

Haematology

- Anaemia (categorized by cell size)
- Anaemia – congenital haemolytic
- Anticoagulants
- Bleeding disorders
- Eosinophilia
- High erythrocyte sedimentation rate (ESR)
- Immunodeficiency
- Leukaemia – acute lymphoblastic leukaemia (ALL)
- Leukaemia – chronic lymphatic leukaemia (CLL)
- Leukaemia – chronic myeloid leukaemia (CML)
- Microangiopathic haemolytic anaemia (MHA)
- Pancytopenia
- Polycythaemia
- Thrombocytosis
- Thrombosis
- Warfarin and heparin

Anaemia – categorized by cell size

Microcytic

Small **T**ypically **I**ron

- S**ideroblastic
- T**halassaemia
- I**ron deficiency

Macrocytic

My **B**lood **H**as **L**arge **E**rythrocytes

- M**yelodysplasia
- B**₁₂ deficiency
- H**aemolysis
- L**iver disease
- E**mbryo (pregnancy)

Normocytic

Exclude **C**hronic **A**naemia

- E**ndocrine (hypopituitary, thyroid, adrenal)
- C**ombined deficiency
- A**cute blood loss/**A**plastic

Topic facts

This mnemonic lists the causes of anaemia categorized by cell size into microcytic, macrocytic and normocytic. These correspond to mean corpuscular or cell volume (MCV) of <76, 76–96 and >96 fL, respectively.

- Hypothyroidism commonly causes macrocytosis but can also cause a normocytic anaemia.
- An MCV >110 fL is most likely to be caused by vitamin B₁₂ or folate deficiency.
- Thalassaemia trait presents with microcytosis and a high red cell count (typically $>5 \times 10^9/L$).
- Chronic disease that typically causes a normocytic anaemia (e.g. cancer, rheumatic disease).

Anaemia – congenital haemolytic Membrane/Enzyme/Haemoglobin

Membrane

Spherocytosis
Elliptocytosis

Enzyme

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Haemoglobin

Thalassaemia
Sickle cell disease

Topic facts

This topic divides the causes of congenital haemolytic anaemia into three categories: defects of the cell membrane, the cell enzymes and haemoglobin.

- Congenital haemolytic anaemia is suggested by a positive family history and the triad of anaemia, splenomegaly and jaundice.
- Hereditary spherocytosis is the most common of the congenital haemolytic anaemias. It has autosomal dominant inheritance.
- Precipitants of a haemolytic episode include infection and oxidative stress (especially drugs such as dapsone, quinine and nitrofurantoin).
- Investigation of haemolytic anaemia: blood film (for spherocytes, elliptocytes), direct Coombs' test (for autoimmune haemolysis), G6PD assay.
- Patients with severe anaemia may require splenectomy.
- G6PD deficiency leads to haemolysis of red blood cells when they are exposed to oxidative stress. In normal cells G6PD maintains levels of the important antioxidant glutathione.

Anticoagulants

APTT

Anti-thrombin 3

Proteins C + S

Topic facts

APTT stands for **activated partial thromboplastin time** – a measure of clotting time. This abbreviation can be used to help recall the body's natural anticoagulants anti-thrombin 3 and proteins C + S.

- The body contains a natural anticoagulant mechanism made up of three factors: anti-thrombin 3, protein C and protein S. Thrombophilic states arise as a result of a deficiency or impaired function of one or more of these factors.
- Factor V Leiden mutation is the most common thrombophilic state. It is caused by a genetic abnormality of clotting factor 5. As a result of the mutation, protein C cannot bind to factor 5 and inactivate the clotting cascade. It has autosomal dominant inheritance.
- Factor V Leiden is investigated by using a PCR (polymerase chain reaction) to identify the abnormal gene or by the activated protein C resistance test. (Protein C is added to a sample of patient's plasma and the APTT is measured. In a normal individual, addition of the natural anticoagulant protein C prolongs the clotting time. In individuals with factor V Leiden protein C is unable to bind and the APTT is unchanged.)
- Isolated protein C and protein S deficiencies are less common. They are both inherited as autosomal dominant conditions. Most patients are identified on thrombophilia screening after recurrent deep vein thrombosis.
- Anti-thrombin 3 deficiency may result as a complication of nephrotic syndrome. Patients with nephrotic syndrome are at risk of arterial and venous thrombosis due to a loss of anti-thrombin 3 in the kidneys.

Bleeding disorders

Capillary/Platelet/Coagulation

Capillary

Inherited

- Collagen diseases (page 161)
- Hereditary haemorrhagic telangiectasia

Acquired

- Severe infection
- Purpuras (senile, steroid, Henoch–Schönlein)

Platelet

- ITP (idiopathic thrombocytopenic purpura – young females ± splenomegaly)
- Marrow infiltration (secondaries, leukaemia)
- Marrow aplasia (drugs, viral)

Coagulation

- Anticoagulant treatment
- Haemophilia A or B
- Von Willebrand's disease

Topic facts

This topic covers disorders that cause excessive bleeding. They are best divided into capillary, platelet and coagulation defects. A clinical hallmark of excessive bleeding is bruising (purpura).

- Von Willebrand's disease is the most common bleeding disorder in the UK. It is an autosomal dominant condition, resulting from an abnormality of chromosome 12.
- Von Willebrand's factor is important for the adhesion of platelets to damaged blood vessel walls. Patients present with excessive bruising, menorrhagia and epistaxis.
- Patients with haemophilia A (X-linked recessive inheritance) lack factor 8. Patients with haemophilia B (Christmas disease) lack factor 9.

Eosinophilia

Severe eosinophilia $>5 \times 10^9/L$

Painful Blisters

- P Parasitic infection
- B Blistering skin diseases

Severe eosinophilia $>5 \times 10^9/L$ + abnormal chest radiograph

High Eosinophils + Lung Trouble

- H Hypereosinophilic syndrome
- E Eosinophilic pneumonia
- L Leukaemia (eosinophilic)
- T Tropical pulmonary eosinophilia

Topic facts

Severe eosinophilia is defined as $>5 \times 10^9/L$ eosinophils. The causes of a severe eosinophilia can be divided into patients with and those without lung involvement.

- Other causes of eosinophilia to be considered include allergies, Churg–Strauss vasculitis and Hodgkin’s lymphoma. These typically cause a less severe eosinophilia ($0.5\text{--}2.0 \times 10^9/L$).
- The blistering skin diseases are pemphigoid, pemphigus and erythema multiforme (nb dermatitis herpetiformis is a blistering skin disease which causes a less severe eosinophilia).
- Parasites associated with eosinophilia include *Strongyloides*, *Filariasis* and *Ascaris* and *Wuchereria bancrofti*. Parasitic eosinophilia is not common in the UK.
- Hypereosinophilic syndrome patients have the triad of eosinophilia, restrictive cardiomyopathy and hepatosplenomegaly.
- Allergies causing eosinophilia include both allergic conditions, such as asthma and allergic rhinitis, and drug allergies (particularly sulfonamides and nitrofurantoin).

High erythrocyte sedimentation rate (ESR) (>100mm/h)**V**asculitis **M**ay **P**rolong **S**edimentation**V**asculitis**M**yeloma**P**olymyalgia rheumatica**S**epsis**Topic facts**

This topic lists the causes of a very high ESR defined as >100 mm/h.

- ESR is a measure of the rate at which red blood cells settle in a blood specimen.
- The rate of sedimentation is affected by several factors, the most important of which is the concentration of proteins in the blood. Protein levels rise in the blood during inflammation as a result of the acute phase response. Fibrinogen, a major acute phase reactant, is an important cause of the increase in sedimentation rate during inflammation.
- Proteins other than acute phase reactants cause elevation of the ESR. High plasma concentrations of immunoglobulins, caused by myeloma or paraproteinaemias, are examples of this.
- The ESR is also affected by the size and shape of the red blood cells. Thus anaemia, old age and pregnancy can lead to an elevation in ESR.
- Polymyalgia rheumatica is characterized by an ESR >100 mm/h and pain and stiffness of the shoulder and pelvic girdles. It is rare before the age of 50 and is associated with giant cell arteritis. Muscle weakness is NOT a feature of polymyalgia; if this is present suspect polymyositis. Treatment is with high-dose steroids.
- Myeloma is a disease of elderly people. The high levels of immunoglobulins cause hyperviscosity and elevation of the ESR. Patients are at risk of arterial and venous thrombosis.

Immunodeficiency

Drugs May Cause Lowered Immunity

Drugs

Myeloma

Common variable hypogammaglobulinaemia

Lymphoma/Leukaemia (CLL)

Infection (HIV)

Topic facts

This mnemonic provides a simplified list of the more common causes of immunodeficiency, which can be categorized into primary (common variable) and secondary (the rest). There are many rare esoteric eponymous primary disorders, but time spent learning these may be better used revising other topics.

- Drug-induced hypogammaglobulinaemia is caused by agents such as phenytoin and penicillamine.
- Myeloma patients have high levels of monoclonal γ -globulins. These have an immunoparetic effect by suppressing the body's immune response to antigens.
- The immunosuppressive effect of immunoglobulins can be used therapeutically in patients with autoimmune disorders. Intravenous immunoglobulin is used to suppress the harmful autoimmune response, e.g. in Guillain-Barré syndrome.
- Common variable hypogammaglobulinaemia is a primary immunodeficiency disorder. Patients have low levels of antibody and a history of recurrent bacterial and fungal infections.
- Haematological neoplasms such as lymphoma and chronic lymphocytic leukaemia are associated with hypogammaglobulinaemia.
- HIV infection leads to impaired cell-mediated immunity through its effect on CD4 T-helper cells.
- Hypogammaglobulinaemia can complicate nephrotic syndrome through renal loss of antibodies.

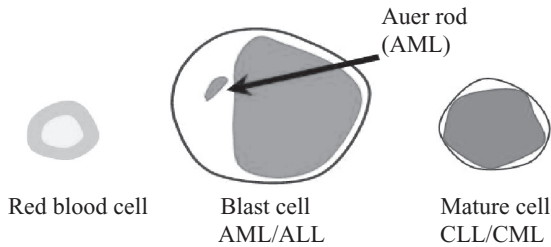
Leukaemia – Acute lymphoblastic leukaemia (ALL)

ALL the kids respond (to treatment).

Topic facts

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children. More than 90 per cent will respond to treatment (with cure rates of around 70 per cent).

- Leukaemias (the bone marrow malignancies) are classified by the cell type and degree of maturity of the cells.
- Acute leukaemias are associated with immature blast cells and rapid disease progression.
- Chronic leukaemias have more mature leukocytes and a slow rate of disease progression.
- Suspect chronic leukaemia in patients with a high white cell count (WCC) (typical values: chronic myeloid leukaemia (CML) >50 neutrophils, chronic lymphatic lymphocytic leukaemia (CLL) >15 lymphocytes).
- In acute leukaemia the WCC may be raised, normal or low. The blast cells seen on the blood film, which are very large (approximately four times the size of red blood cells), are the key feature.
- Acute myeloid leukaemia (AML) can be differentiated from ALL under the microscope by the presence of Auer rods (which are small inclusion bodies).
- Patients with acute leukaemia present with the features of bone marrow failure, i.e. infection, anaemia and bleeding.



Chronic Myeloid Leukaemia

A diagram showing the relative sizes and appearances of blood cells on a blood film.

Leukaemia – Chronic lymphatic leukaemia (CLL)

B disease

- B lymphocytes (95 per cent)
- Bone marrow failure
- Bleeding
- Broken cells (smear cells)

Topic facts

This mnemonic summarizes the pathology, presentation and blood film findings of chronic lymphatic leukaemia (CLL).

- CLL is the most common form of leukaemia affecting adults in the UK.
- Ninety-five per cent of CLL is of B-cell origin.
- CLL is most commonly found in the late middle-aged to elderly population.
- The disease proceeds through a number of stages. Initially patients are asymptomatic and the only feature may be lymphocytosis (high WCC). Subsequently lymphadenopathy develops, followed by hepatosplenomegaly and eventually bone marrow failure.
- Presenting symptoms are a result of bone marrow failure (anaemia, infection, bleeding).
- Patients may also complain of lethargy, weight loss and night sweats.
- Investigation is with a blood film and bone marrow.
- The blood film shows large numbers of mature lymphocytes.
- Increased fragility of the mature B-cell membranes causes a number of the cells to break open on preparation of a slide. These are called smear cells and are typical of CLL.
- First-line treatment is with chlorambucil.
- Patients with CLL are susceptible to folate deficiency caused by increased consumption as the result of rapid cell turnover.

Leukaemia – chronic myeloid leukaemia (CML)

Myeloid Leukaemia **P**atient

Middle age

Leukoerythroblastic blood picture

Philadelphia chromosome

Topic facts

The age of onset, blood film findings and pathology of chronic myeloid leukaemia (CML) are summarized in this mnemonic.

- CML is a myeloproliferative disorder in which there is increased turnover of the granulocyte cell line (neutrophils, basophils, eosinophils).
- The blood film shows high numbers of granulocytes and myeloid precursor cells (metamyelocytes, myelocytes). Nucleated red blood cells are also seen.
- The combination of myeloid precursors and nucleated red blood cells is termed a 'leukoerythroblastic picture' (also called a leukaemoid reaction).
- The causes of a leukoerythroblastic picture include bone marrow infiltration (leukaemia, lymphoma, myelofibrosis, other neoplasms) and severe stressors (sepsis, severe inflammation, tissue necrosis, haemorrhage).
- Almost all patients with CML are Philadelphia chromosome positive. The Philadelphia chromosome is created from a translocation of the long arms of chromosome 9 and 22 – t(9:22).
- You may be asked to differentiate between the diagnosis of CML and myelofibrosis in a patient presenting with splenomegaly and myeloid precursors. Both disorders present with a leukocytosis and leukoerythroblastic picture:
 - CML patients are Philadelphia chromosome positive (myelofibrosis patients are negative)
 - myelofibrosis patients have a high NAP (neutrophil alkaline phosphatase) score (CML patients have a low NAP score).

Microangiopathic haemolytic anaemia

Microangiopathic Haemolytic Anaemia Causes Blood Vessel Damage

Mucinous adenocarcinoma

HUS/TTP (haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura)

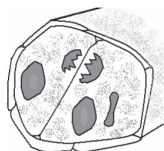
Accelerated hypertension

Connective tissue diseases

Burns

Vasculitis

Disseminated intravascular coagulation (DIC)



A fibrin strand haemolysing a red blood cell into fragment (helmet) cells.

Topic facts

This topic covers the causes of microangiopathic haemolytic anaemia (MHA).

- MHA, as the name suggests, affects the small blood vessels. It damages the endothelial cell walls and causes fibrin strand deposition.
- The most common causes of MHA are DIC and HUS/TTP.
- The deposited fibrin strands slice open red blood cells as they pass through the vessel, resulting in a haemolytic anaemia. Some of the damaged red cells are able to reseal and are described on the blood film as fragment or helmet cells.
- Other haematological features include a high reticulocyte count and polychromasia.
- Suspect DIC in patients with prolonged coagulation times and high fibrinogen degradation products with a MHA blood picture. DIC prolongs all clotting times (APTT, INR [international normalized ratio], TT [thrombin time], BT [bleeding time]).
- HUS is associated with infection with *Escherichia coli*. A history of gastrointestinal symptoms, fever and renal impairment is highly suggestive.

Pancytopenia

Pancytopenia

My **S**pleen **I**njures **C**ells

- M**arrow infiltration
- S**pleen (hypersplenism)
- I**diopathic acquired
- C**ongenital (Fanconi's anaemia)

Pancytopenia with a raised MCV (>96 fL)

Impaired **M**arrow **P**roduces **S**ome **B**ig **C**ells

- I**nfections (Epstein-Barr virus – [EBV])
- M**yoedema/**M**yelodysplasia
- P**aroxysmal nocturnal haemoglobinuria (PNH)
- S**ystemic lupus erythematosus (SLE)
- B**₁₂ and folate deficiency
- C**ytotoxics

Topic facts

There are two memory aids in this topic; they cover the more common causes of pancytopenia categorized by the presence or absence of a raised MCV, defined as >96 fL.

- Pancytopenia is defined as a deficiency of all of the blood cells (white cells, platelets and red cells). There are a large number of causes of pancytopenia and the most useful way to categorize them is by red cell size.
- Marrow infiltration includes lymphoma, leukaemia, myeloma and secondary metastasis to the bones.
- Fanconi's anaemia is a congenital autosomal recessive condition associated with bone marrow failure, developmental abnormalities and a reduced life expectancy.

Polycythaemia

Primary/Secondary/Inappropriate

Primary

Polycythaemia rubra vera

Secondary (hypoxia driven)

Chronic lung disease

Right-to-left cardiac shunts (often congenital)

High altitude

Inappropriate

Tumours: renal, liver, brain

Topic facts

Polycythaemia is defined as an elevated haemoglobin, red cell count and packed cell volume (PCV). The causes of polycythaemia are best categorized into primary, secondary and inappropriate.

- Red cell production is regulated by the hormone erythropoietin, which is made in the kidney in response to tissue hypoxia.
- Primary polycythaemia is termed 'polycythaemia rubra vera' (PRV). There is uncontrolled production of red cells independent of erythropoietin. PRV is a myeloproliferative disorder.
- PRV patients typically have raised platelet and neutrophil counts (red cells, platelets and neutrophils come from the same myeloid line which is over-actively proliferating). Use this to help differentiate primary polycythaemia from other causes.
- Secondary causes of polycythaemia are a response to tissue hypoxia and elevated levels of erythropoietin. This can be thought of as appropriate polycythaemia.
- Inappropriate polycythaemia therefore refers to polycythaemia in which there are elevated erythropoietin levels in the absence of a hypoxic drive, e.g. erythropoietin-producing tumours.

Thrombocytosis

Massive **B**leeding **I**ncreases **P**latelet **C**ount **S**ignificantly

Myeloproliferative disease

Bleeding

Inflammation/**I**ron deficiency

Primary thrombocytosis

Connective tissue disease/**C**ancer

Splenectomy

Topic facts

Thrombocytosis (elevated platelet count) is defined as $>400 \times 10^9/L$. The causes are summarized as follows.

- Primary thrombocytosis (essential thrombocythaemia) patients typically have platelet counts above $1000 \times 10^9/L$. Associated features of myeloproliferative disease (polycythaemia, splenomegaly) help to differentiate it from secondary causes.
- Myeloproliferative disease is included as a separate heading because platelet counts can also rise in association with other myeloproliferative disorders such as PRV.
- The spleen is important in the destruction of platelets and thus levels may remain elevated post-splenectomy. The clue will be the presence of Howell–Jolly bodies in the blood film report.
- Thrombocytosis is commonly found in patients with iron deficiency. MRCP questions may provide a clue to this by reporting the blood film. Look for microcytosis, anisocytosis, poikilocytosis and hypochromasia. A picture of koilonychia (spooning of the nails) may be shown (however, this can be inherited as an autosomal dominant familial trait).
- Inflammation and bleeding cause a transient thrombocytosis.

Thrombosis

Pathologically **S**ticky **B**lood **T**hromboses **A**ll **V**essels

- P**aroxysmal nocturnal haemoglobinuria (PNH)
- S**ickle cell
- B**ehçet's syndrome
- T**hrombophilia
- A**ntiphospholipid syndrome
- V**asculitides

Topic facts

The conditions that can cause both arterial and venous thrombosis are summarized in this topic.

- PNH is a rare, acquired disorder of red blood cells. The cell membranes are susceptible to lysis by the complement system. Patients present with dark urine and thrombosis. Haemolytic anaemia is present (low haemoglobin with a raised reticulocyte count). Ham's test is positive (red cell lysis in acidified serum).
- Sickle cell disease (HbSS) is an autosomal recessive disorder. HbSS causes sickling during deoxygenation.
- Sickle crises are precipitated by stresses such as infection, dehydration and hypoxia. Patients are likely to have an African, Middle Eastern or Mediterranean background (heterozygous individuals are resistant to malaria). Thrombotic presentations include: pulmonary syndrome, cerebral syndrome, bony crisis and avascular necrosis.
- Behçet's syndrome is identified by a history of orogenital ulceration and the presence of pathergy (the development of erythematous papules >2 mm in diameter at sites of skin trauma, e.g. injection sites).
- Antiphospholipid syndrome patients have a history of clots, miscarriage and a livedo reticularis type rash.

Note that homocystinuria can also cause both arterial and venous thrombosis.

Warfarin and heparin

Clotting factors II, VII, IX, X

Topic facts

The vitamin K-dependent clotting factors that warfarin inhibits are shown above.

- **Warfarin** – important facts:
 - extrinsic pathway
 - monitor with the INR (international normalized ratio) test
 - vitamin K-dependent pathway (vitamin K is a fat-soluble vitamin essential for the production of factors II, VII, IX and X; it enables the γ -carboxylation of the profactors to their active state)
 - the peak effect of warfarin occurs 48 h after ingestion
 - warfarin has an early prothrombotic effect action as a result of its effects on proteins C + S (the body's natural anticoagulants).
- **Heparin** – important facts:
 - intrinsic pathway
 - monitor with the APTT (activated partial thromboplastin time) test
 - heparin potentiates the action of anti-thrombin 3 (which in turn activates thrombin and clotting factors VIII, IX, XI and XII)
 - half-life 2 h
 - low-molecular-weight heparins do not prolong the APTT; they have a predictable anticoagulant effect and do not require monitoring unless in long-term use; in this case use the factor Xa assay to assess the degree of anticoagulation
 - heparin-induced thrombocytopenia (HIT) is an immune reaction; it occurs in 5 per cent of patients and presets with thrombosis. Platelet activating antibodies cause platelets to clump. This causes simultaneous thrombosis and thrombocytopenia.