Investigation and management of anaemia

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Abstract

The average lifespan of an erythrocyte is 120 days, and maintenance of a normal haemoglobin requires the rate of production of erythroid cells to match the rate of loss from the circulation. Where this is insufficient, anaemia ensues. Deficiency of haematinics (iron, vitamin B_{12}, folate), bone marrow infiltration or chronic inflammation and organ dysfunction can all result in impaired erythropoiesis. Abnormalities of the erythroid membrane, globin chains or intracellular enzymes shorten red cell lifespan, resulting in a congenital haemolytic anaemia. Acquired haemolysis is commonly immune or microangiopathic in aetiology. A detailed history including dietary, drug and family history, followed by interpretation of the full blood count, examination of the blood film and appropriate interpretation of simple tests (e.g. vitamin B_{12}, folate, ferritin), often identifies the cause of the anaemia. Older patients and those with complex co-morbidities can have multiple factors contributing to their anaemia. Management of anaemia is primarily focused on treating the underlying cause. Blood transfusion is reserved for cases of acute-onset symptomatic anaemia and cases of anaemia with no remedial cause.

Keywords Anaemia; folate; haematinic; haemolysis; iron deficiency; megaloblastic; microangiopathic; thalassaemia; vitamin B_{12}

Key points

- Anaemia arises from inadequate red cell production or decreased red cell survival
- Anaemias can be microcytic, normocytic or macrocytic
- Microcytic anaemias are most commonly caused by iron deficiency anaemia or thalassaemia trait
- Causes of macrocytic anaemia include vitamin B_{12} or folate deficiency, haemolysis, myelodysplasia and alcohol excess
- Haemolysis can be congenital (e.g. hereditary spherocytosis) or acquired (e.g. autoimmune haemolytic anaemia)
- Anaemia in the elderly is commonly multifactorial

Defining anaemia

Anaemia, in which the haemoglobin (and hence oxygen-carrying capacity of the blood) is insufficient to meet the body's physiological needs, is the most common blood abnormality. The normal haemoglobin range varies with age and sex, and for adults is defined by the World Health Organization as a haemoglobin less than 130 g/litre in men and less than 120 g/litre in women. Anaemia arises from either inadequate production of erythrocytes or loss of red cells from the circulation because of either destruction or blood loss. Iron deficiency anaemia is the most common cause of anaemia worldwide. Anaemia itself is a descriptor not a diagnosis, and the underlying cause(s) should always be sought.

Clinical manifestations of anaemia

Beyond the presence of pallor, anaemia is often asymptomatic when of slow onset in otherwise healthy individuals. Decreased oxygen-carrying capacity of the blood can result in shortness of breath on exertion, exertional angina and fatigue, while a compensatory increase in cardiac output can result in tachycardia, an ejection systolic murmur (flow murmur) and even cardiac failure in elderly individuals. Acute-onset anaemia (e.g. haemorrhage, haemolysis) is usually symptomatic.

Pathophysiology of anaemia

The average lifespan of an erythrocyte is approximately 120 days, and senescent erythrocytes are removed by cells of the reticuloendothelial system, predominately in the spleen. The loss of erythrocytes from the circulation is balanced by the production of new erythrocytes in bone marrow. When the rate of production falls below the rate of loss of red cells from the circulation, anaemia ensues (Table 1). Production of erythrocytes within the bone marrow depends on an adequate supply of nutrients, hormonal and cytokine stimulation and a functioning bone marrow microenvironment. Particularly in elderly patients[1] or those with multiple co-morbidities, multiple factors can contribute to anaemia.

Classifying and investigating anaemia

Although the kinetic approach to anaemia is useful for understanding the pathophysiology, a morphological approach based on red blood cell volume is more commonly used in clinical practice. Anaemias are divided into three groups: microcytic (reduced cell volume), normocytic (normal cell volume) and macrocytic (increased cell volume).

Beyond establishing symptoms of anaemia, a comprehensive history should be taken to help identify the cause. This should include dietary intake, evidence of blood loss, medications, travel, ethnic origin and family history, as well as co-morbidities. Initial laboratory investigations should include a full blood count, reticulocyte count, blood film, renal function, bilirubin and measurement of ferritin, vitamin B_{12} and folate. In cases of inadequate red cell production unexplained by haematinic or hormonal deficiency, a bone marrow biopsy is usually required to establish the cause.

Microcytic, hypochromic anaemia

Microcytic, hypochromic anaemias are characterized by a low mean corpuscular volume (MCV) and mean cell haemoglobin (MCH). The differential diagnosis includes:

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Kinetic approach to the causes of anaemia

Decreased release of red blood cells into circulation		Increased loss of red blood cells from circulation	
Decreased red cell production	**Red cell destruction (haemolysis)**	**Haemorrhage**	**Splenic pooling**
Nutritional: iron/B_{12}/folate deficiency Organ dysfunction: renal, liver, endocrine Aplasia: drugs, viruses, immune Infiltration: carcinoma, leukaemia, fibrosis Multifactorial: including inflammation	Congenital: membranopathy, enzymopathy, haemoglobinopathy Acquired: immune, fragmentation, infectious	Acute: e.g. ruptured vessel Chronic: e.g. menorrhagia, gastrointestinal tract loss	Secondary to splenomegaly

Table 1

- iron deficiency
- thalassaemia syndromes (reduced synthesis of α- or β-globin chains)
- some cases of anaemia of chronic disease (reduced iron availability)
- congenital sideroblastic anaemias (defective haem synthesis).

Iron deficiency anaemia

Red blood cells are reduced in size and number, and there is increased variation in red blood cell size and shape as the deficiency becomes more severe, reflected in an increased red cell distribution width. The reticulocyte count is reduced as red blood cell production is impaired. Blood film features include the presence of hypochromia (increased central pallor), pencil-shaped cells and a few target cells. The white cells are normal. The platelet count can be normal or increased. A low serum ferritin confirms the diagnosis of iron deficiency. Ferritin is an acute-phase reactant and can be elevated to within the normal range when iron deficiency occurs in the presence of inflammation. In these circumstances, iron-binding studies demonstrating an increased total iron-binding capacity and low transferrin saturation support the diagnosis of iron deficiency.

Causes of iron deficiency are listed in Table 2, and the cause should always be sought. Further investigations can include a coeliac screen, urine dipstick for haematuria, and investigation of the upper and lower gastrointestinal tract.[2]

Management is twofold: replacement of iron and correction of the underlying cause. Oral iron replacement is the treatment of choice and should be continued for a least 3 months after correction of the anaemia to replenish the body's iron stores. With impaired absorption or intolerance of oral iron preparations, parenteral iron replacement is indicated. Red cell transfusion is reserved for correction of uncompensated or symptomatic anaemia.

Thalassaemia trait

This is suspected where there is a microcytic anaemia with a normal or increased ferritin concentration. The MCH and MCV are disproportionately low for the haemoglobin compared with iron deficiency anaemia, and the red cell count is usually high normal or increased. The blood film shows small blood cells with little variation in size. Target cells and basophilic stippling may be present, but pencil cells are not seen. The diagnosis of β-thalassaemia trait can be made by demonstrating a raised haemoglobin A_2 on a haemoglobinopathy screen.[3] A putative diagnosis of α-thalassaemia trait is usually made from the red cell indices and the presence of a normal haemoglobin A_2. DNA analysis can be performed to confirm the diagnosis where this would influence clinical decision-making (e.g. for confirmation of an α^0 mutation – deletion of both α genes on the same chromosome – in partners to ascertain the risk of having a baby with Barts hydrops fetalis).

Anaemia of chronic disease

This arises in the context of chronic inflammation including chronic infection, connective tissue disease, heart failure, malignancy and renal disease. It is most commonly normocytic and normochromic but can be microcytic when an abnormal cytokine profile results in a reduced release of iron from macrophages and a functional iron deficiency affecting developing erythroid cells within the bone marrow. Other factors (e.g. folate deficiency, reduced red cell survival) often contribute to the anaemia. The C-reactive protein concentration and erythrocyte sedimentation rate are usually raised. Treatment is directed toward the underlying cause(s).

Causes of iron deficiency anaemia

Cause	Examples
Inadequate intake	Vegetarian/vegan Malnutrition
Increased physiological demands	Prematurity and toddlerhood Adolescent growth spurt Pregnancy
Impaired absorption	Coeliac disease Previous gastrointestinal surgery Gastrointestinal tract tuberculosis
Blood loss	Menorrhagia Gastrointestinal tract Urological tract
Haemoglobin loss	Chronic intravascular haemolysis with haemoglobinuria

Table 2

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