Summary

Anaemia is defined as a haemoglobin (Hb) level <120 g/L (<12 g/dL) in females and <140 g/L (<14 g/dL) in males or, alternatively, as an Hb level <125g/L (<12.5 g/dL) in adults.[1] [2] [3] It is the most common haematological disorder seen in general medical practice. Risk factors include extremes of age, female sex, lactation, and pregnancy. The most common cause internationally is iron deficiency.[4] Anaemia can cause significant morbidity if left untreated, and is often the presenting sign of a more serious underlying condition.[5] The rate at which anaemia develops is often as important as the severity, as a rapid decline can overwhelm the compensatory mechanisms of the body.

Pathophysiology

Erythropoiesis takes place within the bone marrow and is controlled by the stromal network, cytokines, and the hormone erythropoietin. A series of differentiation steps results in the generation of reticulocytes (red blood cells [RBCs] with an intact ribosomal network). Reticulocytes remain in the bone marrow for 3 days before being released into the circulation. After one further day in the circulation, reticulocytes lose their ribosomal network and become mature RBCs, which circulate for 110-120 days before being removed from the circulation by macrophages. At steady state, the rate of RBC production equals the rate of RBC loss. Anaemia develops when the rate of RBC production decreases and/or the rate of RBC loss increases.

Morphological classification of anaemia

The most clinically useful classification system is based on the mean corpuscular volume (MCV).[6] [7] [8]

- Microcytic (MCV <80 femtolitres [fL]).

- Normocytic (MCV 80-100 femtolitres [fL]); further subclassified according to the reticulocyte count as:
  - Hyperproliferative (reticulocyte count >2%): the proportion of circulating reticulocytes increases as part of a compensatory response to increased destruction or loss of RBCs. The cause is usually acute blood loss or haemolysis.
• Hypoproliferative (reticulocyte count <2%): these are primarily disorders of decreased RBC production, and the proportion of circulating reticulocytes remains unchanged.

• Macrocytic (MCV >100 femtolitres [fL]); further subclassified as:
  
  • Megaloblastic: a deficiency of DNA production or maturation resulting in the appearance of large immature RBCs (megaloblasts) and hypersegmented neutrophils in the circulation.
  
  • Non-megaloblastic: encompasses all other causes of macrocytic anaemia in which DNA synthesis is normal. Megaloblasts and hypersegmented neutrophils are absent.
Aetiology

Anaemia occurs when the production of red blood cells (RBCs) is decreased, the destruction of RBCs is accelerated, or there is a loss of RBCs due to bleeding. In many cases, a combination of these mechanisms is present. Anaemia is the most common haematological disorder seen in general medical practice. Risk factors include extremes of age, female sex, lactation, and pregnancy.

Nutrient deficiency, acquired bone marrow disease, genetic disorders, drugs, toxins, and chronic systemic diseases may all lead to reduced RBC production.

Haemolytic anaemias are a group of anaemias resulting from increased destruction of RBCs with a resultant increase in circulating indirect bilirubin.[9] [10] [11] Clinical jaundice appears once bilirubin levels rise above 34.2 to 68.4 mmol/L (2-4 mg/dL). Additional disease-specific symptoms may also be present. The resulting anaemia can be microcytic or hyperproliferative normocytic, depending on the cause.

Microangiopathic haemolytic anaemias are often considered as a group. They produce a hyperproliferative normocytic anaemia. The underlying disease process produces endothelial damage and activates the coagulation cascade, leading to fibrin deposition on the damaged endothelial surfaces. In small vessels, the endothelial fibrin causes mechanical fragmentation and shearing of RBCs, leading to haemolysis. The irregular-shaped RBC fragments produced by this process are called schistocytes and can be seen on a peripheral blood smear.

Haemodilution can occur following expansion of plasma volume. This drop in haemoglobin concentration is known as 'dilutional anaemia'. This is often iatrogenic (e.g., following intravenous fluid administration) and may result in unnecessary transfusions.

Blood loss

Acute haemorrhage

- Any acute haemorrhage can cause a normocytic anaemia. A reticulocytosis is seen within 6 hours of the onset of bleeding. By contrast, chronic slow bleeding leads to ongoing iron loss and produces a microcytic anaemia due to iron deficiency.
- The most common causes are trauma (including gunshot wounds, major fractures, or crush injuries), acute gastrointestinal (GI) bleeding, rupture of a vascular aneurysm (especially abdominal aortic aneurysm), and recent surgery.
- Patients are at increased risk of haemorrhage if they are taking anticoagulant therapy, have an underlying defect in haemostasis, or have a consumptive or dilutional coagulopathy following repeated blood transfusions.

Gradual, prolonged bleeding

- Bleeding due to any cause produces iron depletion, because two-thirds of the total body iron is contained in circulating haemoglobin (Hb).
- Excessive menstrual losses are a common cause in females.
- The GI tract is a common site of bleeding. Common causes include haemorrhoids, salicylate ingestion, peptic ulcer disease, hiatal hernia, diverticulosis, neoplastic disease, and ulcerative colitis.
- Rare causes include hookworm, cows’ milk allergy in infants, Meckel's diverticulum, schistosomiasis, trichuriasis, and hereditary haemorrhagic telangiectasia. Rare sources of blood loss from other sites include pulmonary bleeding (seen in idiopathic pulmonary haemosiderosis and Goodpasture's
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syndrome), blood donation, and self-harm. In addition, any underlying disorder that impairs haemostasis increases the risk of bleeding and iron deficiency anaemia.

Nutrient deficiency or depletion


- The most common cause of anaemia worldwide. It includes a range of underlying causes.
  Approximately 4% of women in the US aged between 20 and 49 years have been estimated to be iron deficient.[16] The formation of the haem moiety in haemoglobin, myoglobin, and cytochrome requires iron; inadequate intake or absorption of iron, or excessive iron loss, leads to a microcytic anaemia.
- Meat provides the main source of haem iron, and iron deficiency is common in geographical regions where meat is sparse and there is poor dietary iron intake. There is a strong relationship between pica (a medical disorder in which children develop an appetite for non-nutritive substances) and iron deficiency.
- Gradual prolonged bleeding due to any cause produces iron depletion, because two-thirds of the total body iron is contained in circulating Hb.
- Iron malabsorption occurs due to achlorhydria, gastric surgery, destruction of small bowel absorptive area in chronic diseases such as coeliac disease, or following extensive resection of the proximal small bowel.
- Runner’s anaemia is caused by volume expansion accompanied by increased destruction of RBCs due to repetitive impact of the foot on the ground.
- Haemoglobinuria (iron loss in the urine) is rare. The usual cause is paroxysmal nocturnal haemoglobinuria, but haemoglobinuria can occur following rapid intravascular haemolysis of any cause.
- Pregnancy increases physiological demand on iron, which is needed for fetal brain and placental development.

Vitamin B12 deficiency[8]

- Vitamin B12 is an essential co-factor in DNA synthesis, being obtained only from the diet or by supplementation. Dietary sources include animal and dairy products such as meat, poultry, milk, and eggs. Deficiency produces neurological disorders and a megaloblastic anaemia.
- Causes include decreased dietary intake (e.g., chronic malnutrition, alcohol abuse, strict vegan diets), diminished breakdown of dietary vitamin B12 (due to pernicious anaemia, previous gastric or intestinal surgery, atrophic gastritis), or malabsorption (gastric malabsorption, Crohn’s disease, coeliac disease, bacterial overgrowth). One systematic review concluded that there is no clear evidence linking anaemia to subnormal B12 levels in the geriatric population.[17]

Folate deficiency[8] [18]

- Folate is an essential co-factor in DNA synthesis, being obtained only from the diet or by supplementation. Dietary sources include green leafy vegetables, citrus fruits, and animal products. Deficiency produces a range of signs, including a swollen, red, painful tongue; angular stomatitis; patchy hyperpigmentation of the skin and mucous membranes; a persistent mild pyrexia (in the absence of infection); and a megaloblastic anaemia.
- Common causes include decreased dietary intake (e.g., chronic malnutrition, alcohol abuse, dietary restriction of protein intake), impaired absorption (achlorhydria, coeliac disease, tropical sprue, zinc
deficiency, bacterial overgrowth), and increased folate requirement (infancy, pregnancy, lactation, malignancy).
• Patients with vitamin B12 deficiency can have excessive renal folate excretion. Similarly, chronic alcohol abuse can lead to excessive biliary folate excretion.
• Rarely, hypothyroidism and congenital enzyme deficiencies may impair folate metabolism.

Generalised malnutrition

• Often causes iron deficiency. Patients often have associated vitamin B12 and/or folate deficiency, in which case the resulting anaemia is normocytic. Associated copper deficiency is rare, but should be considered in patients on prolonged total parenteral nutrition (TPN).

Acquired bone marrow disease

Myelodysplastic syndrome[19]

• A heterogeneous group of clonal stem cell disorders. Uncontrolled proliferation and clonal expansion of neoplastic multipotential haematopoietic stem cells compromise the production of normal cells, producing a range of cytopenias.
• Usually due to acquired chromosomal abnormalities, but can be caused by chemotherapy or radiotherapy.
• The anaemia is a non-megaloblastic macrocytic anaemia, but the peripheral blood smear may show hypersegmented neutrophils similar to those seen in megaloblastic macrocytic anaemias. A normal random distribution of red cell width (RDW) in the setting of macrocytic anaemia in an older adult should raise this suspicion.

Leukaemias

• Acute lymphocytic leukaemia, acute myelogenous leukaemia, and chronic myelogenous leukaemia are caused by the uncontrolled proliferation and clonal expansion of abnormal progenitor cells. These diseases affect progenitor cells at different stages of the differentiation process, but all cause anaemia by compromising the production of normal RBCs.

Infiltration of the bone marrow by secondary malignancy

• Metastasis of solid tumours to the bone marrow can cause anaemia by infiltration of the marrow space. Any tumour can metastasise to the bone marrow, but the most commonly seen are neuroblastoma in children, and breast, prostate, and lung cancer in adults. Metastasis to the bone marrow is a poor prognostic sign.

Aplastic anaemia (AA)[20][21]

• A disorder of stem cell failure, leading to pancytopenia in the absence of splenomegaly.
• Can be due to an inherited bone marrow failure syndrome or acquired (induced by a variety of disorders, e.g., autoimmune or toxic) where immune mechanisms with local activation of interferon gamma may be a common aetiological pathway.
• Affected patients typically present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and, less often, fatigue due to anaemia.
• Toxic causes include benzene, dipyrone, chloramphenicol, penicillamine, and gold.
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• Patients with paroxysmal nocturnal haemoglobinuria can develop aplastic anaemia, although the mechanism is not known.

• Definitive diagnosis is established following bone marrow aspiration and biopsy. In AA, characteristic findings include the following:[20]
  - Profoundly hypocellular marrow with a decrease in all elements; marrow space is composed of fat and marrow stroma
  - Residual haematopoietic cells that are morphologically normal
  - The absence of malignant infiltrates or fibrosis
  - Haematopoiesis is non-megaloblastic.

Pure red cell aplasia

• Caused by congenital or acquired impairment of erythroid progenitor cells. Acquired forms can be self-limiting or chronic.

• Self-limiting acquired disease can be caused by infections or medications. The most common infectious cause is parvovirus B19. Other infectious causes include infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps.

• Medications exert a toxic effect on erythroid progenitor cells that is reversible once the medication is discontinued. Examples include anti-epileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, chloramphenicol (which can also cause aplastic anaemia), sulphonamides, isoniazid, and procainamide.

• Chronic acquired disease is caused by autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polyarteritis nodosa, scleroderma), persistent infection (persistent parvovirus B19 infection in immunosuppressed patients, chronic active hepatitis), and thymomas.

• Congenital forms are produced by in-utero damage of erythroid progenitor cells. The cause is unknown.

• Autoimmune diseases can also cause autoimmune haemolytic anaemia.

Toxin exposure

Drugs

• Certain drugs may produce immune-mediated or direct RBC haemolysis; interfere directly with DNA synthesis; impair the absorption, metabolism, or action of important DNA synthesis co-factors; or have a toxic effect on progenitor cells in the bone marrow.

• A wide range of drugs are known to cause haemolytic anaemia. Common examples include penicillin, methyldopa, levodopa, quinidines, cephalosporins, and some non-steroidal anti-inflammatory drugs (NSAIDs).

• Drugs that directly interfere with DNA synthesis include purine analogues (6-mercaptopurine, thioguanine, aciclovir), pyrimidine analogues (5-fluorouracil, azacitidine, zidovudine), and ribonucleotide reductase inhibitors (hydroxycarbamide, cytarabine arabinoside).

• Antifolates act by impairing folic acid function, and include methotrexate and trimethoprim. Anticonvulsants (phenytoin, phenobarbital, primidone) interfere with folate absorption. Other drugs that can decrease folate levels include oral contraceptives and cycloserine.
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- Drugs that interfere with vitamin B12 metabolism include p-aminosalicylic acid, metformin, colchicine, neomycin, and biguanides.
- Drugs and chemicals that produce a toxic effect on a range of progenitor cells, producing aplastic anaemia, include benzene, chloramphenicol, penicillamine, and gold.
- Drugs that produce a toxic effect on erythroid progenitor cells, producing pure red cell aplasia, include anti-epileptic medications (phenytoin, carbamazepine, sodium valproate), azathioprine, chloramphenicol (which can also cause aplastic anaemia), sulfonamides, isoniazid, and procainamide.
- Drugs that inhibit erythroid stimulation and suppress erythropoietin production include ACE inhibitors and angiotensin-II receptor blockers.[22]

Radiation exposure

- Radiation exposure can produce a pancytopenia.

Lead toxicity

- Occurs after occupational or home exposure to lead. Anaemia can occur because lead competes with zinc, an important co-factor in haem synthesis. Some patients also have a concurrent iron deficiency anaemia.

Alcohol abuse

- Long-term alcohol intake directly suppresses the bone marrow, independent of any concurrent liver disease or vitamin deficiency. The effect resolves only after months of abstinence, and may persist even after normalisation of vitamin B12 and folate levels.

Chronic systemic disease

Anaemia of chronic disease[6] [23]

- Can be a mild hypoproliferative normocytic anaemia or, in severe cases, a microcytic anaemia when co-existing with iron deficiency anaemia. It is caused by chronic inflammation. Proinflammatory cytokines, especially interleukin-6 (IL-6), trigger a cascade of events, mediated via upregulation of hepcidin, that decrease RBC production (by lowering serum iron and erythropoietin levels) and increase RBC destruction (by stimulating erythrophagocytosis and oxygen free radical formation).[24]
- Common underlying processes include infection, neoplasms, autoimmune reactions, and injury to tissue from trauma or major surgery.

Chronic kidney disease[25]

- Produces a normocytic or microcytic anaemia. The aetiology is complex and multifactorial. The main cause is decreased erythropoietin production, leading to decreased RBC production and a hypoproliferative normocytic anaemia. Inhibitors of erythropoiesis accumulate, further exacerbating the effects of decreased erythropoietin. Serum ferritin may be elevated in chronic kidney disease, but patients should still receive concurrent iron supplementation with erythropoietin-stimulating agent (ESA) therapy as long as serum ferritin is <500 micrograms/L.[26]
- Other causes of anaemia may also be present. Secondary hyperparathyroidism exacerbates anaemia in patients with renal failure, but the mechanism is unclear. Concurrent hyperparathyroidism should also be addressed, as treatment improves the management of anaemia in this setting.[26] Chronic blood loss, inflammation, and nutritional deficiency cause an iron deficiency anaemia (which would be microcytic rather than normocytic). Patients often need to reduce their protein intake, which leads to...
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decreased meat in the diet and poor iron intake. Poor iron absorption may also occur. Erythropoietin therapy and chronic inflammation can cause functional iron deficiency, produced by an inability to mobilise iron stores effectively.

**Chronic liver disease**

- A mild to moderate non-megaloblastic macrocytic anaemia is a common feature of a range of liver diseases, and is produced by a combination of intravascular dilution due to volume overload, increased RBC destruction, and impaired bone marrow compensatory responses.

**Hypothyroidism**

- Causes a mild hypoproliferative normocytic anaemia due to the loss of the stimulatory effect of thyroid hormones on erythropoiesis.

**Immune reactions**

**Autoimmune haemolytic anaemia**[27] [28]

- RBCs are attacked by autoantibodies and targeted for extravascular destruction. This usually occurs either as part of other autoimmune conditions (e.g., systemic lupus erythematous, rheumatoid arthritis, or scleroderma) or in relation to a lymphoproliferative disorder (usually non-Hodgkin’s lymphoma or chronic lymphocytic leukaemia).
- Autoimmune diseases can also cause pure red cell aplasia.

**Alloimmune haemolytic anaemia**

- Can be caused by transfusion reactions, usually due to ABO incompatibility.

**Infections**

A range of infections can produce a haemolytic anaemia, including cytomegalovirus, infectious mononucleosis, and toxoplasmosis. Leishmamiasis produces combined RBC haemolysis, bone marrow suppression, and blood loss.

Causes of pure red cell aplasia include parvovirus B19, infectious mononucleosis, viral hepatitis, malaria,[29] respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps.

**Genetic disorders**

**Thalassaemias**[30] [31]

- Haemolytic anaemias. A group of autosomal-recessive genetic conditions that result in decreased or absent production of the alpha-globin (alpha-thalassaemia) or beta-globin (beta-thalassaemia) chains in the Hb molecule. The decreased or absent globin production results in impairment of erythropoiesis. Increased RBC destruction occurs, producing haemolytic anaemia.
- Alpha-thalassaemia has at least four distinct forms: silent carrier (one affected alpha-globin gene), which does not cause anaemia; alpha-thalassaemia trait (two affected alpha-globin genes); Hb H disease (typically three affected alpha-globin genes); and Hb Bart hydrops fetalis syndrome (typically deletion of all four alpha-globin genes), which is incompatible with life. Polymerase chain reaction
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(PCR) DNA testing and Southern blot analysis may be used to determine the specific defect in alpha-thalassaemia trait.[32]

- Beta-thalassaemia is classified as silent carrier, beta-thalassaemia minor, beta-thalassaemia intermedia, or beta-thalassaemia major, depending on the clinical and haematological features. Disease severity depends on the underlying mutation, and ranges from asymptomatic (in silent carriers and beta-thalassaemia minor) to a severe transfusion-dependent anaemia with skeletal changes (beta-thalassaemia major). Note that in the presence of iron deficiency, a normal HbA2 does not exclude beta-thalassaemia trait. Genetic testing is not typically performed as increases in haemoglobin F are readily seen on electrophoresis.

Sickle cell anaemia[30]

- A haemolytic anaemia caused by an autosomal-recessive single gene defect in the beta chain of Hb (HbA), which results in sickle cell Hb. RBCs containing sickle cell Hb become rigid and are distorted into a crescent shape.
- Patients are prone to episodes of vaso-occlusion due to the rigid, deformed RBCs, and to a prothrombotic state created by the accompanying leukocytosis, which increases cytokine release. Persistent pain in the abdomen, chest, or skeleton and dactylitis are the key presenting symptoms.

Hereditary spherocytosis

- A haemolytic anaemia caused by an autosomal-dominant inherited abnormality of RBCs that produces defects in the skeletal proteins of the red cell membrane. As a result, RBCs lose their biconcave structure and become spherical (spherocytes). Spherocytes are fragile, and are selectively removed and destroyed by the spleen. Increased RBC destruction leads to anaemia with hyperbilirubinaemia and splenomegaly.
- Disease severity ranges from asymptomatic to a transfusion-dependent anaemia with jaundice, depending on the severity of the underlying membrane defect.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency[33]

- An inherited (X-linked) haemolytic anaemia due to an enzyme deficiency that is common among populations originating from parts of the world where malaria is or was common, such as sub-Saharan Africa, Asia, the Mediterranean region, and the Middle East.
- G6PD catalyses a reaction that is linked to the generation of reduced glutathione, a key antioxidant defence of the cell. Deficiency of the enzyme renders cells vulnerable to oxidant damage towards the end of their lifespan. RBCs rely solely on reduced glutathione as an antioxidant defence, so deficiency of G6PD increases RBC destruction.
- The severity of the disease varies, depending on the severity of the underlying mutation. Most patients are asymptomatic. Symptomatic disease produces episodes of acute haemolysis, with pallor and jaundice, following exposure to oxidant stress. Triggers include fava beans (favism), sulfa drugs, aspirin, nitrofurantoin, naphthalene, and febrile illness. The resulting haemolysis is usually self-limiting. Life-threatening symptoms are more common with the Mediterranean variant.

Congenital bone marrow failure syndromes

- Fanconi anaemia is the most common. It is usually autosomal recessive, but can also be X-linked. Mutations in 13 genes have been identified. The genes code for proteins that form a nuclear complex involved in the DNA damage response. However, the precise mechanisms by which the mutations produce bone marrow failure are not known.
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- Dyskeratosis congenita is characterised by the triad of abnormal nails, reticulated skin rash, and leukoplakia. X-linked, autosomal-dominant, and autosomal-recessive inheritance patterns have been observed. The genetic defects all decrease telomerase function. Telomeres maintain chromosomal stability, and the bone marrow is heavily dependent on telomere preservation to support its high rate of cell proliferation. Loss of telomerase produces bone marrow failure.
- Shwachman-Diamond syndrome is a rare autosomal-recessive disease that produces exocrine pancreatic dysfunction, anaemia, neutropenia (which can be intermittent), and skeletal abnormalities. About 90% of patients harbour mutations in a gene known as the SBDS gene, but the relationship of the mutations to bone marrow failure is not understood.

Microvascular disease

Haemolytic uraemic syndrome (HUS)[34]

- Damage to the endothelium of the glomerular bed produces haemolytic anaemia (due to fragmentation and shearing of RBCs), thrombocytopenia (due to platelet consumption), and nephropathy.
- Causes include verotoxins, produced by *Escherichia coli*; neuraminidase, produced by streptococcal species; inherited defects in proteins that control complement; and drugs (cyclosporine and some chemotherapy agents).

Disseminated intravascular coagulation (DIC)[34][35]

- An acquired syndrome produced by activation of coagulation pathways, resulting in the formation of intravascular thrombi and the depletion of platelets and coagulation factors.
- DIC can be triggered by major trauma; burns; organ failure (pancreatitis, acute liver failure); sepsis[36] or severe infection; severe obstetric disorders (amniotic fluid embolism, eclampsia, abruptio placenta, retained dead fetus syndrome); malignancies (acute myelocytic leukaemia or metastatic mucin-secreting adenocarcinoma); major vascular disorders (haemangiomas, large aortic aneurysms); and severe toxic or immunological reactions.
- A haemolytic anaemia is produced by fragmentation and shearing of RBCs against clots in the small vessels.

Thrombotic thrombocytopenic purpura (TTP)[34][37]

- A clinical syndrome of microangiopathic haemolytic anaemia and thrombocytopenic purpura.
- Believed to be due to the production of abnormally large von Willebrand factor (vWF) multimers. The abnormal vWF triggers aggregation of circulating platelets at sites of high intravascular shear stress, which in turn results in thrombi in the microvasculature system.
- A haemolytic anaemia is produced by fragmentation and shearing of RBCs against clots in the small vessels. Thrombocytopenia is produced by excessive consumption of platelets; purpura and other signs of bleeding appear in a small proportion of patients. Thrombus formation in the microvasculature also produces severe central nervous system (CNS) symptoms and renal disease.

Haemangiomas[34]

- Vascular tumours that occur as a result of abnormal angiogenesis and overproliferation of blood vessels. These range from obvious superficial lesions to internal organ haemangiomas.
- A local consumptive coagulopathy (Kasabach-Merritt syndrome) can occur as a complication, leading to thrombus formation and thrombocytopenia. Shearing and fragmentation of RBCs against the clots in the small vessels of the haemangiomas can lead to a haemolytic anaemia.
• Kasabach-Merritt syndrome can also produce DIC in severe cases.

Malignant hypertension

• A hypertensive emergency with systolic BP >210 mmHg and diastolic BP >130 mmHg, associated with rapid deterioration of vital organ function. Common causes include untreated essential hypertension, renal disease, eclampsia, use of sympathomimetic drugs, and use of monoamine oxidase inhibitors. The disease is more common in older people, males, and those of black ethnicity.
• Causes endothelial injury and endothelial fibrin deposition. Mechanical RBC shearing and fragmentation, resulting from high pressures and fibrin in the small vessels, produces haemolytic anaemia.

Prosthetic valves and surfaces[38]

• The shear stresses and turbulence created by the foreign surface cause shearing and fragmentation of RBCs. Improved prosthetics have reduced the incidence of this complication, and the anaemia, if it occurs, is usually mild.

Other causes

Pregnancy[39]

• Anaemia in pregnancy may be due to a dilutional effect, as the plasma volume expands out of proportion to the RBC mass. To account for this effect, anaemia in pregnancy is defined as an Hb <10 g/dL. Iron deficiency is the cause in 95% of cases, due to an increase in demand for iron, and one third of women will have either iron deficiency or folate deficiency by the third trimester.[40]
• Despite being an important problem in pregnancy with effective treatment available, there is a lack of high-quality evidence on the benefits of a national screening programme for anaemia in pregnancy in terms of reduced maternal and infant morbidity.[41]

Thermal burns

• Patients with burns affecting more than 10% of the body's surface area can develop a haemolytic anaemia due to intravascular haemolysis of RBCs (at the site of the burn and systemically), loss of red cell mass due to thrombus formation, and damage to RBCs from systemically released proteases and oxygen free radicals.[42]

Hospital-acquired anaemia

• New-onset anaemia in hospitalised patients with previously normal haemoglobin. Hospital-acquired anaemia (HAA) is typically related to increased phlebotomy and iatrogenic blood loss from invasive procedures or haemodilution. Acute inflammatory response to illness decreases compensatory erythropoiesis. HAA is associated with increased morbidity and length of hospital stay.[43]
Urgent considerations

(See Differentials for more details)

Anaemia is life threatening if there is more than 40% loss of total body volume. These patients should receive packed red blood cell (RBC) transfusions for stabilisation as soon as possible, especially if there are underlying cardiac or pulmonary comorbidities. A reticulocyte count, ferritin, and peripheral smear should be obtained before transfusion, if possible, as this makes subsequent work-up more accurate. Dilutional, or consumptive, coagulopathy from tissue injury may result from the decrease of platelets and coagulation factors (factor V, factor VIII, and fibrinogen) in massive transfusions and must be corrected by the addition of these factors.

Generally, healthy individuals tolerate extreme anaemia well, with cardiovascular status being the major limiting factor. The landmark TRICC study showed that, in haemodynamically stable patients without active bleeding, Hb levels between 70 g/L (7 g/dL) and 90 g/L (9 g/dL) were well tolerated with equivalent or lower mortality/morbidity outcomes compared with a liberal transfusion trigger of <100 g/L (<10 g/dL).[44] It is generally recommended that determination of transfusion requirements are based upon severity of illness parameters rather than arbitrary Hb levels. Clinical guidelines from the AABB (formerly known as the American Association of Blood Banks) suggest a restrictive transfusion threshold of 70 g/L (7 g/dL) in hospitalised haemodynamically stable patients, and 80 g/L (8 g/dL) in those undergoing orthopaedic or cardiac surgeries, or with pre-existing cardiovascular disease, unless there is an underlying acute coronary syndrome, severe thrombocytopenia, or chronic transfusion dependence.[45] Transfusion thresholds in ischaemic coronary artery disease and resuscitation of septic shock remain controversial.

Acute haemorrhage

Causes of acute haemorrhage include trauma (such as gunshot wounds, major fractures, and crush injuries), acute gastrointestinal (GI) bleeding, rupture of a vascular aneurysm (especially abdominal aortic aneurysm), and recent surgery. Rapid evaluation, identification, and control of bleeding are essential before any further work-up. Dilution does not occur acutely, so haemoglobin (Hb) and haematocrit levels do not provide an accurate reflection of the degree of blood loss and anaemia. Perfusion to critical organs must be maintained through early goal-directed therapy, including crystalloid volume resuscitation (using 2-4 times the estimated volume of blood loss), blood pressure support, and tissue perfusion.

A meta-analysis concluded that the use of hydroxyethyl starch (HES) solutions to decrease volume overload in large volume resuscitations was associated with increased risk of acute kidney injury and death.[46] HES solutions for infusion have been significantly restricted across the European Union and are contraindicated in critically ill patients and those with sepsis or renal impairment. These measures were introduced to protect patients from the increased risk of kidney injury and death associated with HES.[47] The restrictions followed a January 2018 review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee, which recommended that HES should be suspended from the market because, despite initial warnings, it was still being used in these at-risk patient populations.[48]

Cross-matched blood (or O negative, if cross-match is unavailable) should be given as soon as possible.

In addition, bleeding following major trauma requires coagulation support and monitoring, and the appropriate use of local haemostatic measures, tourniquets, calcium, desmopressin, and consideration for tranexamic acid.[49][50]
Tranexamic acid has been shown to reduce mortality in trauma patients with haemorrhage when given within 3 hours of injury, and should be administered as soon as possible in people with acute severe haemorrhage due to trauma.[49] [51] A meta-analysis of data from over 40,000 patients with traumatic bleeding or post-partum haemorrhage found that delays in administration of tranexamic acid were associated with reduced survival (survival benefit decreasing by about 10% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit).[52]

Definitive management of acute haemorrhage depends on the underlying cause, but usually requires surgery.

**Microangiopathic haemolytic anaemias**

Haemolytic uraemic syndrome, disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP) produce life-threatening rapid haemolysis.[34] The underlying cause must be quickly assessed and treatment tailored accordingly to minimise end-organ damage and the likelihood of death. Treatment of DIC is aimed at the underlying cause. Corticosteroids and immunosuppression should be commenced if haemolytic uraemic syndrome or TTP are suspected. Intravenous immunoglobulins (IVIG) or urgent plasmapheresis may be necessary for rapid clearance of autoantibodies. Antibody screening should be done prior to blood transfusion. Antibody-free blood products should be used to prevent additional alloimmune haemolysis.

**Malignant hypertension**

This condition is characterised by very high blood pressure in association with bilateral retinal changes, including exudates and haemorrhages, with or without papilloedema. The most common symptoms include headaches (often occipital), visual disturbances, chest pain, dyspnoea, and neurological deficits. Results include cerebral infarction or haemorrhage, transient blindness or paralyses, seizures, stupor, or coma. The initial goal of therapy in hypertensive emergencies is to reduce mean arterial BP by no more than 25% (within minutes to 1 hour), then, if stable, to 160/100 to 110 mmHg within the next 2 to 6 hours. Labetalol is the agent of choice.

**Sickle cell vaso-occlusive crisis**

This is a common complication of sickle cell anaemia, which presents with severe pain precipitated by cold, dehydration, infection, or ischaemia (often due to strenuous exercise). The crisis may give rise to skeletal pain due to bone infarction or avascular necrosis, especially of the hip or shoulder. Other presentations include acute abdominal pain and acute chest syndrome, which is clinically indistinguishable from pneumonia. Treatment involves adequate analgesia, hydration with oral or intravenous fluids, oxygen, and treatment of the underlying cause.

**Combined vitamin B12 and folate deficiency**

If a patient has folate deficiency, it is essential to check for and correct any co-existing vitamin B12 deficiency before giving folate. Folate is believed to exacerbate inhibition of vitamin B12-containing enzymes, thereby worsening vitamin B12-associated neuropathy and subacute combined degeneration of the spinal cord.[53] If vitamin B12 levels are normal, methylmalonic acid levels should be checked to definitively exclude vitamin B12 deficiency, as this is a more sensitive test. An elevated serum methylmalonic acid indicates vitamin B12 deficiency, unless there is a history of renal insufficiency, where levels may be artificially elevated due to inadequate renal clearance.
Leukaemias or aplastic anaemia

Usually present with a normocytic anaemia and co-existing neutropenia and thrombocytopenia. Circulating blasts may be reported on peripheral smear. If these conditions are suspected, an immediate haematology consultation is required for bone marrow biopsy and flow cytometry studies. If the anaemia requires transfusion, only leuko-reduced, irradiated blood products should be used, as these patients may be transplant candidates.[20] [54]

Decreased physiological reserve

It is important to identify patients with decreased physiological reserve, such as those with co-existing cardiovascular or pulmonary disease, as these patients are less able to tolerate anaemia and have more severe symptoms.
Assessment of anaemia

Approach

Patients may present in several ways. The urgency with which anaemia is evaluated depends on the severity at presentation. Patients with an acute severe haemorrhage present with hypovolaemia and symptoms and signs of the underlying cause.[9]

Initial assessment

Evaluation should include identification of any source of active or acute bleeding.

- The initial goal in a patient with acute bleeding is rapid haemodynamic stabilisation. Up to 30% of total blood volume (TBV) may be lost before clinical manifestations are appreciated at rest. Key signs include hypotension, pallor, cold clammy skin, a thready pulse, tachycardia, dyspnoea or air hunger, altered mental status, confusion, and coma. Flat neck veins when supine indicate at least 30% to 40% total body volume loss. All orifices should be examined for bleeding. The mechanism and site of any trauma should also be determined.

- History of prior episodes of gastrointestinal (GI) bleeding, gastritis, inflammatory bowel disease, non-steroidal anti-inflammatory drug (NSAID) or corticosteroid use, alcohol use, or cirrhosis should prompt suspicion of GI bleeding. NSAIDs and corticosteroids are associated with peptic ulcer disease. Alcohol use and cirrhosis are associated with coagulation disorders and oesophageal varices. A lower GI bleed presents with fresh red rectal bleeding (haematochezia). Melena and/or haematemesis with or without abdominal pain indicate an upper GI bleed. Sudden tearing pain should prompt suspicion of a ruptured vascular aneurysm; the pain may be spontaneous, or precipitated by trauma or by cocaine or amphetamine use. Loss of consciousness may occur if a major vessel is involved. A history of hypertension or collagen disorders may also be present. A wide pulse pressure suggests a ruptured aneurysm. A pulsatile abdominal mass may indicate an abdominal aortic aneurysm. Flank or abdominal ecchymosis suggests intra-abdominal bleeding.

- If there is a history of recent surgery, ongoing blood loss at the surgical site must be considered. A detailed history of the pre-, intra-, and postoperative course should be obtained, including any complications noted during the operation. A history of bleeding disorders or excessive bruising may indicate an underlying coagulation disorder. Any antibiotics administered should be noted, as some can produce a decrease in platelet levels.

- Jaundice, especially accompanied by fatigue and pallor, with episodic dark urine suggests a haemolytic process, especially with recent infection, new medications, or history of malignancy.

- Tests are guided by the history and examination and the suspected aetiology of active bleeding. These may include the following procedures.

  - FBC, which shows a normocytic anaemia with a high reticulocyte count (>2%) and a normal or decreased haematocrit (Hct). Dilution does not occur initially, so haemoglobin (Hb) and Hct do not accurately reflect the true severity of the anaemia.

  - Prothrombin time/activated partial prothrombin time, which is usually normal, but tested to identify patients with decreased coagulation due to anticoagulants, underlying defects in haemostasis, or consumptive coagulopathy. In patients with upper GI bleeding, elevated urea may be seen, even in absence of renal issues, due to digestion of blood, which is a source of urea.

  - Abdominal ultrasound scan: allows rapid identification of intra-abdominal bleeding and indicated if abdominal trauma or a ruptured abdominal aortic aneurysm are suspected.
• Joint x-rays, indicated in patients with trauma to identify fractures. Long-bone fractures can be a significant source of bleeding.
• Upper GI endoscopy, required to identify sources of upper GI bleeding. Nasogastric lavage with saline is no longer routinely recommended in initial management unless it is done to facilitate subsequent direct visualisation for endoscopic procedures.[55] [56] [57]
• Colonoscopy, required to identify sources of lower GI bleeding. A retrospective review of the medical records of a sample of patients with colorectal cancer found that anaemia was one of the commonest symptoms/signs in those considered to have had a missed diagnostic opportunity (a clinical encounter where, even in the presence of presumptive symptoms of colorectal cancer, the colorectal cancer diagnostic process was not started).[58]
• Capsule endoscopy may have diagnostic, but not therapeutic, utility in situations where there is concern for GI bleeding in inaccessible areas such as the small bowel.[59]
• Exploratory laparotomy, which may be required in patients with abdominal bleeding to identify the source, especially if there is a history of abdominal trauma or previous abdominal surgery.
• Computed tomography (CT) scanning of the body region affected by trauma or aneurysm rupture, which will identify internal injuries or the extent and nature of the aneurysm, and identify sources of bleeding.

Many anaemic patients with no acute or active bleeding are asymptomatic, and the anaemia is only noted on an FBC taken as part of the assessment of an unrelated condition. Symptoms of anaemia may include pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise. FBC should be ordered if these symptoms are present. Jaundice is an additional sign seen in patients with haemolytic anaemias.

The first step in diagnosis is to identify the type of anaemia that is present, using the results of the FBC. Due to their relative reproducibility, mean corpuscular volume (MCV) and red cell width (RDW) are the most useful components in the initial classification of most anaemias.

The anaemia may be:

• Microcytic (MCV <80 femtolitres [fL]): serum iron studies should be performed.[60]
• Normocytic (MCV 80-100 femtolitres [fL]): the reticulocyte count should be examined to determine whether the anaemia is hypoproliferative (<2%) or hyperproliferative (>2%).
• Macrocytic (MCV >100 femtolitres [fL]): the peripheral smear should be examined for megaloblasts and hypersegmented neutrophils. If these cells are present, the anaemia is megaloblastic. If they are absent, the anaemia is non-megaloblastic.
Microcytic anaemia: abnormal serum iron studies

A low serum iron, an elevated total iron-binding capacity (TIBC), and a low ferritin indicate iron deficiency anaemia.

- Iron deficiency produces an associated reactive thrombocytosis that provides an additional clue. Iron deficiency is not a diagnosis and requires further investigation to elucidate the cause.[13] [14] [15]
- Diets low in meat produce iron deficiency. Generalised malnutrition often produces combined vitamin B12 and/or folate deficiency, in which case the resulting anaemia is normocytic. Children may have pica.
- There may be a history of bleeding. Females may have a history of excessive menstrual losses. Coffee-ground vomiting, haematemesis, or melaena indicate upper GI bleeding. NSAIDs and corticosteroids are associated with peptic ulcer disease. Alcohol use and cirrhosis are associated with coagulation disorders and oesophageal varices. Fresh red rectal bleeding indicates a lower GI bleed. Rectal pain may indicate haemorrhoids, which will be seen on rectal examination. Haemoptysis may indicate Goodpasture's syndrome or idiopathic pulmonary haemosiderosis. Rarely, a history of excessive blood donation or self-harm may be elicited. Patients who are avid runners may have runner's anaemia from repetitive mechanical trauma (also known as march haematuria). A history of gastric surgery, coeliac disease, or extensive small bowel resection suggests malabsorption as the cause. Pregnancy is a common cause. A history of dark-coloured urine may indicate paroxysmal nocturnal haemoglobinuria.
- Signs of iron deficiency include koilonychia, angular cheilosis, glossitis, and thinning hair.
- Investigations are guided by the history and examination, and include the following.
Assessment of anaemia

Diagnosis

- Faecal occult blood testing, which should be done in all patients and is positive if GI bleeding is present.
- Upper GI endoscopy, which should be performed if there is a history of upper GI bleeding or a positive faecal occult blood test. It may identify sources of an upper GI bleed (peptic ulcer disease, gastritis, oesophageal varices), hiatus hernia, Meckel's diverticulum, or increased gastric pH in achlorhydria.
- Following negative endoscopy in the setting of persistent iron deficiency anaemia, *Helicobacter pylori* may be considered when malignancies, B12 deficiency, and idiopathic thrombocytopenic purpura have been excluded.[61]
- Immunoglobulin A-tissue transglutaminase (IgA-tTG) test should be performed in all patients and is positive in coeliac disease.
- Colonoscopy, which should be performed if there is a history of lower GI bleeding or a positive faecal occult blood test. It may reveal malignancy, diverticulosis, ulcerative colitis, or rare causes such as hereditary haemorrhagic telangiectasia; malignancy should be considered in all patients aged over 40 years with symptoms of rectal bleeding or a positive faecal occult blood test.
- Flow cytometry should be considered if there is a history of passing red urine, or RBC results consistent with a haemolytic anaemia. It detects decreased expression of RBC surface proteins (CD55 and CD59) and is diagnostic of paroxysmal nocturnal haemoglobinuria.
- Transvaginal ultrasound, which may reveal causes of menorrhagia including hyperplasia, dysplasia, fibroids, or polyps; malignancy should be considered in patients with menorrhagia who are over 40 years old.
- Stool microscopy, which may identify hookworm, whipworm, or *Schistosoma* eggs. This should be performed if clinical features suggest the diagnosis or there is a history of travel to endemic areas.

A low serum iron, a low total iron-binding capacity, and a low/normal ferritin suggest co-existence of anaemia of chronic disease with iron deficiency.

- A history of an underlying inflammatory process (infection, neoplasms, autoimmune reactions, and injury to tissue from trauma or major surgery) is usually present. A serum erythropoietin level should be considered; the result is usually normal or mildly elevated. Hypothyroidism and vitamin C deficiency may produce a falsely low ferritin level.[62]

**Microcytic anaemia: normal serum iron studies**

The most important cause to exclude is thalassaemia. A family history is usually present. The disease is more common in individuals of Mediterranean, Middle Eastern, or Southeast Asian descent. The severity ranges from asymptomatic to severe transfusion-dependent symptoms.[30] [31]

The examination findings may be normal, or reveal splenomegaly, jaundice, abdominal distension, and icterus. Morphological changes including skeletal abnormalities, a large head, chipmunk facies, and misaligned teeth are seen in beta-thalassaemia intermedia and major.

Distinct features on the FBC that suggest the diagnosis include a marked decrease in MCV (usually close to 70 femtolitres [fL]) with a low mean corpuscular Hb, target cells on the peripheral smear, and an elevated reticulocyte count (>2%). A Mentzer’s index (MCV/RBC) <13 is suggestive of thalassaemia, and an index >14 suggests iron deficiency.[63] In a meta-analysis of various mathematical indices used to distinguish between iron deficiency anaemia and thalassaemias, the microcytic to hypochromic RBC ratio (M/H) showed
the best performance, although the authors concluded that none were high enough to make definitive diagnoses.[64] Initial workup of thalassaemia relies on Hb electrophoresis. The presence of Hb H, Hb Bart, and concomitant haemoglobinopathies (Hb E, Hb S, Hb C, Hb D) is suggestive of alpha-thalassaemia, although more accurate diagnosis relies on DNA genotyping. A high HbF with minimal or absent HbA and an elevated HbA2 is suggestive of beta-thalassaemia.

**Normocytic anaemia: hypoproliferative**

Potential diagnoses

- These include disorders that decrease RBC production.
- Haematological malignancies and aplastic anaemia[20] are the most important diagnoses to exclude, and are usually associated with multiple cytopenias.
- An isolated anaemia is usually due to pure red cell aplasia, which may be self-limiting or persistent. Chronic kidney disease[25] or hypothyroidism can also cause an isolated anaemia.
- Secondary hyperparathyroidism exacerbates the anaemia of chronic kidney disease.

**History**

- Symptoms of bleeding, easy bruising, night sweats, or weight loss suggest haematological malignancy or aplastic anaemia. Parvovirus infection, infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps can result in a self-limiting pure red cell aplasia, and these should be excluded.
- Antiepileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, sulfonamides, isoniazid, and procarcinamide cause pure red cell aplasia. Benzene, penicillamine, and gold can cause aplastic anaemia. Chloramphenicol can cause either aplastic anaemia or pure red cell aplasia. Chemotherapy causes pancytopenia.[65] Discontinuation of causative medications leads to resolution of the anaemia.
- Radiotherapy, especially to pelvic or sternal areas, can cause pancytopenia.
- A history of immunosuppression or chronic hepatitis suggests persistent pure red cell aplasia. There may be a history or features of chronic kidney disease or hypothyroidism.

**Examination**

- Ecchymoses or petechiae due to thrombocytopenia suggest haematological malignancy, myelodysplastic syndrome, or aplastic anaemia. Lymphadenopathy or fever suggest malignancy or infections (e.g., infectious mononucleosis). Splenomegaly may be seen in haematological malignancies.
- Clinical features of systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polyarteritis nodosa, or scleroderma resulting in persistent pure red cell aplasia may be present. Abnormal lung examination (if lung cancer is the primary cancer) or a breast mass (if breast cancer is the primary) may be present.
- A positive Trousseau's sign or Chvostek's sign in patients with chronic kidney disease indicates hypocalcaemia, probably due to associated secondary hyperparathyroidism.

**Initial investigations**

- Should be guided by the history and examination findings.
- FBC may show an associated cytopenia and characteristic changes specific to a haematological malignancy. A pancytopenia suggests aplastic anaemia, or may be due to chemotherapy or...
Assessment of anaemia

radiotherapy. An isolated anaemia suggests pure red cell aplasia or anaemia due to chronic kidney disease.

- Bone marrow biopsy is required for the definitive diagnosis of acute leukaemia (acute lymphocytic leukaemia, acute myelogenous leukaemia), chronic myelogenous leukaemia (CML), aplastic anaemia, or bone marrow metastases.

- Antiparvovirus antibodies are positive in parvovirus infection, the most common infectious cause of pure red cell aplasia.

Other tests to consider

- Hepatitis serology, to exclude acute or chronic active hepatitis
- Monospot test or Epstein-Barr virus (EBV) IgM, to exclude infectious mononucleosis
- Thick and thin peripheral smear, to exclude malaria if history and clinical findings suggest the diagnosis
- Thyroid function tests; thyroid-stimulating hormone (TSH) is elevated and free thyroxine (T4) reduced in hypothyroidism
- Antinuclear antibodies, which are positive in systemic lupus erythematosus or scleroderma
- Rheumatoid factor, which is positive in rheumatoid arthritis
- Serum creatine kinase (CK), which is elevated in dermatomyositis
- Chest x-ray, which may show infiltrates in atypical pneumonia or a smooth mass in thymoma
- Erythropoietin levels, which may be inappropriately decreased in patients with chronic renal failure. Serum calcium and parathyroid hormone levels should be considered if associated secondary hyperparathyroidism is suspected.

Normocytic anaemia: hyperproliferative

Potential diagnoses

- Include haemolytic anaemias.
- These conditions can be caused by microangiopathic haemolytic anaemias, autoimmune haemolytic anaemia, drugs, infections, inherited conditions, transfusion reactions, or burns.

History

- Drugs that can cause haemolysis include penicillin, methylidopa, levodopa, quinidines, cephalosporins, and some NSAIDs. Cyclosporine, tacrolimus, clopidogrel, oral contraceptive pills, and some chemotherapy drugs may cause haemolytic uraemic syndrome. Discontinuation of causative medications leads to resolution of the anaemia.
- There may be a history suggestive of microangiopathic disease. Known triggers of disseminated intravascular coagulation (DIC) include ongoing severe infection, sepsis, malignancy, obstetric emergency, trauma, burns, envenomation, drug overdose, or any cause of endothelial damage. The presence of acute-onset neurological symptoms, including headache, confusion, focal weakness, seizures, or coma, should prompt suspicion of thrombotic thrombocytopenic purpura (TTP). Female patients may have associated menorrhagia. Sudden-onset dizziness, headache, mental status changes, loss of sensation or motor strength, chest pain or pressure, dyspnoea, or oedema in a patient with known hypertension should prompt suspicion of malignant hypertension; a history of renal failure or eclampsia may also be present. An expanding vascular skin lesion in a young infant or child should prompt suspicion of a haemangioma. A history of prosthetic valve replacement may indicate haemolysis induced by the prosthesis.
Assessment of anaemia

Diagnosis

• Cutaneous burns affecting more than 10% of the body surface area can cause a haemolytic anaemia, or trigger DIC.
• Infective causes include cytomegalovirus (CMV), infectious mononucleosis, toxoplasmosis, and leishmaniasis. Bloody diarrhoea should prompt suspicion of *Escherichia coli* infection and haemolytic uraemic syndrome.
• Patients with inherited haemolytic anaemias such as sickle cell anaemia, hereditary spherocytosis, or glucose-6-phosphate dehydrogenase (G6PD) deficiency may have a positive family history. Persistent pain in the skeleton, chest, or abdomen; priapism; lower-extremity skin ulcers; or an acute pneumonia-like syndrome suggest sickle cell anaemia.
• There may be a previous history of autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, or scleroderma) or lymphoproliferative disorders (usually non-Hodgkin's lymphoma or chronic lymphocytic leukaemia), which can lead to autoimmune haemolytic anaemia. Note that autoimmune diseases may also cause pure red cell aplasia, in which case the reticulocyte count would be low, with normal lactate dehydrogenase, haptoglobin, and bilirubin levels.
• Recent blood transfusion may indicate haemolysis due to a transfusion reaction.
• Occupational or home exposure to lead should prompt suspicion of lead toxicity.

Examination

• Features of microangiopathic disease: there may be purpura or ecchymoses due to bleeding. Systolic BP >210 mmHg and diastolic BP >130 mmHg indicate malignant hypertension; associated signs may include new murmurs, S3 on auscultation of the heart, jugular venous distension, rales or lower-extremity oedema, oliguria or polyuria, focal neurological signs, and hypertensive retinopathy. Cutaneous reddish-brown or violaceous vascular lesions may indicate haemangioma.[34]
• Splenomegaly is seen in hereditary spherocytosis. Clinical features of underlying autoimmune diseases may be present. Lymphadenopathy may indicate infectious mononucleosis, leukaemia, lymphoma, or autoimmune disease.

Initial investigations

• The FBC and peripheral blood smear should be examined for clues to the underlying cause. A thrombocytopenia with schistocytes strongly suggests a microangiopathic haemolytic anaemia. Spherocytes suggest autoimmune haemolytic anaemia or hereditary spherocytosis. Hereditary spherocytosis is also associated with increased mean corpuscular Hb. Sickling of RBCs is diagnostic of sickle cell anaemia.[30] Heinz bodies, eccentrocytes, or bite cells are seen in G6PD deficiency.
• If haemolytic anaemia is suspected, serum lactate dehydrogenase, haptoglobin, and bilirubin should be measured. Elevated lactate dehydrogenase and bilirubin levels with a decreased haptoglobin are strongly suggestive of a haemolytic anaemia. Clinical jaundice is seen once bilirubin levels rise above 34.2 to 68.4 mmol/L (2-4 mg/dL).

Tests to consider in suspected microangiopathic haemolytic anaemias

• Serum creatinine, which may be elevated in patients with haemolytic uraemic syndrome or malignant hypertension. Kidney biopsy provides a definitive diagnosis of haemolytic uraemic syndrome.
• Prothrombin time and activated partial prothrombin time, which are prolonged in DIC but normal in other microangiopathic haemolytic anaemias. DIC panel shows elevated D-dimers and fibrin degradation products with low fibrinogen in patients with DIC. X-rays and magnetic resonance imaging (MRI) scanning of suspected regions reveal internal haemangiomas.

Tests to consider in other haemolytic anaemias
Assessment of anaemia

Diagnosis

- Direct antiglobulin (Coombs') test, which is positive in autoimmune haemolytic anaemia.
- Tests to identify hereditary causes. Sickle cell anaemia is diagnosed on FBC. Osmotic fragility test is positive in hereditary spherocytosis; cells lyse on exposure to hypo-osmotic solution. G6PD assays identify deficiencies of the enzyme.
- Tests to identify infection. Monospot test or EBV IgM is positive in infectious mononucleosis. CMV IgM is positive in CMV infection. Double-sandwich IgM enzyme-linked immunosorbent assay (ELISA) or IgG avidity test is positive for IgM in acute toxoplasmosis. Splenic or bone marrow aspirate shows amastigotes of the parasite in leishmaniasis.
- Blood lead levels, which are elevated in lead toxicity.

**Macrocytic anaemia: megaloblastic**

Potential diagnoses

- The main causes to consider are vitamin B12 or folate deficiency, or drugs that interfere with DNA synthesis. Autoimmune thyroid disease may coexist with pernicious anaemia and atrophic gastritis, which decrease B12 absorption. Therefore, screening for B12 deficiency when the aetiology of hypothyroidism is thought to be autoimmune is recommended.[66]
- Discontinuation of causative medications leads to resolution of the anaemia.

**History**

- Poor intake due to malnutrition, alcohol abuse, or strict vegan or low-protein diets can produce deficiency of vitamin B12 and/or folate.
- A history of coeliac disease, tropical sprue, Crohn's disease, previous gastric or intestinal surgery, or bacterial overgrowth may indicate malabsorption.
- A swollen, red, painful tongue; angular stomatitis; patchy hyperpigmentation of the skin and mucous membranes; and a persistent mild pyrexia are symptoms of folate deficiency.
- Drug history: known causative medications include purine analogues, pyrimidine analogues, reductase inhibitors, methotrexate, trimethoprim, anticonvulsants, oral contraceptives, cycloserine, p-aminosalicylic acid, metformin, colchicine, neomycin, and biguanides. Hydroxyurea, in particular, is known to cause oval macrocytosis with MCV >110 femtolitres (fL).

**Initial investigations**

- Serum vitamin B12 levels are decreased and serum methylmalonic acid levels are elevated in vitamin B12 deficiency. The latter is more sensitive and should be used to definitively exclude vitamin B12 deficiency. An MCV of >115 fL is typically seen in nutritional deficiency.
- Serum folate levels are low in folate deficiency. If folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected. Normal serum homocysteine levels make folate deficiency unlikely. RBC folate is a more accurate indicator of folate deficiency than serum folate level.
- Anti-intrinsic factor and parietal cell antibodies are positive in pernicious anaemia.

**Macrocytic anaemia: non-megaloblastic**

Potential diagnoses
Assessment of anaemia

Diagnosis

• Causes to consider include alcohol abuse, myelodysplastic syndrome, chronic liver disease, and congenital bone marrow failure syndromes.

History

• High alcohol intake indicates alcohol-induced anaemia, which usually persists for months after total abstinence. A history of chronic liver disease indicates liver disease-induced anaemia.
• History of prior exposure to petroleum distillates (especially benzene), chemotherapy, or radiotherapy should prompt suspicion of myelodysplastic syndrome.
• A history of fever, chills, fatigue, weakness, recurrent infection, anorexia, night sweats, shortness of breath, and easy bruising should prompt suspicion of myelodysplastic syndrome.
• Recurrent infections in an infant should prompt suspicion of congenital bone marrow failure syndromes.

Examination

• May reveal stigmata of chronic alcoholism or chronic liver disease.
• Dyskeratosis congenita is characterised by the triad of abnormal nails, reticulated skin rash, and leukoplakia.
• Skeletal abnormalities and growth retardation are seen in Shwachman-Diamond syndrome.

Investigations

• FBC shows associated neutropenia and thrombocytopenia with macro-ovalocytes in myelodysplastic syndrome.
• Bone marrow aspiration and biopsy shows myeloblasts with immature precursors in myelodysplastic syndrome. Diagnostic features of congenital bone marrow failure syndromes are also identified.
• Cytogenetics reveal chromosomal translocations in myelodysplastic syndrome.
• Additional tests for congenital bone marrow syndromes: diepoxybutane or mitomycin-c fragility test is positive in Fanconi anaemia. Genetic testing reveals underlying mutations.
## Differentials overview

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## Uncommon

- Generalised malnutrition
- Cytotoxic chemotherapy
- Radiotherapy
- Alcohol abuse
- Lead toxicity
- Hypothyroidism
- Autoimmune haemolytic anaemia (AIHA)
- Transfusion reaction
- Malaria
- Viral hepatitis
- Toxoplasmosis
- Leishmaniasis
- Parvovirus B19 infection
- Infectious mononucleosis
- Cytomegalovirus (CMV)
- Sickle cell anaemia
- Thalassaemias
- Hereditary spherocytosis
- Glucose-6-phosphate dehydrogenase deficiency (G6PD)
- Bone marrow failure syndromes
- Haemolytic uraemic syndrome
- Disseminated intravascular coagulation (DIC)
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<td>Prosthetic valves and surfaces</td>
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## Differentials

### Common

#### Trauma

<table>
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<th>Exam</th>
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<tr>
<td>history of trauma (including gunshot wounds, major fractures, crush injuries); history of prior bleeding episodes; or use of anticoagulants or non-steroidal anti-inflammatory drugs (NSAIDs)</td>
<td>evidence of injury (wounds, bruises, deformities), hypotension, pallor, tachycardia, dyspnoea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total body volume loss</td>
<td>» FBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response, thrombocytopenia from dilutional effect of multiple transfusions</td>
<td>» diagnostic laparotomy: identification of bleeding source</td>
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<td>» CT scan of affected body region: identification of internal injuries</td>
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<td>» FBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
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#### Acute gastrointestinal (GI) bleeding

<table>
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<tr>
<td>history of prior episodes of GI bleeding, gastritis, peptic ulcer disease, hiatal hernia, neoplastic disease, non-steroidal anti-inflammatory</td>
<td>hypotension, pallor, tachycardia, dyspnoea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least</td>
<td>» FBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
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### Common

#### Acute gastrointestinal (GI) bleeding

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</table>
| drug (NSAID) or corticosteroid use, alcohol use, cirrhosis, anticoagulants, ulcerative colitis, diverticulosis; symptoms of rectal bleeding, melaena, haematemesis, abdominal pain | 30% to 40% total blood volume loss; ascites, hepatomegaly/splenomegaly, cirrhotic hard liver, caput medusae, gynaecomastia, melaena, or bright red blood on rectal examination | **reticulocyte count:** >2%  
**prothrombin time (PTT)/activated partial thromboplastin time:** usually normal; prolonged in cirrhosis, anticoagulant therapy, or underlying defects in haemostasis; elevated urea may be seen | **upper GI endoscopy:** bleeding varices or ulcers if source is from upper GI tract  
**colonoscopy:** visualisation of bleeding lesion or mass |

#### Rupture of a vascular aneurysm

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| sudden tearing pain may be accompanied by loss of consciousness if major vessel involved; history of hypertension, collagen disorders, trauma, cocaine or amphetamine use | hypotension, pallor, tachycardia, dyspnoea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total blood volume loss; wide pulse pressure or absent distal pulses; may rapidly progress to circulatory collapse and death | **FBC:** normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response  
**reticulocyte count:** >2%  
**ultrasoundography of affected region:** shows extent and nature of aneurysm  
Intravascular ultrasound is more accurate if patient is stable.  
**CT scan of affected region:** shows extent and nature of aneurysm | **chest x-ray:** may show widened mediastinum in thoracic aortic aneurysm |

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From the collection of Professor James Brown; used with permission
### Common

#### Rupture of a vascular aneurysm

<table>
<thead>
<tr>
<th>History</th>
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<tr>
<td>recent surgery with at least moderate blood loss; history of bleeding disorders or excessive bruising; use of antibiotics</td>
<td>hypotension, pallor, tachycardia, continuous bleeding from surgical wound, petechiae, purpura; severe bleeding produces dyspnoea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total blood volume loss</td>
<td>FBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
<td>reticulocyte count: &gt;2%</td>
</tr>
<tr>
<td>ultrasound of affected region: shows source and extent of bleeding</td>
<td>CT scan of a ruptured abdominal aortic aneurysm University of Michigan, specifically the cases of Dr Gilbert R. Upchurch reflecting the Departments of Vascular Surgery and Radiology</td>
<td>CT scan of affected region: shows source and extent of bleeding</td>
<td>diagnostic laparotomy: shows source and extent of bleeding</td>
</tr>
</tbody>
</table>
### Common

#### Menorrhagia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| excessive menstrual bleeding lasting >7 days; fatigue, dyspnoea on exertion, pica; use of hormone therapy, history of fibroids | pallor, adnexal masses or fibroids | » FBC: chronic microcytic anaemia with normal WBC; reactive thrombocytosis if iron deficient  
» serum ferritin: <33 picomol/L (<15 micrograms/L) if iron deficient | » pregnancy test: negative  
» prothrombin time/activated partial thromboplastin time: usually normal; prolonged with anticoagulants, underlying defects in haemostasis, or consumptive coagulopathy  
» thyroid-stimulating hormone (TSH)/free thyroxine (T4): elevated TSH with low free T4 in hypothyroidism  
» transvaginal ultrasound: may see hyperplasia, dysplasia, fibroids, or polyps  
Endometrial carcinoma should be excluded in patients >40 years. |

#### Iron deficiency

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of poor dietary iron intake, coeliac disease, Crohn’s disease, ulcerative colitis, small bowel resection, peptic ulcer disease, regular running, chronic blood loss (melaena, haematuria, menorrhagia, haemoptysis, frequent blood donation, self-harm), pica, salicylate ingestion, gastric bypass, hookworm | pallor, dyspnoea, poor exercise tolerance, koilonychia, angular cheilosis, glossitis, thinning hair, systolic flow murmur; haemorrhoids, fresh blood or melaena on rectal examination; evidence of pregnancy; adnexal masses or fibroids | » FBC with peripheral smear: microcytic anaemia with thrombocytosis  
» serum iron studies: low serum iron, elevated total iron-binding capacity, low ferritin, elevated soluble transferrin receptor  
» immunoglobulin A-tissue transglutaminase (IgA-tTG) test: positive in coeliac disease | » upper GI endoscopy: identification of source of upper GI bleeding; elevated gastric pH in achlorhydria  
» colonoscopy: identification of source of lower GI bleeding or chronic inflammation  
» CT colonography: Identification of source of lower GI bleeding Useful alternative for patients who cannot tolerate colonoscopy. |
### Common

#### Iron deficiency

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>infestation, pregnancy, or menorrhagia</td>
<td></td>
<td></td>
<td>- flow cytometry: identification of paroxysmal nocturnal haemoglobinuria</td>
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<tr>
<td></td>
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<td></td>
<td>- transvaginal ultrasound: may see hyperplasia, dysplasia, fibroids, or polyps</td>
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<td></td>
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<td></td>
<td>- stool microscopy: visualisation of hookworm, whipworm, or Schistosoma eggs</td>
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<td></td>
<td>- Helicobacter pylori test: positive result if H pylori present</td>
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<td></td>
<td>Following negative endoscopy in the setting of persistent iron deficiency anaemia,</td>
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<td></td>
<td>H pylori testing may be considered when malignancies, B12 deficiency,</td>
</tr>
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<td></td>
<td></td>
<td>and idiopathic thrombocytopenic purpura have been excluded.</td>
</tr>
</tbody>
</table>

#### Vitamin B12 deficiency

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of coeliac or Crohn's disease,</td>
<td>impaired vibration sense and extremity numbness, vitiligo, glossitis,</td>
<td>FBC with peripheral smear: megaloblastic macrocytic anaemia; basophilic stippling may be seen</td>
<td>- serum vitamin B12 levels: low</td>
</tr>
<tr>
<td>autoimmune thyroid disease, gastric bypass,</td>
<td>poor balance or co-ordination, tachycardia, pallor, hepatosplenomegaly</td>
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<tr>
<td>chronic antibiotic use (intestinal bacterial</td>
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<tr>
<td>overgrowth syndrome), vegan</td>
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</tbody>
</table>
## Common

### Vitamin B12 deficiency

<table>
<thead>
<tr>
<th>History</th>
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</tr>
</thead>
<tbody>
<tr>
<td>diet or alcohol abuse; fatigue, palpitations, distal paraesthesias, depression, confusion, tinnitus, dementia</td>
<td>mild persistent pyrexia, tachycardia, pallor, hepatosplenomegaly, glossitis, angular stomatitis, patchy hyperpigmentation of skin and mucous membranes</td>
<td>serum methylmaionic acid levels: elevated</td>
<td>anti-intrinsic factor antibodies: positive in pernicious anaemia; antiparietal cell antibodies: positive in pernicious anaemia</td>
</tr>
</tbody>
</table>

### Folate deficiency

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<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of coeliac or Crohn's disease, gastric bypass, haemodialysis, pregnancy, alcohol abuse, or use of anti-seizure medications; fatigue, palpitations, headaches</td>
<td>mild persistent pyrexia, tachycardia, pallor, hepatosplenomegaly, glossitis, angular stomatitis, patchy hyperpigmentation of skin and mucous membranes</td>
<td>serum folate: low</td>
<td>serum homocysteine levels: elevated</td>
</tr>
</tbody>
</table>

### Myelodysplastic syndrome

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of prior exposure to petroleum distillates (especially benzene), chemotherapy, or radiotherapy; fever, chills, fatigue, weakness, recurrent</td>
<td>pallor, petechiae, purpura</td>
<td>FBC: macrocytic anaemia with leukopenia, macro-ovalocytes; associated cytopenias include neutropenia and thrombocytopenia</td>
<td>bone marrow aspiration and biopsy: myeloblasts with immature precursors; cytogenetics of bone marrow biopsy:</td>
</tr>
</tbody>
</table>
### Assessment of anaemia

#### Diagnosis

<table>
<thead>
<tr>
<th>Common</th>
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</table>

#### Myelodysplastic syndrome

<table>
<thead>
<tr>
<th>History</th>
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</tr>
</thead>
<tbody>
<tr>
<td>infection, anorexia, night sweats, shortness of breath, easy bruising</td>
<td>pallor, petechiae, purpura, tachycardia, hepatosplenomegaly, lymphadenopathy, painless scrotal enlargement, bleeding gums</td>
<td><strong>FBC with peripheral smear:</strong> pancytopenia, with $\geq 20%$ blasts; normocytic anaemia; may see hypereosinophilia</td>
<td>multiple chromosomal translocations possible, especially 5q-, 7q-, or trisomy 8 (+8)</td>
</tr>
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</table>

#### Acute lymphocytic leukaemia

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>malaise, fatigue, easy bruising or bleeding, recurrent infections, fever, arthralgias, infection, anorexia, night sweats, shortness of breath, bony tenderness, epistaxis, bleeding gums, gingival hyperplasia</td>
<td>pallor, petechiae, purpura, tachycardia, hepatosplenomegaly, lymphadenopathy, painless scrotal enlargement, bleeding gums</td>
<td><strong>FBC with peripheral smear:</strong> pancytopenia, with $\geq 20%$ blasts; normocytic anaemia; may see hypereosinophilia</td>
<td>bone marrow aspirate and biopsy: $\geq 20%$ blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Up to 10% of patients do not have peripherally circulating blasts.</td>
<td>Immunohistochemistry, cytochemistry, and cytogenetics help to further classify disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Reticulocyte count:</strong> $&lt;2%$</td>
<td></td>
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</tbody>
</table>

#### Acute myelogenous leukaemia

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>history of prior chemotherapy or radiotherapy; malaise, night sweats, fatigue, easy bruising or bleeding, recurrent infections, fever, bony tenderness, epistaxis, bleeding gums, gingival hyperplasia</td>
<td>pallor, petechiae, purpura, dyspnoea, tachycardia</td>
<td><strong>FBC with peripheral smear:</strong> pancytopenia, with $\geq 20%$ blasts; normocytic anaemia; may see hypereosinophilia</td>
<td>bone marrow aspirate and biopsy: $\geq 20%$ blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytoplasmic granules indicate myeloid lineage of blasts. May also see Auer’s rods.</td>
<td>Immunohistochemistry, cytochemistry, and cytogenetics help to further classify disease.</td>
</tr>
</tbody>
</table>
### Acute myelogenous leukaemia

<table>
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<tr>
<th>History</th>
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</tr>
</thead>
<tbody>
<tr>
<td>usually in middle-aged patients; fatigue, weight loss, night sweats, early satiety, petechiae, purpura, recurrent fevers, bone pain, gouty arthritis</td>
<td>tender splenomegaly, painful sternum, lymphadenopathy, splenomegaly</td>
<td>»FBC with peripheral smear: normocytic anaemia; myeloid maturing cells, elevated basophils, and eosinophils</td>
<td>»cytogenetics: t(19;22) Philadelphia chromosome - bcr-abl translocation</td>
</tr>
<tr>
<td>Peripheral blood film of a patient with acute myelogenous leukaemia showing myeloid blasts with an Auer rod</td>
<td>FBC with peripheral smear: normocytic anaemia; myeloid maturing cells, elevated basophils, and eosinophils</td>
<td>»serum uric acid: elevated</td>
<td>Due to elevated leukocyte count and turnover.</td>
</tr>
<tr>
<td>From the collection of Dr Kavita Raj and Dr Priyanka Mehta; used with patient consent</td>
<td>»reticulocyte count: &lt;2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chronic myelogenous leukaemia

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Peripheral blood film of a patient with acute myelogenous leukaemia showing myeloid blasts with an Auer rod</td>
<td>FBC with peripheral smear: normocytic anaemia; myeloid maturing cells, elevated basophils, and eosinophils</td>
<td>»cytogenetics: t(19;22) Philadelphia chromosome - bcr-abl translocation</td>
<td>Due to elevated leukocyte count and turnover.</td>
</tr>
<tr>
<td>From the collection of Dr Kavita Raj and Dr Priyanka Mehta; used with patient consent</td>
<td>»reticulocyte count: &lt;2%</td>
<td>Serum uric acid: elevated</td>
<td></td>
</tr>
</tbody>
</table>

Peripheral blood film of a patient with acute myelogenous leukaemia showing myeloid blasts with an Auer rod. From the collection of Dr Kavita Raj and Dr Priyanka Mehta; used with patient consent.
# Assessment of anaemia

## Diagnosis

### Common

#### Hairy cell leukaemia

<table>
<thead>
<tr>
<th>History</th>
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<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>weakness, fatigue, weight loss, night sweats, early satiety, petechiae, purpura, recurrent fevers, abdominal discomfort or fullness due to large spleen</td>
<td>massive splenomegaly</td>
<td>FBC with peripheral smear: pancytopenia with normocytic anaemia</td>
<td>bone marrow aspirate and biopsy: core biopsy shows hairy cells</td>
</tr>
</tbody>
</table>

Characteristic mononuclear 'hairy' cells, which stain positive for tartrate-resistant acid phosphatase (TRAP)

reticulocyte count: <2%

- Cytospin prepared from bone marrow aspirate illustrates the typical cell cytology, with oval- to bean-shaped nuclei and moderate amounts of cytoplasm with irregular cytoplasmic borders (Wright Giemsa 100x oil)
- From the collection of Lynn Moscinski, MD; used with permission

#### Acquired aplastic anaemia

<table>
<thead>
<tr>
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<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>history of hepatitis, HIV, benzene exposure, use of known causative medications, radiation exposure, paroxysmal nocturnal haemoglobinuria; malaise, fatigue, easy bruising or bleeding, recurrent infections, fever</td>
<td>pallor, petechiae, purpura, dyspnoea, tachycardia</td>
<td>FBC with peripheral smear: pancytopenia with mild macrocytosis; normocytic anaemia</td>
<td>bone marrow aspirate and biopsy: hypocellular with decrease in all elements, replaced mostly by fat cells; no infiltration by fibrosis or malignant cells</td>
</tr>
</tbody>
</table>

reticulocyte count: <2%

- serum vitamin B12: normal
- folate: normal
### Common

#### Infiltration by secondary malignancy

<table>
<thead>
<tr>
<th>History</th>
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</tr>
</thead>
</table>
| weight loss, malaise, fevers, fatigue, dyspnoea, easy bleeding or bruising; history of solid organ malignancy (particularly breast, prostate, lung, neuroblastoma) | pallor, petechiae, purpura, tachycardia, abnormal exam or presence of mass (if solid organ malignancy), bruising, cachexia | **FBC with peripheral smear:** pancytopenia, teardrop cells, poikilocytes; **normocytic anaemia**  
**reticulocyte count:** <2%  
**bone marrow aspirate and biopsy:** infiltration of marrow space by malignant cells  
Provide history to pathologist so appropriate stains can be ordered if metastatic malignancy is suspected. | **CT imaging:** identification of site of primary malignancy |

#### Pure red cell aplasia

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| self-limiting disease: history of use of known causative medications, clinical features of causative infections (parvovirus B19, infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, mumps); chronic disease: history of autoimmune disease (systemic lupus erythematosus [SLE], rheumatoid arthritis, dermatomyositis, scleroderma, polyarteritis nodosa), persistent infection, or thymoma | clinical signs of underlying infection or autoimmune disease | **FBC:** normocytic anaemia  
**reticulocyte count:** <2%  
**trial of discontinuation of causative medication:** anaemia resolves  
**antiparvovirus B19 antibodies:** positive in parvovirus infection  
The most common infectious cause. | **thick and thin peripheral smear:** intracellular parasites seen with Wright's or Giemsa staining in malaria infection  
**serum IgM + IgG anti-HAV:** positive in hepatitis A infection  
**serum IgM + IgG HBCAb:** positive in hepatitis B infection  
**serum HBsAg:** positive in hepatitis B infection  
**serum IgM + IgG anti-HCV:** positive in hepatitis C infection  
**antinuclear antibodies:** positive in SLE or scleroderma |
## Common

### Pure red cell aplasia

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ds-DNA, Smith’s antigen: positive in SLE</td>
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<tr>
<td></td>
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<td></td>
<td>rheumatoid factor: positive in rheumatoid arthritis</td>
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<td></td>
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<td></td>
<td>serum creatine kinase (CK): elevated in dermatomyositis</td>
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<td></td>
<td>chest x-ray: infiltrates in atypical pneumonia; smooth mass in thymoma, typically projecting into one of the hemi-thoraces and obscuring the aortic arch, or silhouette sign</td>
</tr>
</tbody>
</table>

### Drug toxicity

<table>
<thead>
<tr>
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<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>known or suspected ingestion of causative drug prior to onset of anaemia, poor exercise tolerance</td>
<td>pallor, jaundice (with haemolytic anaemia only), dyspnoea</td>
<td>FBC with peripheral smear: typically normocytic anaemia; inhibitors of DNA synthesis, folate, or vitamin B12 produce megaloblastic macrocytic anaemia</td>
<td>serum bilirubin: elevated in haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reticulocyte count: &lt;2% if drugs suppress bone marrow; &gt;2% if drugs produce haemolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>trial of discontinuation of causative medication: anaemia resolves</td>
<td></td>
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</tbody>
</table>

### Anaemia of chronic disease

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of known chronic inflammatory,</td>
<td>pallor, fatigue, dyspnoea; specific</td>
<td>FBC: normocytic anaemia</td>
<td>serum erythropoietin level:</td>
</tr>
</tbody>
</table>
### Common

#### Anaemia of chronic disease

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
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<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>autoimmune, or infectious states; sustained physiological stress, renal failure; vasculitis or collagen vascular diseases, poor exercise tolerance; anaemia correlates with severity of inflammatory process</td>
<td>signs of underlying disease</td>
<td>May be microcytic if anaemia of chronic disease is co-existent with iron deficiency anaemia.</td>
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<tr>
<td></td>
<td></td>
<td>»serum iron studies: low/normal serum iron, low total iron-binding capacity and normal/elevated ferritin; ferritin normal or elevated in acute-phase reaction When anaemia of chronic disease is co-existent with iron deficiency anaemia, these parameters may be different.</td>
<td>normal or elevated; often decreased in chronic kidney disease Elevation, if present, is usually inadequate to compensate for the degree of anaemia.</td>
</tr>
</tbody>
</table>

#### Chronic kidney disease

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| chronic kidney disease, poor exercise tolerance; features of secondary hypoparathyroidism: muscle cramps, bone pain | pallor, fatigue, dyspnoea; signs of renal failure: jaundice, skin bruising, lung rales, pericardial rub, oedema, poor concentration or memory, myoclonus; positive Chvostek's sign or Trousseau's sign in associated hyperparathyroidism | »FBC: normocytic or microcytic anaemia with thrombocytosis
»reticulocyte count: <2%
»serum creatinine: elevated
»urinalysis: haematuria and/or proteinuria
»serum iron studies: low serum iron and normal/elevated ferritin, high total iron-binding capacity in iron deficiency
»serum erythropoietin level: normal or decreased | »serum calcium level: decreased in associated secondary hyperparathyroidism
»serum intact parathyroid hormone level: increased in associated secondary hyperparathyroidism
»renal ultrasound: small kidney size; presence of obstruction or hydronephrosis; kidney stones
»kidney biopsy: identification of underlying kidney pathology |
## Common

### ♦ Chronic liver disease

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<tr>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of chronic liver disease, poor exercise tolerance; may be</td>
<td>pallor, fatigue, dyspnoea, jaundice,</td>
<td>»FBC: non-megaloblastic macrocytic anaemia; thrombocytopenia may be</td>
<td>»abdominal ultrasound, CT, or MRI scanning: liver</td>
</tr>
<tr>
<td>asymptomatic or with fatigue, weakness, weight loss, recurrent</td>
<td>lower-extremity swelling; hand and nail</td>
<td>increased in hepatic synthetic dysfunction</td>
<td>surface nodularity, small liver, possible</td>
</tr>
<tr>
<td>infections, decreased libido; altered mental status in hepatic</td>
<td>features: leukonychia, palmar erythema,</td>
<td>»prothrombin time: decreased in hepatic synthetic dysfunction</td>
<td>hypertrophy of left/caudate lobe, evidence of</td>
</tr>
<tr>
<td>encephalopathy</td>
<td>finger clubbing, spider angiomata; facial</td>
<td>»liver function tests (LFTs): abnormal; pattern depends on underlying</td>
<td>ascites or collateral circulation</td>
</tr>
<tr>
<td></td>
<td>features: telangiectasia, bruising,</td>
<td>cause or subsequent cirrhosis</td>
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<td></td>
<td>rhinophyma, parotid gland swelling,</td>
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<td>paper-dollar appearance of skin,</td>
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<td>seborrhoeic dermatitis, xanthelasma;</td>
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<td></td>
<td>abdominal features: caput medusae,</td>
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<td></td>
<td>bruising, heptomegaly, splenomegaly,</td>
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<td></td>
<td>abdominal distension; in males, loss of</td>
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<td>secondary sexual hair and testicular</td>
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<td></td>
<td>atrophy, gynaecomastia</td>
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### ♦ Pregnancy

<table>
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<tr>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>pregnancy, especially in third trimester</td>
<td>abdominal distension consistent with</td>
<td>»FBC: microcytic anaemia with thrombocytosis in iron deficiency; megaloblastic macrocytic anaemia in folate deficiency</td>
<td>»serum iron studies: low serum iron, elevated</td>
</tr>
<tr>
<td></td>
<td>pregnancy</td>
<td></td>
<td>total iron-binding capacity, low ferritin,</td>
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<td></td>
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<td>elevated soluble transferrin receptor in iron</td>
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<td></td>
<td></td>
<td></td>
<td>deficiency</td>
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<td>»serum folate: low in folate deficiency</td>
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</tbody>
</table>

## Uncommon

### ★ Generalised malnutrition

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>protein calorie deprivation;</td>
<td>loss of subcutaneous fat, apathy and</td>
<td>»FBC with peripheral smear:</td>
<td>»serum vitamin B12: low</td>
</tr>
<tr>
<td></td>
<td>lethargy,</td>
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</table>
### Uncommon

#### Generalised malnutrition

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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>malabsorption syndrome; neglect; history of an eating disorder</td>
<td>depigmentation, enlarged abdomen, winged scapula, flaky skin, bipedal oedema</td>
<td>microcytic anaemia in iron deficiency; megaloblastic macrocytic anaemia in vitamin B12 and folate deficiency; normocytic anaemia with combined vitamin and mineral deficiencies</td>
<td>» serum iron studies: low serum iron, elevated total iron-binding capacity, and low ferritin in iron deficiency</td>
</tr>
</tbody>
</table>

#### Cytotoxic chemotherapy

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of myelosuppressive chemotherapy; fatigue; headaches; poor exercise tolerance | pallor, lethargy, dyspnoea | FBC: pancytopenia with a normocytic anaemia | » serum folate: low
» serum copper level: low
Copper deficiency needs to be considered in patients on prolonged total parenteral nutrition. |

Counts usually reach nadir 7 to 10 days after administration of chemotherapy.

» reticulocyte count: <2%

#### Radiotherapy

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>history of recent radiation exposure, especially to pelvic or sternal areas; fatigue, headaches, poor exercise tolerance</td>
<td>pallor, lethargy, dyspnoea, skin erythema on radiation sites</td>
<td>FBC: anaemia (pancytopenia)</td>
<td>bone marrow aspirate and biopsy: marrow fibrosis or malignant infiltration</td>
</tr>
</tbody>
</table>

» reticulocyte count: <2%
## Uncommon

### Alcohol abuse

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of chronic high alcohol intake</td>
<td>overweight status, increased prominence of superficial cutaneous vasculature, peripheral neuropathy, alterations in normal dentition and halitosis, possible signs of liver disease: hepatomegaly or small liver, jaundice, ascites</td>
<td>»FBC: macrocytic anaemia</td>
<td>»diagnostic interview: diagnosis of alcohol dependence</td>
</tr>
</tbody>
</table>

### Lead toxicity

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
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<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of occupational or recreational exposure to lead products or old paint; neuropsychiatric disturbance, insomnia, abdominal pain, poor appetite, pica</td>
<td>blue gingival line (Burton's line), hypertension, gout (saturnine gout); wrist or foot drop</td>
<td>»FBC with peripheral smear: normocytic anaemia with basophilic stippling; microcytic anaemia if associated iron deficiency is present</td>
<td>»reticulocyte count: &gt;2%</td>
</tr>
</tbody>
</table>

### Hypothyroidism

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>weakness, lethargy, slow speech, feeling cold, forgetfulness, constipation, weight gain, poor exercise tolerance</td>
<td>pallor; dyspnœa; coarse, dry skin; eyelid oedema; thick tongue; facial oedema; bradycardia</td>
<td>»FBC: non-megaloblastic macrocytic anaemia</td>
<td>»serum TSH: elevated</td>
</tr>
</tbody>
</table>

### Autoimmune haemolytic anaemia (AIHA)

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of autoimmune diseases (SLE, rheumatoid arthritis, or scleroderma),</td>
<td>pallor, lethargy, dyspnœa, tachycardia, jaundice, splenomegaly (especially if</td>
<td>»FBC with peripheral smear: normocytic anaemia, with spherocytes</td>
<td></td>
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</tbody>
</table>
### Uncommon

#### Autoimmune haemolytic anaemia (AIHA)

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphoproliferative disorders (non-Hodgkin’s lymphoma or chronic lymphocytic leukaemia), recent viral illness, or mononucleosis; may be asymptomatic; symptoms include weakness, fatigue, headaches, poor exercise tolerance, prior gallstones, dark urine, clay-coloured stools</td>
<td>extravascular haemolysis</td>
<td>reticulocyte count: &gt;2%; usually 4% The elevated reticulocyte count may incorrectly increase mean corpuscular volume (MCV) on automated counters.</td>
<td>lactate dehydrogenase (LDH): elevated haptoglobin: low direct antiglobulin (Coombs’) test: usually positive; negative in 5% to 10% of cases serum bilirubin: elevated</td>
</tr>
</tbody>
</table>

*Peripheral blood smear with spherocytes, reticulocytes, and a nucleated red blood cell (RBC)*

*From the collection of John Densmore, Department of Medicine, University of Virginia; used with permission*
### Uncommon

## Transfusion reaction

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>multiple prior transfusions; fever, back pain, and dyspnoea, usually within 6 hours of transfusion</td>
<td>pallor, lethargy, dyspnoea, dark urine, jaundice</td>
<td><strong>»ABO typing:</strong> discrepancy to blood used for transfusion. Most commonly a clerical error. Stop transfusion immediately and stabilise patient.</td>
<td><strong>»direct antiglobulin (Coombs') test:</strong> IgG anti-A, anti-B, or anti-AB detected on circulating red cells.</td>
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<td></td>
<td><strong>»serum bilirubin:</strong> elevated</td>
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<tr>
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<td><strong>»inspection of plasma in centrifuged, anticoagulated venous blood sample:</strong> clear or pink-red within first few hours of haemoglobinaemia.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>»inspection of centrifuged urine:</strong> clear red in haemoglobinaemia.</td>
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</tbody>
</table>

## Malaria

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of mosquito bite or habitation in malaria-prone region; fatigue, dyspnoea, fevers and prostration, decreased exercise tolerance, headaches, malaise; symptoms usually cycle every 48 to 72 hours, coinciding with red blood cell (RBC) destruction</td>
<td>jaundice or pallor, splenomegaly, dyspnoea, high flow cardiac murmur, pulmonary oedema, dark urine, fevers</td>
<td><strong>»FBC:</strong> normocytic anaemia ± thrombocytopenia and leukopenia.</td>
<td><strong>»serum bilirubin:</strong> elevated</td>
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<tr>
<td></td>
<td></td>
<td><strong>»reticulocyte count:</strong> &gt;2%; usually 4%</td>
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<tr>
<td></td>
<td></td>
<td><strong>»thick and thin peripheral smear:</strong> intracellular parasites seen with Wright's or Giemsa staining. Banana-shaped gametocytes or multiple signet-ring forms in RBCs are typical for <em>Plasmodium falciparum</em>, which requires hospital admission.</td>
<td></td>
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</tbody>
</table>
## Uncommon

### Viral hepatitis

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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>perinatal exposure, direct body fluid transmission, exposure to foodborne outbreak (in hepatitis A); nausea, vomiting, abdominal pain, fever, malaise, fatigue and headache, dark urine, acholic (clay-coloured) stools, jaundice, pruritus (in hepatitis B); hepatitis C is usually asymptomatic</td>
<td>jaundice, hepatomegaly, RUQ pain, acholic stools, maculopapular or urticarial skin rash (in hepatitis B); usually normal in hepatitis C</td>
<td>»FBC: normocytic anaemia</td>
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<tr>
<td></td>
<td></td>
<td>reticulocyte count: &lt;2%</td>
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<td></td>
<td>serum aminotransferases: elevated</td>
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<td>serum IgM + IgG anti-HAV: positive in hepatitis A infection</td>
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<tr>
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<td>serum IgM + IgG HBcAb: positive in hepatitis B infection</td>
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<td>serum HBsAg: positive in hepatitis B infection</td>
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<tr>
<td></td>
<td></td>
<td>serum IgM + IgG anti-HCV: positive in hepatitis C infection</td>
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### Toxoplasmosis

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>usually seen in pregnant or immunosuppressed patients and newborns; history of exposure to domestic cats, sheep, or cattle, or to raw meat</td>
<td>jaundice, fever, fatigue, lethargy, rash, hepatosplenomegal; newborns infected in utero may have chorioretinitis, microcephaly, seizures, mental retardation</td>
<td>»FBC: normocytic anaemia and thrombocytopenia; may see leukocytosis and eosinophilia</td>
<td>»PCR for Toxoplasma gondii: positive</td>
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<tr>
<td></td>
<td></td>
<td>reticulocyte count: &gt;2%; usually 4%</td>
<td></td>
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<td></td>
<td></td>
<td>IgM enzyme-linked immunosorbent assay (ELISA) or IgG avidity test: IgM detected in acute infection; IgG detected in chronic or previous exposure IgM may persist long after infection; its absence excludes infection.</td>
<td></td>
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</tbody>
</table>
### Uncommon

#### Toxoplasmosis

<table>
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<tr>
<th>History</th>
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</thead>
<tbody>
<tr>
<td>history of exposure to sandfly bite, especially in tropical or subtropical zones; AIDS, immunosuppression, or malnutrition; fatigue and anorexia; prolonged, persistent, low-grade intermittent fevers; failure to thrive, distended abdomen</td>
<td>pallor, jaundice, hepatosplenomegaly, lymphadenopathy, diarrhoea, skin ulcerations, nasopharyngeal ulcerations</td>
<td>» Sabin-Feldman dye test: IgG antibodies positive</td>
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</tbody>
</table>

#### Leishmaniasis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>history of exposure to sandfly bite, especially in tropical or subtropical zones; AIDS, immunosuppression, or malnutrition; fatigue and anorexia; prolonged, persistent, low-grade intermittent fevers; failure to thrive, distended abdomen</td>
<td>pallor, jaundice, hepatosplenomegaly, lymphadenopathy, diarrhoea, skin ulcerations, nasopharyngeal ulcerations</td>
<td>» FBC: normocytic anaemia, thrombocytopenia, leukopenia, erythroblastosis</td>
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</tr>
</tbody>
</table>

#### Parvovirus B19 infection

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>acute infection: characteristic skin rash with or without arthralgia</td>
<td>acute infection: ‘slapped cheek’ appearance followed by a reticular erythematous eruption on extremities, and arthritis of hands, wrists, knees, or ankles</td>
<td>» FBC: normocytic anaemia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &gt;2%</td>
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#### Infectious mononucleosis

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<tr>
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<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>fatigue, malaise, sore throat, nausea, ocular pain, photophobia</td>
<td>fever, lymphadenopathy, pharyngitis, rash, tender splenomegaly, palatal petechiae, periorbital oedema, jaundice</td>
<td>» FBC with peripheral smear: normocytic anaemia, with spherocytes and atypical lymphocytes</td>
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<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &gt;2% and usually 4% in lactate dehydrogenase (LDH): elevated</td>
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<tr>
<td></td>
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<td>» haptoglobin: low</td>
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</table>
### Uncommon

#### Infectious mononucleosis

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>infection is usually asymptomatic; a maculopapular rash following administration of antibiotics may occur; fatigue occurs due to anaemia; symptomatic infection is a sign of underlying immunosuppression</td>
<td>usually normal; jaundice occurs due to haemolytic anaemia; symptomatic infection produces fever, lymphadenopathy, pharyngitis, rash, tender splenomegaly, palatal petechiae, periorbital oedema</td>
<td>haemolytic anaemia, &lt;2% in pure red cell aplasia</td>
<td>monospot test or Epstein-Barr virus (EBV) IgM: positive</td>
</tr>
</tbody>
</table>

#### Cytomegalovirus (CMV)

<table>
<thead>
<tr>
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<tbody>
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<td>infection is usually asymptomatic; a maculopapular rash following administration of antibiotics may occur; fatigue occurs due to anaemia; symptomatic infection is a sign of underlying immunosuppression</td>
<td>usually normal; jaundice occurs due to haemolytic anaemia; symptomatic infection produces fever, lymphadenopathy, pharyngitis, rash, tender splenomegaly, palatal petechiae, periorbital oedema</td>
<td>haemolytic anaemia</td>
<td>monospot test or Epstein-Barr virus (EBV) IgM: positive, lactate dehydrogenase (LDH): elevated, haptoglobin: low</td>
</tr>
</tbody>
</table>

#### Sickle cell anaemia

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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>known diagnosis of sickle cell disease in patient and/or parents; prior painful vaso-occlusive crises; fatigue, poor exercise tolerance, persistent pain in skeleton, chest, or abdomen, priapism, gallstones, stroke, lower-extremity skin ulcers, pneumonia-like syndrome</td>
<td>high fever, pallor, lethargy, dyspnoea, jaundice during acute crisis</td>
<td>FBC: normocytic anaemia, reticulocyte count: &gt;2%; usually 4%</td>
<td>CMV IgM: positive</td>
</tr>
</tbody>
</table>
# Uncommon

## Sickle cell anaemia

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<tr>
<th>History</th>
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</tr>
</thead>
<tbody>
<tr>
<td>family history of blood disorders, especially requiring repeated transfusions; Mediterranean, Middle Eastern, or Southeast Asian descent; variable severity ranging from asymptomatic to severe transfusion-dependent symptoms</td>
<td>splenomegaly, jaundice, abdominal distension, icterus; skeletal abnormalities, large head, chipmunk facies, and misaligned teeth seen in beta-thalassaemia intermedia and major</td>
<td><em>FBC with peripheral smear:</em> microcytic anaemia with mean corpuscular volume (MCV) typically closer to 70 fL, low mean corpuscular haemoglobin (Hb); target cells seen</td>
<td><em>serum ferritin:</em> elevated in iron overload</td>
</tr>
</tbody>
</table>

## Thalassaemias

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<tr>
<td>family history of blood disorders, especially requiring repeated transfusions; Mediterranean, Middle Eastern, or Southeast Asian descent; variable severity ranging from asymptomatic to severe transfusion-dependent symptoms</td>
<td>splenomegaly, jaundice, abdominal distension, icterus; skeletal abnormalities, large head, chipmunk facies, and misaligned teeth seen in beta-thalassaemia intermedia and major</td>
<td><em>FBC with peripheral smear:</em> microcytic anaemia with mean corpuscular volume (MCV) typically closer to 70 fL, low mean corpuscular haemoglobin (Hb); target cells seen</td>
<td><em>serum ferritin:</em> elevated in iron overload</td>
</tr>
</tbody>
</table>
### Uncommon

#### Hereditary spherocytosis

<table>
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<tr>
<th>History</th>
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<th>1st Test</th>
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</thead>
</table>
| family history of blood disorder, splenectomy, or pigmented gallstones; may be asymptomatic if extramedullary haematopoiesis compensates | may be normal or show pallor, jaundice, lower leg skin ulcers, splenomegaly | FBC with peripheral smear: normocytic anaemia, with increased mean corpuscular haemoglobin and spherocytes  
reticulocyte count: >2%  
*osmotic fragility test:* positive (cells lyse on exposure to hypo-osmotic solution) | direct antiglobulin (Coombs’) test: negative  
Excludes immune-mediated haemolytic anaemias. |

#### Glucose-6-phosphate dehydrogenase deficiency (G6PD)

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<tr>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| usually in males of African, Mediterranean, Sardinian, or Sephardic Jewish descent; self-limiting episodes of acute haemolysis when exposed to oxidant stress; life-threatening symptoms more common with the Mediterranean variant | pallor, jaundice, mild dyspnoea | FBC with peripheral smear: normocytic anaemia with Heinz bodies, eccentrocytes, or bite cells  
Heinz bodies are rapidly cleared by the spleen within 24 hours, resulting in ‘bite cells’.  
reticulocyte count: >2%  
serum haptoglobin: decreased  
lactate dehydrogenase (LDH): elevated | G6PD enzyme assays: quantitative or qualitative abnormalities  
May be falsely negative during the acute haemolytic event, owing to the destruction of affected cells.  
serum bilirubin: elevated indirect bilirubin  
direct antiglobulin (Coombs’) test: negative  
Distinguishes glucose-6-phosphate dehydrogenase deficiency from immune haemolytic anaemias. |
### Bone marrow failure syndromes

<table>
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<tr>
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<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| recurrent infection shortly after birth, fever, easy bleeding or bruising, organ abnormalities, short stature | ill-appearing, with weight loss, pallor, lethargy, dyspnoea, petechiae, purpura, and/or thrush | «FBC with peripheral smear: pancytopenia with normocytic or macrocytic anaemia Causes include Fanconi anaemia, dyskeratosis congenita, and Shwachman-Diamond syndrome.» | «bone marrow aspiration and biopsy: varies depending on underlying cause»
| | | »reticulocyte count: <2% | «diepoxynbutane or mitomycin-c fragility test: positive in Fanconi anaemia»
| | | | «genetic testing: characteristic genetic mutations detected»

### Haemolytic uraemic syndrome

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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</thead>
</table>
| acute renal failure usually following an enteric bacterial infection (Escherichia coli 0157:H7) with bloody diarrhoea, or Streptococcus pneumoniae | pallor, lethargy, dyspnoea, petechiae, purpura, bloody diarrhoea; usually self-limiting in children | «FBC with peripheral smear: normocytic anaemia, thrombocytopenia, schistocytes» | «prothrombin time/activated partial thromboplastin time: normal Excludes disseminated intravascular coagulation (DIC).»
| | | »erythrocyte count: >2% | «serum haptoglobin: decreased»
| | | | «lactate dehydrogenase (LDH): elevated»
| | | | «serum bilirubin: elevated»
| | | | «direct antiglobulin (Coombs') test: negative Excludes immune-mediated haemolytic anaemias.»
| | | | «kidney biopsy: hyaline arteriolar thrombi in absence of inflammatory changes in vessel wall»
| | | | «serum bilirubin: elevated»
| | | | «lactate dehydrogenase (LDH): elevated»
| | | | «direct antiglobulin (Coombs') test: negative Excludes immune-mediated haemolytic anaemias.»
| | | | «kidney biopsy: hyaline arteriolar thrombi in absence of inflammatory changes in vessel wall»
## Uncommon

### Disseminated intravascular coagulation (DIC)

<table>
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<th>1st Test</th>
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</thead>
<tbody>
<tr>
<td>ongoing severe infection, sepsis (typically gram-negative), malignancy, obstetric emergency, trauma, burns, envenomations, drug overdose, any cause of endothelial damage</td>
<td>diffuse bleeding, especially from puncture sites or minor trauma; unprovoked clots; clinical signs of underlying cause</td>
<td>«FBC with peripheral smear: normocytic anaemia, thrombocytopenia, schistocytes</td>
<td>«prothrombin time: prolonged</td>
</tr>
<tr>
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<td></td>
<td>» activated partial thromboplastin time: varies depending on factor VII levels</td>
<td>«DIC panel: elevated D-dimer and fibrin degradation products with low fibrinogen</td>
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<td>Fibrinogen may be normal or elevated as an acute-phase reactant.</td>
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### Thrombotic thrombocytopenic purpura

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<tr>
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</thead>
<tbody>
<tr>
<td>non-specific prodrome followed by headache, confusion, focal weakness, seizures, coma; menorrhagia may be seen due to bleeding</td>
<td>pallor, lethargy, dyspnoea, purpura, ecchymoses</td>
<td>«FBC with peripheral smear: normocytic anaemia with schistocytes</td>
<td>«reticulocyte count: &gt;2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» direct antiglobulin (Coombs') test: negative</td>
<td>«DIC panel: elevated D-dimer and fibrin degradation products with low fibrinogen</td>
</tr>
<tr>
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<td>Excludes immune-mediated haemolytic anaemias.</td>
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### Haemangioma

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<tr>
<th>History</th>
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</thead>
<tbody>
<tr>
<td>typically young child or infant with expanding vascular skin lesion;</td>
<td>depends on location of lesion(s), which are typically reddish-brown</td>
<td>«FBC with peripheral smear:</td>
<td>«x-ray of suspected region: soft-tissue shadows, phleboliths</td>
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### Uncommon

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<tr>
<th>♦ Haemangioma</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
</tr>
<tr>
<td><strong>Exam</strong></td>
</tr>
<tr>
<td><strong>1st Test</strong></td>
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<tr>
<td><strong>Other tests</strong></td>
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</tbody>
</table>

$\text{reticulocyte count:}>2\%$

### Malignant hypertension

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<th>≈ Malignant hypertension</th>
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<td><strong>History</strong></td>
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<td><strong>Exam</strong></td>
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<td><strong>1st Test</strong></td>
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<td><strong>Other tests</strong></td>
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### ♦ Prosthetic valves and surfaces

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## Uncommon

### Prosthetic valves and surfaces

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<td>Excludes immune-mediated haemolytic anaemias.</td>
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### Cutaneous burns

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<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
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<td>burn injury to at least 10% of total body surface area (TBSA); multiple surgical procedures</td>
<td>epidermal or dermal loss consistent with burn injury</td>
<td>FBC with peripheral smear: normocytic anaemia with thrombocytopenia; schistocytes from peripheral destruction seen on blood smear</td>
<td>reticulocyte count: &gt;2%</td>
</tr>
</tbody>
</table>
Guidelines

Europe


Published by: British Society for Haematology (BSH)
Last published: 2017

Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia (https://b-s-h.org.uk/guidelines/)

Published by: British Society for Haematology
Last published: 2017

The diagnosis and management of primary autoimmune haemolytic anaemia (https://b-s-h.org.uk/guidelines/)

Published by: British Society for Haematology
Last published: 2016

Guidelines for the diagnosis and management of adult aplastic anaemia (https://b-s-h.org.uk/guidelines/)

Published by: British Society for Haematology
Last published: 2015

Chronic kidney disease: managing anaemia (https://www.nice.org.uk/guidance/ng8)

Published by: National Institute for Health and Care Excellence
Last published: 2015

Guidelines for the management of iron deficiency anaemia (https://www.bsg.org.uk/clinical/bsg-guidelines.html)

Published by: British Society of Gastroenterology
Last published: 2011
North America

Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage (http://www.aabb.org/programs/clinical/Pages/default.aspx)

Published by: AABB (formerly known as American Association of Blood Banks)
Last published: 2016


Published by: Canadian Society of Nephrology
Last published: 2008
Key articles


References


Assessment of anaemia


Assessment of anaemia

Images

**Figure 1: Microcytic anaemia**

*From the collection of Dr Robert Zaiden; used with permission*

**Figure 2: Megaloblastic macrocytic anaemia**

*From the collection of Dr Robert Zaiden; used with permission*
Figure 3: Classification of anaemia: MCV, mean corpuscular volume; fL, femtolitres

Created by the BMJ Knowledge Centre

Figure 4: Algorithm for the assessment of anaemia
Figure 5: CT scan of a ruptured abdominal aortic aneurysm

University of Michigan, specifically the cases of Dr Gilbert R. Upchurch reflecting the Departments of Vascular Surgery and Radiology
Figure 6: Chest x-ray showing a widened mediastinum

From the collection of Professor James Brown; used with permission
Figure 7: Peripheral blood film of a patient with acute myelogenous leukaemia showing myeloid blasts with an Auer rod

From the collection of Dr Kavita Raj and Dr Priyanka Mehta; used with patient consent
Assessment of anaemia

Figure 8: Cytospin prepared from bone marrow aspirate illustrates the typical cell cytology, with oval- to bean-shaped nuclei and moderate amounts of cytoplasm with irregular cytoplasmic borders (Wright Giemsa 100x oil)

From the collection of Lynn Moscinski, MD; used with permission

Figure 9: Peripheral blood smear with spherocytes, reticulocytes, and a nucleated red blood cell (RBC)

From the collection of John Densmore, Department of Medicine, University of Virginia; used with permission
Figure 10: Red cells in sickle cell disease

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.
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