

Differential diagnosis of anaemia: what are the difficulties; when are transfusions appropriate?

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- Blood loss is the most common cause of anaemia in the developed world
- Blood loss is not always recognised
- Tissue iron stores can be depleted following the loss of 1200ml of blood in males and 600ml in women
- Anaemia is often a major signal of disease
- Serial evaluations of blood parameters can be useful

A number of approaches can be taken to determine the causes of anaemia. The kinetic approach explores the mechanism(s) for the fall in haemoglobin (Hb) level. This may reflect decreased Hb or red blood cell (RBC) production, increased RBC destruction (haemolysis inherited or acquired) or blood loss. Blood loss is the most common in the developed world. This may be from obvious causes (e.g. menorrhagia), from occult bleeding (e.g. caecal carcinoma) or induced bleeding. Blood loss is not always readily recognised for example, factitious bleeding, blood loss during or after surgery or bleeding into the thigh or retroperitoneal cavity (i.e. during anticoagulant therapy).

Tissue iron stores can be depleted following the loss of 1200ml of blood in males and 600ml in women. As the availability of iron is normally rate limiting for RBC production iron deficiency may reduce the marrow response and worsen the anaemia.

In the case of anaemia of chronic disease (ACD) there is reduced absorption of iron from the gastrointestinal tract and a decrease in the release of iron from macrophages. In this state erythropoietin levels are also compromised which, with the reduced availability of iron, result in reduced RBC production.

Anaemia is often a major signal of disease. History, physical examination and laboratory tests are undertaken to establish:

- Is the patient bleeding (currently or in the past)?
- Is there evidence for increased RBC destruction (haemolysis)?
- Is the bone marrow suppressed?
- Is the patient iron deficient? If so, why?
- Is the patient deficient in folate or B12? If so, why?

The history will endeavour to ascertain the causes of anaemia. These will include signs of co-morbidities (tar like stools in a patient with ulcer-type pain). Duration of anaemia (recent, suggesting acquired anaemia; lifelong, indicative of an inherited haemoglobinopathy). Ethnicity and country of origin will inform about lifelong anaemia. And information on any medication therapy that may cause bleeding (NSAIDs) may provide a further insight. Past history of disease (e.g. liver), receipt of blood transfusions and work and environmental exposure will provide further information. An assessment of nutritional status is especially important in the elderly and those with high alcohol consumption.

The physical examination will seek signs of multisystem involvement and severity of the condition (e.g. tachycardia, dyspnea). Signs of jaundice and pallor may be noted but are generally poor performance characteristics. Evidence of lymphadenopathy and hepatosplenomegaly may indicate an underlying haematological problem. Bone tenderness and pain, especially over the sternum, may suggest marrow space extension and possible CML, lytic lesions or signs of recurrent infection. Digital examination of the rectum is mandatory and should be accompanied by a faecal occult blood test.

There are a multitude of laboratory tests that can be requested. Available as standard is the full blood count (FBC), differential white blood cell (WBC), platelet and reticulocyte count. The red cell distribution width does not indicate why the size varies or the shapes therefore a peripheral smear offers greater insights. With regard the RBC indices the MCV if low (microcytosis) points toward iron deficiency (ID). Values in excess of 115fl are indicative of B12 or folate deficiency. The mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration results generally parallel those of the MCV where low levels indicate ID or thalassemia.

The reticulocyte count can help distinguish the different types of anaemia. If the anaemia is stable but the count low it provides strong evidence for deficient production of RBCs and a reduced marrow response to the anaemia. Haemolysis or blood loss may be associated with a low count if there is a concurrent disorder that impairs RBC production (e.g. infection; chemotherapy). In association with pancytopenia, a low count is suggestive of aplastic anaemia, whereas a zero count plus normal white blood cells (WBC) and platelets points to red cell aplasia.

Of the WBC investigations leucopenia plus anaemia may reflect bone marrow suppression, hypersplenism or deficiencies of B12 or folate.

Serial evaluations of blood parameters can be useful. For example if the Hb declines by several grams in a week, with zero RBC production and normal

destruction (approximately 1%/day) then the decrease in Hb will be 7% in a week or 10.5 g/l Hb (0.07 x 150). Any reduction in Hb level above this is indicative of blood loss.

Evaluation for ID will be through history, seeking evidence of menorrhagia, symptoms of peptic ulcer disease etc., preliminary laboratory data (low MCV, low MCH, high RDW, increased platelet count) with additional investigation of plasma iron levels, iron binding capacity (transferrin), transferrin saturation, and ferritin.

Haemolysis is characterised by a rapid fall in Hb or reticulocytosis and/or abnormally shaped RBCs (especially spherocytes or fragmented RBCs). Further indicators can be an increase in serum lactate dehydrogenase (LDH), increased indirect bilirubin and a reduction in serum haptoglobin concentration. Whereas a raised LDH and reduced haptoglobin is 90% specific for haemolysis a normal LDH and serum haptoglobin >25mg/dl is 92% certain for ruling out haemolysis.

Bone marrow examination (aspiration) is a test that has declined in use – perhaps too far. It is the ‘gold standard’ for the diagnosis for iron deficiency (absence of stainable iron). It can be justified if pancytopenia is suspected, where abnormal RBCs are identified in the circulation (e.g. blast forms) when aplastic anaemia, myelodysplasia or myeloproliferative disease are suspected or in circumstances where megaloblastic erythropoiesis, pure RBC aplasia, alcohol or drug induced anaemia or sideroblastic anaemia is suspected.

With regard the issue of when a transfusion should be used there is little consensus. The Serious Hazards of Transfusion (SHOT) committee seek to minimise transfusion frequency and volume due to the risks and scarcity of blood. The British Society of Haematologists suggest a threshold of 70g/l or 100g/l if there is immediate risk to tissue oxygenation of the brain or any other organ. The British Society of Gastroenterologists and Royal College of Physicians indicate that in the context of an acute GI bleed the threshold is 80g/l. With improved diagnosis and recognition that a large proportion of anaemias are caused by iron deficiency, invariably a chronic condition, then iron supplementation is becoming an increasingly recognised alternative to blood.