Peripheral Blood Film

Full blood count

Red cell parameters

Haemoglobin (Hb) concentration - guideline normal values: 130-180 g/L in adult males and 115-165 g/L in adult, non-pregnant females. The identification of the type of anaemia is aided by:

- Mean corpuscular (cell) volume (MCV) - guideline normal values: 77-95 fL. This is a good starting point for the evaluation of anaemia and usefully classifies anaemia into macrocytic and microcytic anaemias.
- Mean corpuscular (cell) Hb (MCH) - guideline normal values: 27.0-32.0 pg. High values are found in macrocytosis and low values are seen in iron deficiency.
- Mean corpuscular (cell) Hb concentration (MCHC) - guideline normal values: 320-360 g/L. This is of particular use in the evaluation of microcytic anaemias. High values are seen in severe or prolonged dehydration, hereditary spherocytosis and cold agglutinin disease. MCHC is low in iron-deficiency anaemia and thalassaemia.

Abnormal Hb levels

See also the separate Anaemia in Pregnancy, Childhood Anaemia and Sickle Cell Disease and Sickle Cell Anaemia articles.

Anaemia with low MCV (microcytic):

- Iron-deficiency anaemia - look at serum ferritin level.
- Anaemia of chronic disease.
- Thalassaemia.

Anaemia with normal MCV (normocytic):

- Recent bleeding.
- Anaemia of chronic disease (including renal disease).
- Combined iron and B12/folate deficiency.
- Most non-haematinic deficiency causes.

Anaemia with high MCV (macrocytic): see the separate Macrocytosis and Macrocytic Anaemia article.

High Hb

It is important first to ascertain the validity of this result if it does not tie in with known clinical findings. At this point, exclude dehydration and diuretic therapy, both of which may increase the haematocrit (Hct). Anoxia is the major stimulus to red blood cell production and therefore an elevated Hb may be found:

- Where there has been recent travel to high altitude (>3000 m).
- In hypoxic respiratory conditions - eg, chronic obstructive pulmonary disease (COPD).
- Heavy cigarette smoking (as a result of increased carboxyHb levels).
- Ventilatory impairment secondary to gross obesity and alveolar hypotension.
Secondary causes such as:

- Spurious polycythaemia (pseudopolycythaemia or Gaisbock’s syndrome) - hypertensive, obese, cigarette smokers who drink to excess.
- Primary proliferative polycythaemia (polycythaemia rubra vera) - plethoric facies with a history of pruritus after change of environmental temperature/bathing, and splenomegaly.
- Inappropriate erythropoietin excess - this occurs in a variety of benign and malignant renal disorders. May also be a rare complication of some tumours - eg, hepatoma, uterine fibroids and cerebellar haemangioblastoma.

In these patients, there must be an additional evaluation of the risk of thrombosis.

**Haematocrit or packed cell volume (PCV)**
Guideline normal values (Hct): 0.40-0.52 in adult males and 0.36-0.47 in adult females. These terms are sometimes used interchangeably. Essentially, the PCV measures the red cells that have settled to the bottom of a micro-capillary tube after this has been centrifuged. The Hct is similar but derived using automated blood counters. These values are high in polycythaemia of any cause and low in anaemia of any cause.

**Red cell count (RCC)**
Guideline normal values: 4.5-6.5 x 10^{12}/L in adult males and 3.8-5.8 x 10^{12}/L in adult females. This is useful in the diagnosis of polycythaemic disorders and thalassaemias where the RCC is high, and of hypoproliferative anaemias and aplasias where it is low.

**Red cell distribution width (RDW)**
RDW measures the range of cell size in a sample of blood. The term anisocytosis refers to how great this range is. It may be of value in some anaemias. For example, a microcytic anaemia with a normal RDW suggests a beta thalassaemia trait, whereas the same anaemia with a high RDW points towards iron deficiency. Interpretation of this measurement tends to be more the preserve of haematology staff.

**White cells**
The FBC provides a total white cell count (WCC)/white blood cell count (WBC) and an automated differential WCC. Typically, this includes information about neutrophils, lymphocytes, monocytes, eosinophils and basophils.

The FBC report often shows the % of each type of white cell but, unless the absolute WCC is known (as x 10^{9}), it may be of limited value.

**Neutrophils (polymorphs or polymorphonucleocytes)**
Guideline normal values: 2.5-7.5 x 10^{9}/L, comprising 40-75% of WBCs.

Raised in:

- Bacterial infections.
- Trauma, surgery, burns.
- Haemorrhage, inflammation, infarction.
- Polymyalgia rheumatica, polyarteritis nodosa.
- Myeloproliferative disorders.
- Certain drugs - eg, steroids.
- Transient leukaemoid reaction in Down's syndrome.
- Mild increase: stress (eg, postoperatively), exercise.
- Moderate increase: heat strokes, patients with solid tumours.
- Large increase in numbers may be seen in leukaemias, disseminated malignancy and severe childhood infections.

Decreased in:
See also the separate Neutropenic Patients and Neutropenic Regimes article.
**Lymphocytes**
Guideline normal values: 1.3-3.5 x 10^9/L, comprising 20-45% of WBCs. Normal infants and children aged <5 have a higher proportion and concentration than adults.

Raised in:
- Viral infections - eg, Epstein-Barr virus (EBV), cytomegalovirus, rubella. Large numbers of abnormal/atypical lymphocytes are characteristically seen in EBV infection (these are T lymphocytes reacting against EBV-infected B lymphocytes).
- Toxoplasmosis, whooping cough, brucellosis, tuberculosis (TB), syphilis.
- Chronic lymphocytic leukaemia (CLL).

Decreased in:
- Steroid therapy.
- Systemic lupus erythematosus.
- Uraemia.
- Legionnaires' disease.
- AIDS.
- Marrow infiltration.
- Post-chemotherapy/radiotherapy.

**Eosinophils**
Guideline normal values: 0.04-0.44 x 10^9/L, comprising 1-6% of WBCs.

Raised in: see the separate *Eosinophilia* article.

**Monocytes**
Guideline normal values: 0.2-0.8 x 10^9/L. comprising 2-10% of WBCs.

Raised in:
- Acute and chronic infections (especially TB, brucellosis, protozoan disease).
- Malignant disease (especially M4 and M5 acute myeloid leukaemia and Hodgkin's disease).
- Myelodysplasia.

**Basophils**
Guideline normal values: up to 0.01 x 10^9/L, comprising 0-1% of WBCs.

Raised in:
- Viral infections.
- Urticaria.
- Hypothyroidism.
- Post-splenectomy, haemolysis, polycythaemia rubra vera.
- Chronic myeloid leukaemia (CML), malignancy.
- Ulcerative colitis.
- Systemic mastocytosis (or urticaria pigmentosa).

**The platelet count**
The normal platelet count is 150-400 x 10^9/L.

**Causes of thrombocytopenia** (decreased platelet count): see the separate *Thrombocytopenia and Platelet Function Disorders* article.

**Causes of thrombocytosis/thrombocythaemia** (increased platelet count): see the separate *Thrombocytosis* article.
Peripheral blood film

A peripheral blood film will provide information on the following:

- The erythrocytes (RBCs): a note will be made of their size, shape, any membrane changes, colour and stippling. Any inclusion bodies (eg, Howell-Jolly bodies or malarial parasites) will also be noted. Other abnormalities include red cell rouleaux, red cell nucleation and the presence of reticulocytes.
- The leukocytes (WBCs): the number and morphology of these cells are noted, as well as abnormalities such as toxic granulation or dysplastic changes. Presence of abnormal cells is important (eg, leukaemic blasts).
- Platelets: number, size and shape are commented on.
- Other abnormalities such as parasites, plasma cells and occasional circulating carcinoma cells may be found.

Abnormalities of erythrocytes

The RBC is a pink biconcave disc-shaped cell, about the size of a small lymphocyte nucleus. Normally, healthy cells are roughly the same size, shape and colour. Morphological abnormalities are rarely specific to one condition; they can occur in a range of problems.

A glossary of terms

The lists below are not exhaustive but examples of some of the conditions that cause the defects.

- **Acanthocytes** are spiculated (spikey) RBCs that are found in some cases of alpha,beta-lipoproteinaemia, chronic liver disease and alpha-thalassaemia trait. There is also an hereditary acanthocytosis.
- **Anisocytosis** is variation in RBC size which may occur in thalassaemia, iron-deficiency anaemia or megaloblastic anaemia.
- **Basophilic stippling** describes the presence of small granular bodies within the red cell cytoplasm and occurs when there is disordered and accelerated erythropoiesis so that RBCs with immature cytoplasm are released into the circulation. It may be found in lead poisoning, thalassaemia or other causes of significant anaemia.
- **Bite cells** occur in glucose-6-phosphate dehydrogenase (G6PD) deficiency and in oxidative haemolysis.
- **Burr cells** type of echinocyte: found in patients with uraemia.
- **Cabot's rings** are circular or figure-of-eight structures in RBCs that stain red with Wright's stain and are thought to represent nuclear membrane remnants; they are found in similar conditions to Howell-Jolly bodies (see below).
- **Cigar cell** - see Elliptocytes below.
- **Codocytes** - see Target cells below.
- **Crenated cells** type of echinocyte: most often a storage or EDTA artefact.
- **Dacrocytes** - see Teardrop cells below.
- **Dimorphic picture/appearance** describes heterogeneity in the size of RBCs, usually with two distinct populations. It can be found in partially treated iron deficiency, mixed deficiency anaemias (eg, folate/B12 and iron together), following red cell transfusion or in cases of sideroblastic anaemia.
- **Drepanocytes** - see Sickle cells below.
- **Echinocytes** are cells with many blunt spicules. They may be artefactual - see Crenated cells - or pathological - see Burr cells above.
- **Elliptocytes** oval (ovalocyte) or cigar-shaped cells (cigar cell) that occur in hereditary elliptocytosis, myeloproliferative disorder and myelodysplastic syndrome. Subtype: pencil/rod cell.
- **Erythroblasts (normoblasts)** are immature, nucleated RBCs seen in the peripheral blood in leukoerythroblastic anaemia, haemolysis, hypoxia and marrow infiltration.
- **Fragmented red cells** - see Schistocytes below.
- **Heinz bodies** are denatured Hb due to oxidative damage. They are never seen in normal individuals, as they are removed by the spleen. A small number may therefore be seen post-splenectomy and also with the use of antioxidant drugs or sulfonamides, in G6PD deficiency and with unstable Hb.
- **Howell-Jolly bodies** are nuclear remnants found in RBCs normally removed by the spleen and seen after splenectomy, in cases of megaloblastic and iron-deficiency anaemias and (rarely) in cases of leukaemia.
- **Hypochromia** is impaired staining of RBCs seen commonly in iron-deficiency anaemia and also in thalassaemia and sideroblastic anaemias.

- **Hyposplenic film** is a description of the collection of abnormalities found in these patients. They include Howell-Jolly bodies, target cells, occasional nucleated RBCs, lymphocytosis, macrocytosis and acanthocytes. There may also be evidence of infectious mononucleosis, any viral infection, toxoplasmosis and drug reactions.

- **Leptocytes** see Target cells below.

- **Macrocytosis** is the presence of abnormally large RBCs found when erythropoiesis is disordered or when RBCs are released prematurely from the marrow. They occur in alcohol excess and liver disease, megaloblastic anaemia or as a consequence of haemolysis. They are also found in B12 or folate deficiency, pregnant women, newborn infants, hypothyroidism, chronic respiratory failure, aplastic anaemia and following the use of antimetabolites.

- **Microcytosis** is the presence of abnormally small RBCs often found in association with hypochromia in iron-deficiency anaemia. They are also seen in thalassaemia trait, congenital sideroblastic anaemia and in the anaemia of chronic disorders if these are long-standing.

- **Mouth cell** - see Stomatocyte below.

- **Normoblast** - see Erythroblasts above.

- **Ovalocyte** - see Elliptocytes above.

- **Pappenheimer bodies** are phagosomes, containing ferruginous granules, found in RBCs in diseases such as sideroblastic anaemia, haemolytic anaemia and sickle cell disease. They are also found in carcinomatosis and after splenectomy. They may contribute to spurious platelet counts by electro-optical counters.

- **Pencil cell** type of elliptocyte: occur where there is iron-deficiency anaemia, thalassaemia trait and syndromes and in pyruvate kinase deficiency.

- **Polychromasia** is the heterogeneous staining of RBCs of different ages, with younger cells appearing blue, that occurs after haemorrhage, haemolysis, dyserythropoiesis and treatment with haematinics such as iron and vitamin B12.

- **Poikilocytosis** is the general term used for variation in cell shape.

- **Reticulocytosis** is the presence of >0.8-2% of total RBC in the form of reticulocytes. See 'Reticulocytes' section, below.

- **Rod cell** - see Pencil cell above.

- **Rouleaux** are stacked/clumped groups of RBCs caused by the presence of high levels of circulating acute-phase proteins which increase red cell 'stickiness'. They are often an indicator that a patient has a high ESR and are seen in infections, autoimmune conditions, chronic inflammation, paraproteinaemia and myeloma.

- **Schistocytes** are RBCs fragmented by their passage through intravascular strands of fibrin, found in cases of intravascular haemolysis, renal failure and thrombotic thrombocytopenic purpura amongst others.

- **Sickle cells**, also known as drepanocytes, are found in sickle cell anaemia and other sickle syndromes but not in sickle trait. Their name describes their shape.

- **Spherocytes** are overly round or spheroid RBCs that usually indicate active haemolysis and are also found where there is a delayed post-transfusion reaction, disseminated intravascular coagulation (DIC) and post-splenectomy. They are seen more rarely in cases of hereditary spherocytosis.

- **Spur cells** - see Acanthocytes above.

- **Stomatocyte**, an oval or rectangular area of central pallor, sometimes referred to as a 'mouth', arises as a result of loss of concavity on one side. They can occur in liver disease, electrolyte imbalance and hereditary stomatocytosis.

- **Target cells** - also known as codocytes, leptocytes or Mexican hat cells. They are RBCs with a central area of increased staining, surrounded by a ring of hypodense staining and then a further ring of dense staining at the edge of the cell, giving an appearance akin to an archery target. This occurs as a result of the shift in equilibrium between the erythrocyte and cholesterol. They may be found in liver disease, thalassaemia or sickle cell disease. They occur occasionally in small numbers in iron-deficiency anaemia and sometimes following splenectomy.

- **Teardrop red cells** are found in myelofibrosis, metastatic marrow infiltration and myelodysplastic syndrome.
Reticulocytes
These are young, oversized RBCs that are present when the marrow is actively producing RBCs. They are the intermediary between the nucleated RBC and the mature RBC. Small numbers of reticulocytes are found in normal peripheral blood. They are usually expressed as a percentage of total red cells.

- **Increased count** - they are present after haemorrhage, haemolysis, severe hypoxia, in polycythaemia of any cause and in marrow infiltration. Reticulocytes may rise during marrow recovery following chemotherapy or radiotherapy. They may also be seen following treatment of deficient patients with haematinics when they are a useful measure of response to the treatment.
- **Decreased count** - reticulocyte levels drop where there is marrow infiltration (leukaemia, myeloma, lymphoma or other malignancies) or due to marrow underactivity such as in iron, folate or B12 deficiency or due to autoimmune disease, malnutrition, uraemia, drugs, aplastic anaemia and red cell aplasia.

Abnormalities of leukocytes[1]
As with erythrocytes, each type of leukocyte has characteristics that can be identified on stained specimens, allowing for an easy diagnosis to the well-trained eye. The first thing the haematologist will assess is the absolute number of WBCs. If the count is low, subsequent stain and diagnosis may be tricky. If the count is high, an assessment is made of which cell type predominates (ie lymphocytes versus granulocytes) and any abnormal cells - see 'Glossary of terms', below.

**Glossary of terms**

- **Atypical lymphocytes** - see Reactive lymphocytes below.
- **Auer rods** are seen in myeloblasts and are pathognomonic of acute myeloid leukaemia.
- **Blast cells** are abnormal, immature, nucleated precursor WBCs pushed out from the marrow into the circulation by processes such as myelofibrosis or leukaemic infiltration.
- **Hairy cells** have fine, irregular pseudopods and immature nuclear features. They are seen only in hairy cell leukaemia.
- **Hypersegmented neutrophils** - see Right shift below.
- **Myelocytes, promyelocytes, metamyelocytes** are immature WBCs seen in a leukoerythroblastic picture (see Leukoerythroblastic anaemia/picture below).
- **Left shift** describes immature WBCs that are released from the marrow when there is a cause of marrow outpouring, typically due to infection.
- **Leukoerythroblastic anaemia/picture** describes the presence of immature cells such as myeloblasts and normoblasts in the film. It is seen in cases of marrow infiltration - for example, in metastatic malignancy, prolonged hypoxia or severe infection.
- **Leukaemoid reaction** is a severe, reactive leukocytosis, usually consisting of granulocytes (polymorphonucleocytes). It is seen after burns, in cases of severe infection, following an acute haemolysis or prolonged hypoxia.
- **Pelger-Huet anomaly** describes bilobed neutrophils which may be hereditary (when the neutrophils are functionally normal) or acquired - eg, myelodysplastic syndrome.
- **Reactive lymphocytes** seen in infectious mononucleosis.
- **Right shift** is characterised by the presence of hypersegmented polymorphonucleocytes (>5 lobes to their nucleus), seen in liver disease, uraemia and megaloblastic anaemia.
- **Smear cells** are lymphocytes whose cell membranes have ruptured in preparation of the blood film: seen in chronic lymphocytic leukaemia.
- **Toxic granulation** describes coarse granules seen in neutrophils. They may be seen postoperatively, in inflammatory disorders and in severe infection.

Making the diagnosis in context
The age of the patient is important: viral illnesses can produce bizarre-looking film in children. The myelodysplastic syndromes and malignancies tend to occur in older people. If the patient is well, it may be worth repeating the film to see if the abnormalities have resolved. If the patient is unwell (or has lymphadenopathy or hepatosplenomegaly) then disease has to be excluded.

[1]
Abnormalities of the platelets

- **Clumping** - an in vitro artefact in some individuals and results in spurious blood analyser report of thrombocytopenia. The in vivo content is normal and the platelets work well. Even a small blood clot in the EDTA bottle will affect the result. Taking blood into citrate or heparin will reveal normal platelet counts.
- **Giant platelets** - these occur in essential thrombocytopenia. They result in a raised platelet distribution width (the indicator of the range in platelet size in a blood sample) unlike the normal platelet distribution width seen in reactive thrombocytosis, where there is an increased platelet count but normal sized platelets.
- **Satellitosis** - describes platelets encircling a neutrophil. It occurs when a patient has a serum factor that reacts to the anticoagulant EDTA.

Parasites in the blood film[2]

Blood films are useful for the diagnosis of:

- Babesiosis
- Malaria
- Microfilaria
- Trypanosomiasis

Some diseases require bone marrow aspiration (eg, leishmaniasis). However, development of sensitive monoclonal antibody techniques has made diagnosis on a peripheral blood film more of a dying art. The notable exception to this is in the diagnosis of malaria, where a peripheral smear study remains the gold standard.

Further reading & references

- Atlas of Hematology
- Lab Tests Online - UK.

1. Hematology and Clinical Microscopy Glossary; College of American Pathologists, 2012

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