- Rare ADAMTS1 deficiency (von Willebrand factor cleaving protein)
- Causes - pregnancy; malignancy, HIV, E. coli, drugs - tamoxifen, ciclosporin, COCP
- Symptoms - flu-like prodrome, then bleeding (epistaxis, GI, purpura, bruising), AKI
  - haemolysis - fever, jaundice, fatigue; neuropathy - confusion, dysarthria, paresis
- Investigations - LDH (very high), FBC (anaemia, reticulocytosis), HIV screen
- Management - interim FFP, prednisolone, plasmapheresis; consider rituximab
Disseminated intravascular coagulation (DIC)

- Rapid uncontrolled consumption of clotting factors leads to severe haemorrhagic diathesis
- Triggers - septicaemia, HUS, malignancy, trauma, pregnancy complications, heat stroke
- Symptoms - **acute bleeding** (bruises, venepuncture sites, ENT, GI), fever, confusion, ARDS
- Investigations - coagulation (PT / APTT both prolonged; platelets low), D-dimer (elevated)
- Management - FFP, platelets, cryoprecipitate; consider heparins

Haemoglobinopathies

**Thalassaemia**

- **Autosomal recessive** defects in alpha or beta globin chains leading to *insufficient Hb*
  - both common in Southeast Asia; alpha also in Africa, India; beta in Middle East, China
  - causes **hypochromic microcytic anaemia** and haemolysis if severe
- **HbH disease** - 75% alpha deletion - severe anaemia and haemolysis; Heinz bodies on film
- Beta disease presents later in postnatal period causing FTT, vomiting, sleepiness, irritability
  - **extramedullary haemopoiesis** causes facial bony deformity (‘hair on end’ on X-ray)
- Investigations - serum iron / transferrin saturation / ferritin (high), Hb electrophoresis
- Management - regular transfusions (if severe), chelation, splenectomy, stem cell transplant
- Complications - **haemochromatosis**, high-output cardiac failure, osteoporosis, gout

**Sickle cell**

- **Autosomal recessive** defect in *beta globin* gene causing chronic mild haemolytic anaemia
  - sickle cell trait (heterozygous) - 60% HbA - 40% prevalence in sub-Saharan Africa
- Symptoms (if homozygous - at age 3 - 6 months) - lethargy, FTT, weakness, infection
- Sickle cell crises:
  - vaso-occlusive - infection, dehydration - **pain** (arthritis, abdominal, loin), stroke, priapism
  - aplastic - parvovirus B19 - severe anaemia, *low reticulocytes*, cardiac failure; transfuse
  - sequestration - affects children - massive splenomegaly, hypovolaemic shock
- Investigations - Hb electrophoresis, FBC / blood film (reticulocytosis, sickling)
- Management - annual checkups, avoid smoking (chest syndrome) / alcohol (dehydration)
  - lifelong prophylactic penicillin, immunisation (inc. Hep. B if regular transfusions)
  - consider folate / vitamin D / zinc supplements; **hydroxyurea** (cytotoxic, increases HbF)
  - bone marrow transplant is the only cure (only consider after serious complications)
- Complications - sepsis, **stroke**, pulmonary hypertension, priapism, retinopathy, CKD

Hereditary erythrocyte defects

**Pyruvate kinase deficiency**

- **Autosomal recessive** but may be acquired secondary to leukaemia, sideroblastic anaemia
- Defect of *Embden-Meyerhof anaerobic glycolytic pathway* limiting RBC ATP production
• May cause FTT in children; haemolysis leads to **pigment gallstones**, chronic leg ulcers
• Investigations - FBC (**macrocytic anaemia**, reticulocytosis), bilirubin (often very high)
• Management - consider transfusion, splenectomy (not curative), bone marrow transplant

Glucose-6-phosphate dehydrogenase deficiency (G6PD)

- **X-linked** but often sporadic with variable penetrance - common in Africa, Asia (like malaria)
- Rate-limited enzyme in **pentose phosphate pathway** - inadequate NADPH / **glutathione**
  - glutathione protects RBCs from oxidative stress; deficiency leads to **haemolysis**
- Crisis triggers - DKA, AKI, severe infection, broad beans (favism), nitrofurantoin, aspirin
- Investigations - FBC (macrocytic anaemia, reticulocytosis), **G6PD enzyme**
- Management - avoid crisis triggers; consider transfusion, splenectomy, folic acid

Hereditary spherocytosis

- **Autosomal dominant** - usually **spectrin / ankyrin deficiency** - cause of haemolytic anaemia
- Investigations - blood film (spherocytosis, reticulocytosis), FBC (high MCH - hyperchromia)
- Symptoms - **anaemia, jaundice, splenomegaly**
- Management - supportive if mild; consider prednisolone in haemolytic crises
  - **splenectomy** - after age 6; concurrent cholecystectomy if gallstones; lifelong penicillin V
- Complications - **gallstones** (esp. if Gilbert’s), haemolytic / aplastic crisis (parvovirus B19)

Iron overload

- Caused by HHC, repeated transfusions (> 10), liver disease, porphyria
- Symptoms - fatigue, **arthritis** (esp. hands)
- Investigations - serial ferritin, MRI liver / heart
- Management - chelation (**desferrioxamine SC / deferiprone PO**) with vitamin C
  - chelation may cause growth impairment, hearing loss, agranulocytosis
- Complications - cardiac failure, arrhythmias, pericarditis, liver disease, **diabetes mellitus**

Myelofibrosis

- **Clonal proliferation** of **haemopoietic stem cells** with **myeloid metaplasia** (ectopic cells)
  - may be idiopathic or secondary to leukaemia, lymphoma, myeloma, PRV, HIV, TB, SLE
  - tends to affect white males aged > 40 years; also Ashkenazi Jews
- Symptoms - fever, **night sweats**, weight loss, bone / LUQ pain, anaemia, splenomegaly ++
  - also **bleeding diathesis** inc. DIC, petechiae, oesophageal varices, PUD
  - **extramedullary haemopoiesis** may lead to spinal cord compression, seizures, ascites
- Investigations - blood film (**‘tear-drop’ poikilocytosis**), bone marrow biopsy, MRI
- Management - hydroxyurea, blood transfusion, stem cell transplant (only cure)
- Complications - portal hypertension, amyloidosis, infection (neutropenia), leukaemia, gout
**Polycythaemia**

- Occurs physiologically with high altitude, chronic lung disease, cyanotic heart disease
- other secondary causes include ectopic EPO, HCC, burns, smoking

**Polycythaemia ruba vera** (primary) - myeloproliferation of RBCs, neutrophils, platelets
- RBC precursors not EPO dependent - sensitive to IGF / IL3
- rare; presents in adults aged > 50 years; associated with JAK2, Budd-Chiari, HTN
- symptoms - thrombosis (esp. arterial - stroke, MI), headaches, pruritis (esp. with heat)
- erythromelalgia - distal erythema, warmth pain - unusual
- management - thromboprophylaxis, venesection, antihistamines, hydroxyurea

**Porphyrias**

- Enzyme deficiency in **haem synthesis** producing excess **porphyrins** (toxic precursors)
  - classified as predominantly cutaneous (photosensitive) or neuropsychiatric
  - tends to affect women aged 20 - 40 years; mostly autosomal dominant, often latent
- Intermittent 'acute attacks' in which toxic precursors rapidly accumulate
  - drug precipitants - carbamazepine, phenytoin, erythromycin, methyldopa
  - also menstruation, pregnancy; fasting, smoking, alcohol, infection, distress
- Symptoms - anxiety prodrome then abdominal pain, vomiting, constipation, myopathy
  - also postural hypotension, hyponatraemia (inc. SIADH), psychosis, dark urine
- **Porphyria cutanea tarda** (commonest) - associated with alcohol, iron overload, hep. C
  - leads to photosensitive erythema, bullae, pruritis, hyperpigmentation, hypertrichosis
- Investigations - urinary porphyrins / porphobilinogen (high in acute attack), DNA analysis
- Management - IV **haem arginate**, glucose (may induce remission)
- Complications - respiratory arrest, sudden cardiac death, HTN, liver damage, hepatoma
## Blood film

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<tr>
<th>Entity</th>
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<th>Associations</th>
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<td>poikilocytosis</td>
<td>variable shapes</td>
<td>‘pencil’ - iron deficiency</td>
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<td></td>
<td></td>
<td>‘tear-drop’ - myelofibrosis, BT</td>
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<tr>
<td>acanthocytosis</td>
<td>‘thorny’ RBCs</td>
<td>liver disease (dyslipidaemia)</td>
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<tr>
<td>Heinz bodies</td>
<td>Hb precipitates</td>
<td>G6PD crisis, HbH AT</td>
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<td>Howell-Jolly bodies</td>
<td>nuclear inclusions</td>
<td>hyposplenism</td>
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<tr>
<td>hypersegmented neutrophils</td>
<td>&gt; 5 lobes</td>
<td>megaloblastosis (e.g. B12)</td>
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<td>Pappenheimer bodies</td>
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<td>target cells</td>
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<td>schistocytes</td>
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<td>smudge cells</td>
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<tr>
<td>Reed-Sternberg cells</td>
<td>multinucleated giant cells</td>
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<td>basophilic stippling</td>
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