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22.6.2 Anaemia: pathophysiology, classification, and clinical features

David J. Weatherall† and Chris Hatton

ESSENTIALS Anaemia is defined by the World Health Organization as a reduction of the haemoglobin concentration to less than 130 g/litre (males) or less than 120 g/litre (females). It is a common problem, with a prevalence around 3% for middle-aged men and 14% for middle-aged women in the United Kingdom, and is seen more frequently with age. There is a much greater prevalence in the developing world. Adaptation to anaemia

Reduction in delivery of oxygen to the tissues triggers a variety of compensatory mechanisms, including (1) modulation of oxygen affinity—largely mediated by an increase in red blood cell 2,3-bisphosphoglycerate; (2) increased production of erythropoietin—the main growth factor for red blood cell production; (3) redistribution of flow to benefit the myocardium, brain, and muscle; (4) increase in cardiac output; and (5) reduction of mixed venous oxygen tension to increase the arteriovenous oxygen difference.

Clinical manifestations The clinical picture depends on whether anaemia is of rapid or insidious onset. Acute blood loss presents with features of intravascular volume depletion. Anaemia of gradual onset may (if mild) be asymptomatic or simply manifest as slight fatigue and pallor, or (if more severe) present with features including exertional dyspnoea, tachycardia, palpitations, angina, light-headedness, faintness, and signs of cardiac failure.

Causes and classification Anaemia can be caused by the defective production of red cells or an increased rate of loss of cells, either by bleeding or premature destruction (haemolysis). The causes of defective production of red cells include (1) deficiency of key haematinics, including iron, vitamin B12, or folate; (2) anaemia of chronic disease (see also Chapter 22.6.5); (3) reduced erythropoietin production typically seen in chronic kidney disease; and (4) primary diseases of the bone marrow. Haemolytic anaemias may be classified as either (1) genetic—including membrane defects,

haemoglobin disorders, and enzyme deficiencies; or (2) acquired—including autoimmune and nonimmune disorders. Clinical approach The key issues are to determine (1) the degree of disability caused by the anaemia and hence how quickly treatment must be started, a key question being 'Is blood transfusion required?', and (2) the cause of the anaemia. † It is with great regret that we report that David J. Weatherall died on 8 December, 2018.

section 22 Haematological disorders 5360 The main causes of anaemia can usefully be classified according to the associated red cell morphological changes:

(1) hypochromic, microcytic—including iron deficiency (the commonest cause of anaemia) and thalassaemia (common in some populations); (2) normochromic, macrocytic—vitamin B12 or folate deficiency, alcohol, and myelodysplasia; (3) polychromatophilic, macrocytic—haemolysis; (4) normochromic, normocytic—chronic disorders, renal failure, and diseases of the bone marrow; and (5) leucoerythroblastic—myelofibrosis, leukaemia, and metastatic carcinoma. The reticulocyte count also provides a good way of thinking about the underlying cause of anaemia—whether due to defective production or excess consumption of red cells. Definition of anaemia The main function of the red blood cells is oxygen transport. Hence, a functional definition of anaemia is 'a state in which the circulating red cell mass is insufficient to meet the oxygen requirements of the tissues'. However, many compensatory mechanisms can be brought into play to restore the oxygen supply to the vital centres, and therefore in clinical practice this definition is of limited value. For this reason, anaemia is usually defined as 'a reduction of the haemoglobin concentration, red cell count, or packed cell volume to below normal levels'. It has been extremely difficult to establish a normal range of haematological values, and hence the definition of anaemia usually involves the adoption of rather arbitrary criteria. For example, the World Health Organization recommends that anaemia should be considered to exist in adults whose haemoglobin levels are lower than 130 g/litre (men) or 120 g/litre (women). Children aged 6 months to 6 years are considered anaemic at haemoglobin levels below 110 g/litre, and those aged 6 to 14 years below 120 g/litre. The disadvantage of such arbitrary criteria for defining anaemia is that there may be many apparently normal individuals whose haemoglobin concentration is below their optimal level. Furthermore, the published 'normal values' for adults indicate that there is such a large standard deviation that many women must be considered 'normal' even though they have haemoglobin levels below 120 g/litre. Prevalence of anaemia The prevalence of anaemia has been studied in many populations, but it is difficult to compare data from different sources because of variations in methodology and criteria. Certain patterns emerge, however. An early survey carried out in the United Kingdom established that haemoglobin levels were low in a significant proportion of the population, particularly susceptible groups being children under the age of 5 years and pregnant women. A later random population study, also in the United Kingdom, reported a prevalence of anaemia of 14% for women aged 55 to 64 years and 3% for men aged 35 to 64 years. These and similar studies have shown that anaemia is most common in women of child-bearing age and that it then becomes relatively less frequent, although the prevalence increases again in the 65-and-over age group. Interestingly, it is only in the last group that the prevalence in men and women is almost the same. Where the cause of the anaemia has been analysed in these surveys, most cases have been due to iron deficiency. No doubt these prevalence data vary considerably between the developed countries, but it is clear that nutritional anaemia is relatively common in most populations at certain periods during development and late in life. Adaptation to anaemia The function of the red cell is to carry oxygen between the lungs and the tissues. However, tissue oxygenation is the result of a complex series of interactions of different organ systems, of which the red cell is only one

(Table 22.6.2.1). Obviously the cardiac output, ventilatory function, and state of the capillaries are of great importance as well. Each of these oxygen supply systems is regulated differently. Ventilation responds to changes in pH, CO₂, and hypoxia. Cardiac output responds to the amount of blood entering the heart, and this is regulated mainly by the effects of tissue metabolism as it modifies the resistance to blood flow in the microvasculature. The erythron itself responds to changes in haemoglobin concentration, arterial oxygen saturation, and the oxygen affinity of the circulating haemoglobin. Thus a decreased capacity of any of these components may be compensated for by increased activity of the others in an attempt to maintain tissue oxygenation. Oxygen diffuses across the alveolar membrane and into the blood, which equilibrates with the alveolar gas; the approximate oxygen tension is 75 to 100 mmHg (11–13 kPa). As blood is pumped through the tissue capillaries, oxygen diffuses out. Although the venous oxygen tension varies between organs, the oxygen tension of the pooled venous blood in the pulmonary artery, the 'mixed venous oxygen tension,' is remarkably constant at 40 mmHg (c.5.5 kPa). By reducing the oxygen-carrying capacity of blood, anaemia tends to reduce the arteriovenous oxygen difference, and this may be compensated for by the following mechanisms: (1) modulation of oxygen affinity; (2) increased production of erythropoietin (EPO); (3) redistribution of flow between different organs; (4) increase in cardiac output; and (5) reduction of mixed venous oxygen tension to increase the arteriovenous oxygen difference.

Intrinsic red cell adaptation

The consequences of anaemia on the normal oxygen-binding curve of blood are shown in Fig. 22.6.2.1. Anaemia, by lowering the Table 22.6.2.1 The steps involved in the transport of oxygen to the tissues

Steps

Factors involved

Ambient O₂ tension ↓ Altitude ↓ Ventilation ↓ Alveolar ventilation ↓ Gas-to-blood diffusion ↓ Ventilation/perfusion ratio ↓ Anatomical shunt ↓ Circulation ↓ Cardiac output ↓

Blood: haemoglobin concentration, oxygen dissociation curve

Tissue diffusion

Intercapillary distance

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5361 haemoglobin concentration, proportionately reduces the oxygen-carrying capacity of the blood. As a response to this, there is an increase in the 2,3-bisphosphoglycerate (2,3-BPG) concentration in the red cell, shifting the dissociation curve to the right and significantly enhancing tissue oxygen delivery (Fig. 22.6.2.1). With increasing severity of anaemia there is a progressive increase in 2,3-BPG, which may increase oxygen delivery by as much as 40% for the same haemoglobin concentration. It should be noted, however, that a consequence of this adaptation is a lower venous oxygen content and hence a lower reserve of oxygen available for a further increase in oxygen demand, as might occur during exercise, for example. Hence the increase in 2,3-BPG in anaemia tends to ameliorate the effects of the diminished oxygen-carrying capacity of the blood, so reducing the adaptation required by other steps involved in tissue oxygen delivery (Fig. 22.6.2.2). 2,3-BPG levels vary in a variety of other clinical conditions, some of which are summarized in Box 22.6.2.1.

Erythropoietin EPO is the major hormone involved in the regulation of erythropoiesis. Interaction of EPO with its receptor on red cell precursors results in the stimulation of erythroid-cell division, differentiation, and the prevention of the apoptosis of erythroid progenitors. The hormone is produced primarily in the kidney in adult life and in the liver during fetal development. EPO production is increased by a hypoxic stimulus secondary to anaemia. A nucleotide sequence close to the EPO gene, the hypoxia regulatory element, is responsible for hypoxic regulation of the EPO gene transcription. This, in turn, is controlled by the transcription factor hypoxia inducible factor-1 (HIF-1). HIF-1 is part of a widespread oxygen-sensing mechanism and is found in many cell types that do not express the EPO gene. It is made up of two subunits, HIF-1 α and HIF-1 β ; only the former

is regulated by hypoxia. HIF-1 protein levels are increased by hypoxia and return to normal with adequate oxygenation. In the presence of oxygen HIF-1 α is hydroxylated by an oxygen-sensitive proline hydroxylase. Hydroxylated HIF-1 α becomes a target for interaction with the von Hippel-Lindau protein that initiates the rapid destruction of HIF-1 α . In essence, this complex constitutes the oxygen sensor. Thus, variation in the production of EPO in various conditions, particularly renal disease, may have profound effects on adaptation to anaemia. There is evidence that, at least in some forms of anaemia, there may be a decline in EPO production at a given haemoglobin level with age (see also Chapter 22.6.5). Further details of the mechanisms of action of EPO are given in Chapter 22.3.5.

Local changes in tissue perfusion The total blood volume does not change greatly in anaemia and therefore increased tissue perfusion has to be achieved by shunting blood from less to more vital organs. There is vasoconstriction of the vessels of the skin and kidney; this mechanism has little effect on Oxygen content (vol. %) 20 15 10 5 0 0 20 40 60 80 100 Venous Arterial 3.3 vol.% 4.5 vol. %

Fig. 22.6.2.1 Enhancement of oxygen loading by decreased red cell oxygen affinity in a patient with anaemia. An anaemic patient with a 50% reduction in haemoglobin concentration has only a 27% reduction in oxygen unloading. Based on Klocke RA (1972). Oxygen transport and 2,3-biphosphoglycerate (BPG). Chest, 62 5 Suppl, 795-855.

ANAEMIC NORMAL 40-45% 6.0 5 10 15 Haemoglobin g/100 ml Heart rate Stroke volume BPG 25% 2.6 A-V Cardiac index pV

Fig. 22.6.2.2 The changes in factors involved in oxygen delivery with progressive anaemia. As anaemia becomes more severe, cardiac compensation becomes more significant. P(V)O₂, mixed venous oxygen tension. From Bellingham AJ (1974). The red cell in adaptation to anaemic anoxia. Clin Haematol, 3, 577-94.

Box 22.6.2.1 Some conditions in which there is a change in red cell 2,3-BPG levels leading to modification of oxygen transport

Increased 2,3-BPG; increased P₅₀, reduced whole-blood oxygen affinity • Anaemia • Alkalosis • Hyperphosphataemia • Renal failure • Hypoxia • Pregnancy • Cyanotic congenital heart disease • Thyrotoxicosis • Some red cell enzyme deficiencies

Decreased 2,3-BPG; decreased P₅₀, increased whole-blood oxygen affinity • Acidosis • Cardiogenic or septic shock • Hypophosphataemia • Hypothyroidism • Hypopituitarism • Following replacement with stored blood

section 22 Haematological disorders 5362 renal function. The organs that gain from the redistribution seem to be mainly the myocardium, brain, and muscle. Cardiovascular changes It seems likely that mild anaemia is compensated for by shifts in the oxygen dissociation curve. Overall, oxygen consumption is unchanged in anaemia. However, when the haemoglobin level falls below 70-80 g/litre, there is an increase in cardiac output, both at rest and after exercise (Fig. 22.6.2.2). The stroke rate increases and a hyperkinetic circulation develops, characterized by tachycardia, arterial and capillary pulsation, a wide pulse pressure, and flow murmurs. The circulation time is shortened, left ventricular stroke work is increased, and coronary flow is increased in proportion to the increased cardiac output. It has been found that there is an acute reversal of the high-output state of chronic anaemia in response to orthostatic stress or pressor amines. This suggests that redistribution of blood volume and vasodilatation with reduced afterload play a dominant role in the hyperkinetic circulatory responses to chronic anaemia. The mechanism of the vasodilatation is not known; it may be a direct result of tissue hypoxia. An additional factor that may be of some importance in increasing cardiac output is the reduction in blood viscosity produced by a relatively low red cell mass. Although the normal myocardium may tolerate sustained hyperactivity of this type indefinitely, patients with coronary artery disease or those with extreme anaemia may have impaired oxygenation of the myocardium. In such cases,

cardiomegaly, pulmonary oedema, ascites, and peripheral oedema may occur, and a state of high-output cardiac failure is established. At this stage, the plasma volume is almost always increased. Pulmonary function As blood, regardless of its oxygen-carrying capacity, is almost completely oxygenated in the lungs, the oxygen pressure of arterial blood in an anaemic patient should be the same as that in a normal individual, and hence an increase in respiratory rate should not improve the oxygenation of the tissues. Curiously, however, severe anaemia is associated with dyspnoea. Although in some patients this may be related to incipient cardiac failure, in most cases it appears to be an inappropriate response to hypoxia which is centrally mediated. Clinical manifestations and classification of anaemia Clinical effects of anaemia As anaemia reduces tissue oxygenation it is not surprising that it is associated with widespread organ dysfunction and hence an extremely varied clinical picture. The picture depends on whether the anaemia is of rapid or more insidious onset. After acute blood loss the red cell mass and plasma volume are reduced proportionately and the symptoms are mainly of volume depletion. Depending on the amount of fluid replacement there may be a small fall in the packed cell volume during the first 10 h; volume replacement by the influx of albumin from the extravascular compartment takes between 60 and 90 h. Hence the picture of rapid blood loss is characterized by the typical syndrome of shock, with collapse, dyspnoea, tachycardia, a poor volume pulse, reduced blood pressure, and marked peripheral vasoconstriction. With anaemia of a more insidious onset, the compensatory mechanisms outlined earlier have time to come into play. In mild anaemia there may be no symptoms or simply increased fatigue and a slight pallor. As the anaemia becomes more marked, the symptoms and signs gradually appear. Pallor is best discerned in the mucous membranes but tends to be an unreliable clinical sign in all but the most severe anaemia. Pallor of the nail beds and palmar creases may also be assessed. Cardiorespiratory symptoms and signs include exertional dyspnoea, tachycardia, palpitations, angina or claudication, night cramps, increased arterial pulsation, capillary pulsation, a variety of cardiac bruits, reversible cardiac enlargement, and, if cardiac failure occurs, basal crepitations, peripheral oedema, and ascites. Neuromuscular involvement is reflected by headache, vertigo, light-headedness, faintness, tinnitus, roaring in the ears, cramps, increased cold sensitivity, and haemorrhages in the retina. There may be a low-grade fever. In older people, in whom associated degenerative arterial disease is common, anaemia may present with the onset of cardiac failure. Alternatively, previously undiagnosed coronary narrowing may be unmasked by the onset of angina. Other symptoms of arterial degenerative disease may also be exacerbated or unmasked, for example, intermittent claudication and a variety of neurological pictures associated with cerebral arteriosclerosis. It is important that anaemia is recognized as a contributing factor to the symptoms of these degenerative diseases as its correction may bring about considerable symptomatic improvement. Causes and classification of anaemia A reduction in the red cell mass can result from either the defective production of red cells or an increased rate of loss of cells, by either premature destruction or bleeding. Decreased production of red cells may result from a reduced rate of proliferation of precursors in the bone marrow or from failure of maturation leading to their intramedullary destruction: that is, ineffective erythropoiesis. Based on this approach, we can derive a very simple pathophysiological classification of anaemia, as shown in Box 22.6.2.2, in which the causes are divided into failure of red cell proliferation, defective maturation, haemolysis, and blood loss. Anaemia due to defective proliferation of red cell precursors The major causes of this group of anaemias are an inadequate supply of iron, primary diseases of the bone marrow that involve stem cells or later erythroid precursors, and a reduction in the amount of EPO reaching the red cell precursors (Box 22.6.2.3). Box 22.6.2.2 The main groups of anaemias classified according to the

underlying cause • Reduced red cell production:

— Defective precursor proliferation

— Defective precursor maturation

— Defective proliferation and maturation • Increased rate of red cell destruction:

— Haemolysis • Loss of red cells from the circulation:

— Bleeding

22.6.2 Anaemia: pathophysiology, classification, and clinical features 5363 Red cell precursors require adequate iron supplies for normal proliferation, and the anaemia of iron deficiency tends to be hypoproliferative as well as dyserythropoietic. Chronic inflammatory disorders and related conditions also interfere with the iron supply to erythroid precursors, probably mainly due to hepcidin blocking the release of catabolized red cell iron from reticuloendothelial macrophages. Hepcidin, a peptide hormone produced by the liver, blocks ferroportin, which normally mobilizes iron from macrophages and gut endothelial cells onto transferrin for transportation to the bone marrow (see Chapters 12.7.1 and 22.6.4). Hepcidin levels in the blood are increased in chronic inflammatory disorders. Therefore, the fundamental defect in iron deficiency anaemia and the anaemia of inflammation is similar, in that the supply of iron is inadequate to meet the requirements for erythropoiesis. Defective proliferation of red cell precursors can result from any of the causes of bone marrow failure, including infiltration with leukaemic or other neoplastic cells, damage due to ionizing radiation, drugs, or infection, and various intrinsic lesions of the stem cells or red cell precursors. The intrinsic disorders include the congenital hypoplastic anaemias, involving either all the myeloid elements or the red cell precursors alone (see also Chapter 22.5.1). Finally, decreased proliferation of the red cell precursors may result from EPO deficiency. The most common cause is chronic renal failure. A similar mechanism may be involved in conditions in which the tissue requirement for oxygen is reduced. These include various endocrine disorders such as hypothyroidism and hypopituitarism. It may also explain the mild anaemia associated with haemoglobin variants with decreased oxygen affinity. As a group, the hypoproliferative anaemias are associated with a low reticulocyte count and defective proliferation of the bone marrow precursors. The red cells are usually normochromic and normocytic, although there may be a mild macrocytosis. If the anaemia is due to iron deficiency, the cells are hypochromic. If granulopoiesis is normal, the defect in red cell proliferation is reflected by an increase in the marrow's myeloid:erythroid (M:E) ratio. Defective red cell maturation Defects of red cell maturation may involve primarily nuclear or cytoplasmic maturation (Box 22.6.2.3). Those involving nuclear maturation include vitamin B12 and folic acid deficiency and other causes of megaloblastic anaemia (see also Chapter 22.6.6), and some of the primary marrow disorders including erythroleukaemia. The important causes of defective cytoplasmic maturation include the inherited disorders of globin synthesis, the thalassaemia syndromes (see also Chapter 22.6.7), and the genetic and acquired defects of iron metabolism that characterize the sideroblastic anaemias. There are other genetic defects of red cell maturation, the congenital dyserythropoietic anaemias, in which the aetiology is becoming clearer. Furthermore, agents such as drugs, chemicals, and infections may interfere with erythroid maturation. The main pathological mechanism common to

all the anaemias that result from maturation abnormalities is ineffective erythropoiesis. In other words, there is marked erythroid proliferation but many of the precursors are destroyed in the bone marrow before they enter the circulation. Hence, the characteristic finding is marked erythroid hyperplasia with a reduction in the M:E ratio, associated with a low reticulocyte count. Because of the significant intramedullary destruction of precursors there is usually an elevated level of bilirubin and lactate dehydrogenase. Furthermore, there are nearly always morphological abnormalities of the red cell precursors. The anaemias that are associated with abnormal nuclear maturation, such as those due to vitamin B12 and folic acid deficiency, are characterized by megaloblastic erythropoiesis and macrocytic red cells, while those caused by abnormal cytoplasmic maturation are characterized by normoblastic hyperplasia and hypochromic and microcytic red cells. However, even in these last conditions, there is marked anisocytosis and there may be a proportion of macrocytes in the peripheral circulation. Blood loss Anaemias due to chronic blood loss may develop very insidiously and cause considerable diagnostic problems (see also Chapter 22.6.4). Chronic blood loss from the gastrointestinal tract or uterus of more than 15 to 20 ml/day produces a state of negative iron balance. Assuming that the patient starts with a normal body store of iron, which is usually in the region of 1 g, the bone marrow will be able to maintain a normal haemoglobin

Box 22.6.2.3 Main causes of anaemia due to reduced or defective production of red cells

Reduced proliferation of precursors • Iron deficiency anaemia • Anaemia of chronic disorders:

— Infections, malignancy, collagen disease, etc. • Reduced erythropoietin production:

— Renal disease • Reduced oxygen requirements:

— Hypothyroidism

— Hypopituitarism • Reduced oxygen affinity of haemoglobin • Primary disease of the bone marrow:

— Aplastic anaemia: • Primary • Secondary to drugs, irradiation, chemicals, toxins, etc. • Pure red cell hypoplasia • Infiltrative disorders:

— Haematological malignancy

— Secondary carcinoma

— Marrow fibrosis Defective maturation of precursors • Nuclear maturation:

— Vitamin B12 deficiency

— Folate deficiency

— Erythroleukaemia • Cytoplasmic maturation:

— Iron deficiency

— Disorders of globin synthesis

- Disorders of haem and/or iron metabolism
- Disorders of porphyrin metabolism • Other mechanisms:
- Congenital dyserythropoietic anaemias
- Infection
- Toxins and chemicals

section 22 Haematological disorders 5364 level until the iron stores are totally depleted. At this stage there is no demonstrable iron in the bone marrow and the plasma iron level starts to fall, but the patient is not anaemic. With a further fall in the plasma iron level, the haemoglobin level starts to fall, although at this stage the erythrocyte morphology may be relatively normal, as are the red cell indices. It is only when iron deficiency anaemia is well established that the typical morphological appearances of the red cells develop, and only after extreme periods of iron depletion that the tissue changes of iron deficiency become manifest. Consequently, the often-cited clinical signs of iron deficiency (such as koilonychia) are exceedingly uncommon. From these considerations it is apparent that there may be prolonged blood loss before a patient presents with the symptoms and signs of anaemia. During the earlier stages, the peripheral blood film may not be helpful in diagnosis even though the serum iron level may be extremely low. Indeed, sometimes a dimorphic blood picture with normochromic and hypochromic cell populations may be seen. With chronic blood loss there is quite often a persistent thrombocytosis, and a hypochromic blood picture with thrombocytosis should always raise the possibility of chronic bleeding. In practice, the most common sites of such bleeding are a hiatus hernia, peptic ulcer, the large bowel, or the uterus; malignancy of the gastrointestinal or gynaecological tract must be considered.

Haemolytic anaemia When the lifespan of red cells is shortened there is a reduction in the circulating red cell mass, which leads to relative tissue hypoxia. This in turn causes an increased output of EPO with stimulation of the bone marrow and an increased rate of red cell production. This is reflected by a raised reticulocyte count and a mild macrocytosis due to the presence of young red cells in the peripheral circulation. Due to the increased rate of red cell destruction, there is an increased production of bilirubin (from haem destruction, via biliverdin) which leads to mild icterus and the presence of increased amounts of urobilinogen in the urine and stool. Thus the haemolytic anaemias (Box 22.6.2.4) are characterized by a variable degree of anaemia, a reticulocytosis, and hyperbilirubinaemia. Their pathophysiology is considered in detail in subsequent chapters. Red cells are prematurely destroyed either because of an intrinsic lesion or as a result of the action of an extrinsic agent. The intrinsic abnormalities of the red cells that lead to their premature removal are nearly all genetic defects of the cytoskeleton/membrane, haemoglobin, or metabolic pathways. The extrinsic agents that may cause premature destruction of the cells include a variety of antibodies, chemicals, drugs, and toxins, or bacteria and parasites. In addition, red cells may be damaged by direct trauma in the microcirculation or on body surfaces. Premature destruction of red cells may take place either intravascularly or extravascularly, or, as occurs more commonly, in both sites. The site of destruction depends on the type and degree of damage to the red cell. For example, complement-damaged cells develop large holes in the membrane due to the membrane attack complex, and are destroyed in the circulation, whereas IgG-coated cells are removed mainly by the Fc receptor-bearing cells of the reticuloendothelial

system. Clearly, there are numerous causes of premature destruction of red cells. These will be considered in detail in later chapters in this section. Usually it is easy to recognize that a particular anaemia has a haemolytic basis, by virtue of the reticulocytosis and mild macrocytosis associated with erythroid hyperplasia of the bone marrow, hyperbilirubinaemia, and increased urinary urobilinogen. However, it should be remembered that many anaemias associated with the abnormal proliferation or maturation of red cells have a haemolytic component. For example, there may be a slightly shortened red cell survival in patients with pernicious anaemia or thalassaemia and yet there may be a very poor reticulocyte response. Similarly, there is a haemolytic component in the anaemia due to inflammation or malignancy but again the marrow response is poor.

General approach to the anaemic patient

Clinical assessment The clinical assessment of patients with anaemia has two main objectives. First, it is essential to determine the degree of disability caused by the anaemia and hence how quickly treatment must be started. Second, as much information as possible about the likely cause of the anaemia must be obtained from a detailed clinical history and physical examination. There is no place for the attempted 'blind' treatment of anaemia without first establishing the cause, except in the most urgent clinical settings. In assessing the severity of the anaemia and how urgently treatment should be instituted, a detailed history of the patient's exercise tolerance must be obtained. This should include a specific enquiry of symptoms suggestive of cardiac complications including angina, dysrhythmias, positional dyspnoea, cough, or ankle swelling. The clinical examination should include a careful assessment of the degree of pallor, the position of the neck veins, whether there are warm extremities and a bounding pulse with a large pulse pressure, the presence of ankle or sacral oedema, and whether there are basal crepitations on respiratory examination. Severely ill patients with profound anaemia require immediate treatment in an environment where they can be under constant observation, have regular measurements of their central venous pressure, and be managed by experienced clinical and nursing staff. The risk of precipitating cardiac overload in these cases is such that transfusion must be undertaken slowly and carefully.

Box 22.6.2.4 General classification of haemolytic anaemia

- Genetically determined
 - Defects involving the structure and/or metabolism of the membrane
 - Haemoglobin disorders
 - Enzyme deficiencies involving the main metabolic pathways
- Acquired
 - Immune (iso- or auto-)
 - Nonimmune:

- Trauma

- Membrane defects

- Drugs, chemicals, toxins

- Bacteria, parasites

- Hypersplenism A more detailed description is given in Chapters 22.6.8, 22.6.9, 22.6.10, 22.6.11, and 22.6.12.

22.6.2 Anaemia: pathophysiology, classification, and clinical features 5365 It cannot be emphasized too strongly that in many cases the anaemia is a symptom of a nonhaematological disorder. A detailed history and clinical examination will often provide a clue as to the likely cause of the anaemia, and which laboratory investigations are likely to be most productive for confirming the diagnosis. **Haematological investigation** A preliminary blood count and blood film examination

should classify anaemia into hypochromic-microcytic, and macrocytic or normochromic, normocytic varieties (Box 22.6.2.5). In young women with a history of heavy menstrual loss, it is reasonable to assume that a hypochromic anaemia is due to iron deficiency, and to focus investigation and subsequent management on the gynaecological tract. However, hypochromic anaemia in men, or in postmenopausal women, suggests blood loss requiring urgent investigation until proven otherwise. Serum ferritin, serum iron level, and total iron-binding capacity should be assayed to confirm a diagnosis of iron deficiency. Hypochromic anaemia with a normal serum ferritin may suggest the anaemia of chronic disease, or defects in haemoglobin synthesis such as thalassaemia and sideroblastic anaemia; however, it is important to be certain that iron deficiency is not being masked by the acute phase response, which will raise the ferritin level in many cases. Distinguishing between the anaemia of chronic disease and iron deficiency, especially in the elderly comorbid population, can be challenging, and a therapeutic trial of iron may occasionally be required. The diagnosis of a macrocytic anaemia always requires further investigation. Simple blood tests to exclude readily remediable causes such as vitamin B12 and folate deficiency should be performed in the first instance; a reticulocyte count will also be an indication of whether haemolytic anaemia needs to be included in the differential diagnosis. Where these do not suggest an explanation, a bone marrow examination should be considered. A macrocytosis with a normoblastic bone marrow may result from alcohol abuse, haemolysis, or, occasionally, one of the refractory anaemias with hyperplastic bone marrow. Macrocytic anaemias with megaloblastic bone marrows are usually due to vitamin B12 or folate deficiency and should be investigated accordingly (see Chapter 22.6.6). The normochromic, normocytic anaemias often cause more diagnostic difficulty. Some help can be gained from a determination of whether the white cell and platelet counts are normal. If there is associated neutropenia and thrombocytopenia, a primary disease of the bone marrow is likely; hence, bone marrow examination should be made to determine whether there is hypoplasia of the various precursor forms, hypoplastic or aplastic anaemia, or whether the pancytopenia results from malignant infiltration of the bone marrow. If there are nucleated red cells or immature myeloid cells on the peripheral film (i.e. a leucoerythroblastic picture), a bone marrow examination is essential, as this type of reaction usually indicates infiltration of the bone marrow with abnormal cells, either as part of a primary marrow disease such as leukaemia, or metastatic carcinoma. In the normochromic, normocytic anaemias in which the white cell count and platelet count are normal, assessment of the patient's renal function is important, along with consideration of the possibility of the anaemia of chronic disease. After these conditions have been excluded, there remain the chronic anaemias associated with endocrine deficiencies or the primary red cell hypoplasia. The management of anaemia The management of specific forms of anaemia is described in detail in subsequent chapters. However, a few principles can be outlined here. In general, a cause should always be sought before treatment is instituted. As mentioned previously, most cases of iron deficiency anaemia require further investigation for a source of blood loss. If there is a clear-cut history of poor diet, multiple pregnancies, or obvious heavy menstrual bleeding, it is reasonable to start iron therapy and observe the haemoglobin level both during the period of treatment and for some months after iron therapy has been stopped. A rise in the haemoglobin level of approximately 10 g/litre per week indicates a full haematological response. For the megaloblastic anaemias, blood samples should be obtained for serum folate and vitamin B12 levels. Should haematinic supplementation be needed, a brisk reticulocyte response 5 to 7 days after initiating therapy suggests that there will be a full restoration of the haemoglobin level to normal. Blood transfusion should always be avoided unless the haemoglobin level is dangerously low, in which case it is reasonable to transfuse the patient up to a safe level and then

allow the haemo- globin to return to normal following appropriate treatment of the underlying cause. The decision whether to transfuse an anaemic Box 22.6.2.5 The main causes of anaemia classified according to the associated red cell changes Hypochromic-microcytic (reduced mean red cell volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC)) • Genetic:

— Thalassaemia

— Sideroblastic anaemia • Acquired:

— Iron deficiency

— Sideroblastic anaemia

— Chronic disorders (mildly hypochromic, occasionally) Macrocytic (increased MCV) • With megaloblastic marrow:

— Vitamin B12 or folate deficiency • With normoblastic marrow:

— Alcohol, myelodysplasia Polychromatophilic-macrocytic (increased MCV) • Haemolysis Normochromic-normocytic (normal indices) • Chronic disorders:

— Infection, malignancy, collagen disease, rheumatoid arthritis • Renal failure • Hypothyroidism, hypopituitarism • Aplastic anaemia or primary red cell hypoplasia • Primary disease of bone marrow, leukaemia, myelofibrosis, infiltration with other tumours Leucoerythroblastic (indices usually normal) • Marrow fibrosis • Haematological malignancies • Metastatic carcinoma

Revision #1

Created 2026-01-22 16:42:40 UTC by Omar Ayman

Updated 2026-01-22 16:42:40 UTC by Omar Ayman