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65 Haematological Diseases in the Tropics

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KEY POINTS

- Africa and Asia have more than 85% of the world's anaemic populations and anaemia burden is highest among children and women of reproductive age.
- The accurate diagnosis of anaemia has been neglected; clinical assessment of anaemia is unreliable unless the anaemia is severe.
- In low-income countries, anaemia in an individual is often due to multiple interdependent factors. Removing or treating a single factor may not resolve the anaemia.
- Early diagnosis of sickle cell disease and rapid access to a specialist centre for emergencies such as severe pain crises, strokes and acute chest syndrome, can help to prevent permanent long-term complications.
- Beta-thalassaemia major is fatal in the first few years of life unless regular blood transfusions are given; unless they are accompanied by iron chelation, these transfusions will eventually cause death due to irreversible organ damage from iron overload.
- Malarial anaemia is a particular problem for children and pregnant women and severe anaemia can be caused by *P. falciparum* and *P. vivax*. Malarial anaemia can be reduced with chemoprophylaxis and intermittent treatment, and by anti-mosquito measures such as insecticide-treated bed nets and vector control.
- Anaemia occurs in 70% of HIV-infected patients and is an independent risk factor for death. Prompt treatment of factors associated with anaemia, such as infections and poor nutrition, and commencement of antiretroviral treatment will reduce deaths.
- Blood shortages are common in tropical countries. To increase the availability of blood, transfusions should be prescribed in accordance with guidelines and efforts made to encourage blood donors to donate regularly as repeat donors are the safest type of donor.

Introduction

Haematological disorders are common in low-income countries. They make a substantial contribution to morbidity and mortality of individuals in these regions and have a negative impact on the growth and development of under-resourced nations. Genetic red cells abnormalities are common in low-income countries because they provide protection against malaria and they often co-exist with other causes of anaemia such as malnutrition and chronic illnesses. There is a close association between haematological abnormalities and infections which are a major cause of illness and death in these populations. Morphological abnormalities of blood can often provide clues about the underlying diagnosis and blood film examination is particularly important where diagnostic facilities are limited.

Abnormal Blood Counts

Abnormal blood counts can manifest as various combinations of alterations of numbers of red cells, white cells or platelets. This section will outline some of the most common causes of abnormal blood counts likely to be encountered in clinical practice in low-income countries.

ANAEMIA

Anaemia is one of the most common causes of morbidity in the world and its impact is reflected in several of the health-related Millennium Development Goals. Although anaemia by itself is not a diagnosis, it suggests that there is an underlying disease state which needs to be recognized and treated. It is also a useful indicator of the general health of the population.

The causes of anaemia may be identified systematically by considering the life cycle of the red cells (Figure 65.1). Nutrients necessary for red cell production are absorbed from the gastrointestinal tract and carried through the portal vein to the liver and ultimately reach the bone marrow where erythropoiesis occurs. This process is regulated by erythropoietin, a hormone released from the kidneys mainly in response to hypoxia. Mature

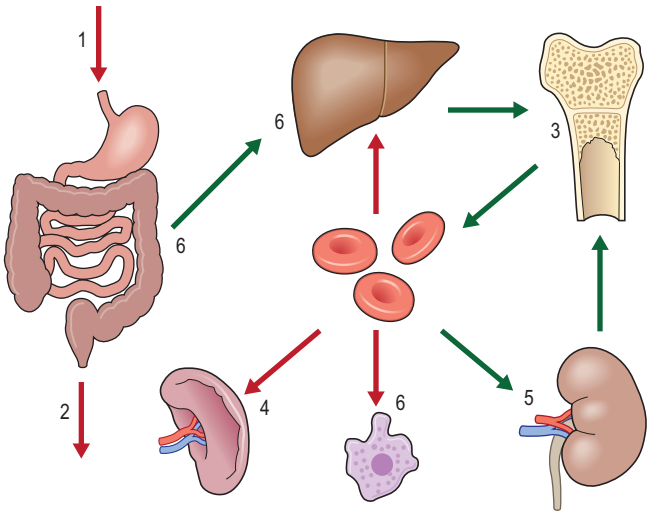


Figure 65.1 Anaemia can result from (1) inadequate nutrients; (2) blood loss; (3) inadequate or abnormal production of red cells in the bone marrow including haemoglobinopathies, myelodysplasia, or infections; (4) haemolysis in the spleen; (5) decreased erythropoietin; and (6) anaemia of chronic disease associated with inflammatory states.

red cells are released into the circulation from the bone marrow and percolate through the tissues and organs. Anaemia can result from defects in any of these stages. Inadequate production of red cells in the bone marrow can be due to lack of nutrients (e.g. iron, B_{12}, folate, vitamin A, copper or zinc), abnormal haemoglobin synthesis (i.e. haemoglobinopathies) or ineffective erythropoeisis from myelodysplasia or infections. Red cells can be lost from the body (e.g. gastrointestinal bleeding) or removed prematurely if they are abnormal or the spleen is enlarged (i.e. haemolysis). Kidney disease can result in decreased erythropoietin. Anaemia of chronic disease (or 'anaemia of inflammation') is due to an inadequate response to erythropoieitin or to increased cytokine-induced hepcidin release in inflammatory states which interferes with iron absorption or iron utilization.

Diagnostic algorithms to determine the cause of anaemia are usually based on a combination of the mean cell volume of the red cells, the reticulocyte count and blood film appearance (Figures 65.2, 65.3). This approach is based on the availability of a haematology analyser and an experienced microscopist. Several conditions which cause anaemia may co-exist in the same individual (e.g. intestinal parasites, malaria and sickle cell disease) and hence a thorough investigation is crucial to identify all potential causes of anaemia.

NEUTROPHILIA

Neutrophils released from the marrow after maturation can either enter the 'circulating pool' or they can remain in the 'marginal pool' where they are loosely attached to the blood vessel wall. Cells in the marginal pool are not sampled when blood is taken for a full blood count.[1] Neutrophilia can therefore result from increased bone marrow synthesis and also from decreased margination which increases the circulating pool. There are many causes of neutrophilia (Box 65.1) but the commonest is bacterial infection in which there is increased bone marrow production of neutrophils and release of neutrophil precursors into the peripheral blood. This 'leukaemoid reaction', characterized by circulating myelocytes and metamyelocytes, can be mistaken for leukaemia but, unlike leukaemia, there is an orderly maturation and proliferation of neutrophils. Leukaemoid reactions have also been described in patients with tuberculosis, juvenile rheumatoid arthritis and dermatitis herpetiformis.[2,3] Decreased margination of neutrophils with egress of cells into the circulation can occur with exercise, adrenaline (epinephrine) injection, emotional stress and postoperatively or in response to drugs (e.g. steroids, β-agonists). Other drugs, such as lithium and tetracycline, produce neutrophilia through increased production.

Neutrophilia is also a feature of bone marrow proliferation which occurs in myeloproliferative neoplasms, particularly chronic myeloid leukemia and myelofibrosis. Teardrop cells and nucleated red blood cells are features of myelofibrosis on the blood film; basophilia and eosinophilia are common with chronic myeloid leukaemia. Molecular testing for the JAK-2 mutation or *BCR-ABL* fusion gene can also help to differentiate between myeloproliferative neoplasms. Rebound neutrophilia can occur following treatment of megaloblastic anaemia or after recovery from neutropenia induced by drugs. Acute haemorrhage can cause neutrophilia, especially if bleeding occurs into the peritoneal cavity, pleural space, joints or adjacent to the dura. This is possibly due to the release of adrenaline and chemokines in response to local inflammation.

The presence of neutrophilia can be useful in raising suspicions about the onset of complications in infections that are not primarily associated with neutrophilia. Examples include meningitis in tuberculosis, orchitis in mumps, bowel perforation in typhoid fever and superadded bacterial infection in measles. The absence of neutrophilia can be helpful in differentiating typhoid and paratyphoid fever from pyogenic infections.

NEUTROPENIA

Neutropenia is defined as an absolute neutrophil count $<1.5 \times 10^9$/L. It is usually classified into severe ($<0.5 \times 10^9$/L), moderate

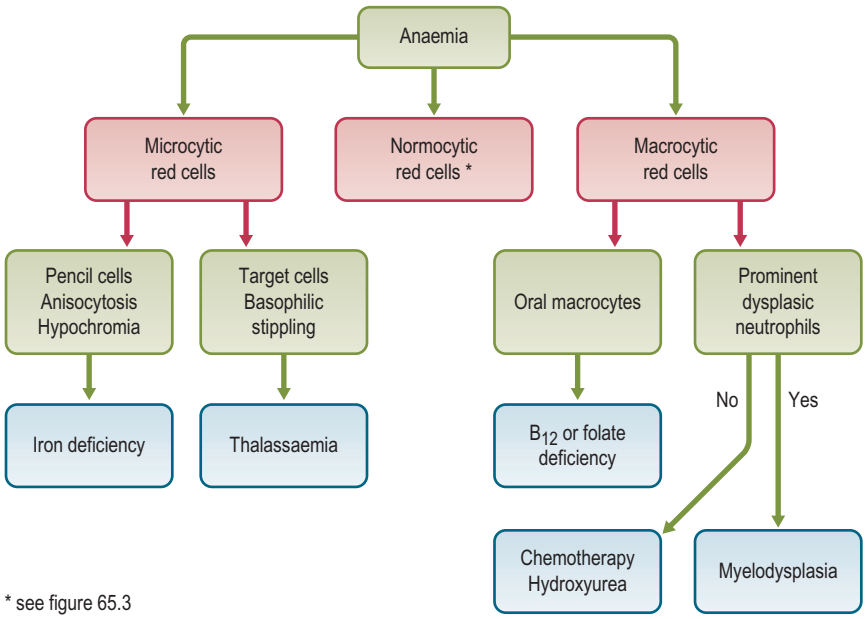


Figure 65.2 Diagnostic algorithm for investigation of anaemia.

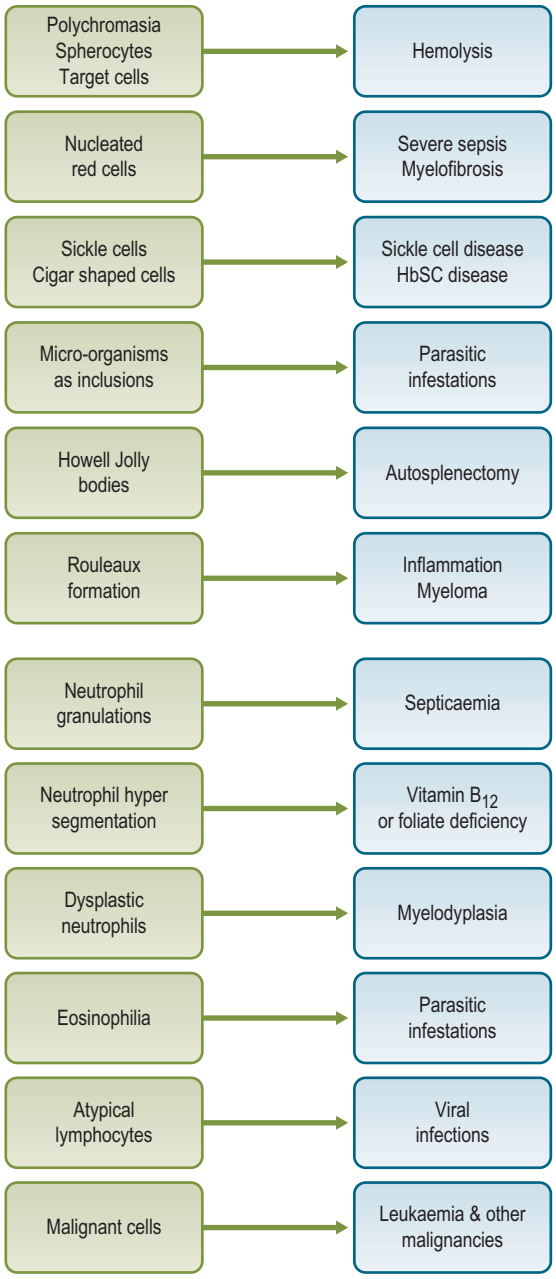


Figure 65.3 Typical appearances of blood film indicating various underlying conditions.

BOX 65.1 CAUSES OF NEUTROPHILIA

- Physical stimuli (cold, heat, exercise, fits, pain, ovulation, trauma, pregnancy, hypoxia)
- Emotional stimuli (fear, panic, depression, anger)
- Infections (all types)
- Inflammatory disorders
- Metabolic disorders (diabetic ketoacidosis)
- Haematological malignancies
- Solid tumours
- Drugs and hormones
- Smoking (commonest cause of mild neutrophilia)
- Acute haemolysis
- Poisoning
- Insect venoms.

(0.5–1.0 × 10^9/L) or mild (1.0–1.5 × 10^9/L). The propensity to develop infections is related to the degree and duration of neutropenia, with higher risk associated with counts below 0.5 × 10^9/L. Africans, African Americans, Yemenite Jews, Palestinians and Saudi Arabians generally have slightly lower neutrophil counts compared with other races. This is thought to be due to an increase in the bone marrow storage pool as ethnic neutropenia is associated with good neutrophil responses to infections.

Neutropenia can be due to impaired or ineffective (intramedullary death of neutrophil precursors despite normal bone marrow production) synthesis by the bone marrow (e.g. myelodysplasia, megaloblastic anaemia, treatment with phenytoin or methotrexate); a shift from the circulating pool to marginated pool (pseudoneutropenia) and increased peripheral destruction (e.g. secondary to antibodies against the neutrophils or increased reticulo-endothelial activity in sepsis or haemophagocytic syndrome) (Box 65.2). Increased consumption of neutrophils can result from increased attachment of cells to endothelium or other leukocytes in inflammatory states. Neutropenia is often the result of a combination of several of these mechanisms.

Infants of hypertensive mothers may have moderate to severe neutropenia, which can last for several days. This is probably related to bone marrow suppression. Moderate to severe neutropenia can also occur in newborn infants as a result of the transfer of maternal IgG anti-neutrophil antibodies in a manner similar to rhesus haemolytic disease of the newborn.[4] Although neutropenia has been described with typhoid fever, minimum neutrophil count seldom falls below 0.6 × 10^9/L and the

BOX 65.2 CAUSES OF NEUTROPENIA

ACQUIRED

Immune

- Neonatal alloimmune neutropenia
- Autoimmune neutropenia (systemic lupus erythematosus, Felty syndrome, drugs)

Nutritional Deficiencies

- Vitamin B_{12}, folic acid, copper

Malignancies

- Myelodysplastic syndrome
- Acute leukaemia
- Myelofibrosis
- Lymphoproliferative disorders
- Bone marrow infiltration by solid cancers
- Large granular lymphocytic leukaemia

Sepsis

- Severe bacterial infections (e.g. typhoid)
- Viral: mononucleosis, HIV varicella, measles, rubella, hepatitis A&B, parvovirus and cytomegalovirus
- Rickettsial infections

Hypersplenism

CONGENITAL (examples)

- Shwachman–Diamond syndrome
- Severe congenital neutropenia
- Cyclic neutropenia
- Dyskeratosis congenital
- Chédiak–Higashi syndrome.

neutropenia may not develop until after the first week of illness. Infectious hepatitis and yellow fever can both cause neutropenia. Overwhelming infections can lead to a failure of bone marrow production of neutrophils, especially in undernourished individuals and alcoholics.

Individuals with severe neutropenia can develop life-threatening septicaemia, often from endogenous flora (e.g. oral cavity), and stringent measures should be taken to avoid situations which may predispose these individuals to infections. They may need prophylactic antimicrobials and should have rapid access to medical care. Fungal infections are less common than bacterial infections in neutropenic individuals, and viral or parasitic infections rarely occur with isolated neutropenia. Granulocyte colony stimulating factor (GCSF) injections can be helpful in raising the neutrophil count in patients with complicating infections since it stimulates the release of neutrophils from the marrow, but GCSF is only useful if there is some bone marrow reserve. Patients with some congenital or immune forms of neutropenia can tolerate persistently low counts without any increase in the incidence of infections.

MONOCYTOSIS AND MONOCYTOPENIA

Monocytosis occurs in chronic infections and inflammatory conditions. Protozoan infections such as typhus, trypanosomiasis and kala-azar may be associated with monocytosis. Chronic and juvenile myelomonocytic leukaemias are malignant disorders in which monocytosis may be severe; acute monocytic leukaemias may present with mild to moderate monocytosis. Monocytosis, and particularly a monocyte : lymphocyte ratio greater than 0.8–1.0, may indicate active progression of tuberculosis and an unfavourable prognosis. The normal ratio of 0.3 or less is restored when the healing process is complete.

A decreased absolute monocyte count occurs in bone marrow failure states such as aplastic anaemia or after chemotherapy. Low monocyte counts can occur with overwhelming sepsis and with splenomegaly. Monocytopenia is a characteristic feature of hairy cell leukaemia and is considered to be a diagnostic hallmark of this disease.

LYMPHOCYTOSIS AND LYMPHOCYTOPENIA

Peripheral blood contains only around 2% of the total body lymphocyte population since these represent the cells present in the blood during their transit into secondary lymphoid organs. Wide variations exist in lymphocyte counts between individuals especially in childhood. Lymphocyte counts exhibit a diurnal pattern; peaking at night with a nadir in the morning.

Lymphocytosis is characteristic of infectious mononucleosis and many atypical and large lymphocytes can be seen in the peripheral blood film. These atypical cells can also occur in cytomegalovirus infection and infectious hepatitis. Absolute lymphocytosis can occur with chronic infections such as brucellosis and in the recovery stages of tuberculosis. Lymphocytosis is unusual in bacterial infections except in the case of pertussis. Heavy smoking is also an often overlooked cause of lymphocytosis and is probably one of the commonest reasons for a mild to moderate increase in the lymphocyte count. Malignant bone marrow disorders, predominantly acute lymphoblastic and chronic lymphocytic leukaemia and non-Hodgkin's lymphomas, can cause lymphocytosis. These lymphocytes may have characteristic morphological changes identifiable in the blood film (e.g. smear cells with chronic lymphocytic leukaemia) and the correct diagnosis can be confirmed by immunophenotyping for specific combinations of cell markers.

Lymphopenia is due to decreased production, redistribution or increased rate of death of lymphocytes. Decreased production usually results from cytotoxic drugs and radiotherapy, while increased lymphocyte death can occur in infections such as influenza and HIV. Occasionally, an isolated low lymphocyte count in the context of an otherwise normal full blood count can be a clue to the diagnosis of HIV. This reflects the destruction of CD4+ T cells by the virus although an expansion of CD8+ T cells may raise the total lymphocyte count to normal levels. Redistribution rather than depletion of total body lymphocyte numbers occurs with steroid treatment or with endogenous secretion of corticosteroids during acute illnesses due to the retention of lymphocytes in secondary lymphoid organs.

EOSINOPHILIA

Eosinophils are involved in innate immunity and hypersensitivity. Their number in the circulation is relatively small compared to other leukocytes because they predominantly reside in tissues such as the gut, skin and lungs which are entry points for allergens and infections. The commonest causes of eosinophilia are helminthic infections, atopy and allergic diseases, and adverse drug reactions. Less common causes are classified under the umbrella term of hypereosinophilic syndromes (Table 65.1). Since parasitic infections are likely to be the commonest cause of eosinophilia in the tropics and in returning travellers, an extensive search for such infections should be undertaken in patients with persistent eosinophilia; initial investigations should be determined by the patient's history of geographical exposure (Figure 65.4).[5–7]

The absolute number of eosinophils in the peripheral blood may not correlate with their tissue distribution or with their potential to cause tissue damage from their granule release. This is because the degree of eosinophilia depends on the extent of tissue invasion and is therefore modest with tapeworms and roundworms resident in the bowel but much higher where invasion occurs, for example with, *Toxocara canis* or filaria. Schistosomiasis almost always causes eosinophilia. *Strongyloides stercoralis* has the capacity to remain in the host for decades after initial infection and causes varying degrees of eosinophilia, with or without other symptoms. Steroid treatment, which may be necessary in cases of eosinophilic tissue damage, can exacerbate clinical problems in patients with *Strongyloides* infection so this parasitic infestation should be excluded before starting steroids for hypereosinophilia.

Mild to moderate eosinophilia is common in asthma although a very high count should prompt a search for Churg–Strauss syndrome or allergic bronchopulmonary aspergillosis. Most drugs including penicillins can cause eosinophilia but the diagnosis can only be made by noting recovery when the drug is discontinued. Eosinophilia can be a feature of Hodgkin's lymphoma. It signifies a more favourable prognosis and may precede the original diagnosis of lymphoma or relapses. In immunocompromised patients, such as those with HIV infection, the finding of eosinophilia may be crucial since the success of antiretroviral treatment may depend on concomitant eradication of parasites.

TABLE 65.1 Investigations in Those with Persistent Eosinophilia Based on Travel History

Fever and respiratory symptoms	Katayama syndrome – *Schistosoma* sp.
	Loeffler syndrome
	Visceral larva migrans/acute toxocariasis
	Tropical pulmonary eosinophilia
	Pulmonary hydatid disease
	Paragonimiasis
	Coccidioidomycosis and paracoccidioidomycosis
	Non-parasitic causes of eosinophilia and respiratory symptoms
Gastrointestinal symptoms	Strongyloidiasis
	Schistosoma mansoni and *S. japonicum*
	Ascariasis
	Tapeworm
	Dwarf tapeworm
	Hookworm
	Whipworm
	Pin worm
	Trichinellosis
	Anisakiasis – *Anisakis* spp. and *Pseudoterranova decipiens*
	Angiostrongylus costaricensis
	Non-parasitic causes of eosinophilia and GI symptoms
Right upper quadrant pain/jaundice	Hydatid disease in the liver
	Fasciola hepatica and *F. giganta*
	Clonorchis sinensis and *Opisthorchis* sp.
	Schistosomiasis – *S. mansoni* and *S. japonicum*
Neurological symptoms	*Angiostrongylus cantonensis*
	Gnathostomiasis
	Neurocysticercosis causing meningitis
	Schistosomiasis/bilharzia and CNS symptoms – *Schistosoma haematobium, S. mansoni, S. japonicum*
	Toxocariasis
	Coccidioidomycosis and paracoccidioidomycosis
Skin and musculoskeletal symptoms	Onchocerca volvulus
	Larva currens
	Lymphatic filariasis
	Loiasis
	Gnathostomiasis
	Trichinellosis
	Swimmers' itch/cercarial dermatitis
Urinary symptoms	Schistosomiasis/bilharzia – *Schistosoma haematobium*

From Checkley AM, Chiodini PL, Dockrell DH, Bates I, Thwaites GE, Booth HL, Brown M, Wright SG, Grant AD, Mabey DC, Whitty CJ, Sanderson F; British Infection Society and Hospital for Tropical Diseases. Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. J Infect. 2010 Jan;60(1):1-20. Copyright Elsevier 2010.

THROMBOCYTOPENIA

Thrombocytopenia is often discovered incidentally in patients during full blood count estimation. A platelet count above $20–30 \times 10^9$/L is usually not associated with any symptoms such as bleeding. If clinically evident haemorrhage does occur at counts above this level, other conditions such as coagulation defects, vascular problems or rarely platelet dysfunction should be suspected. Although the prime role of platelets is in haemostasis, several other important roles have been recognized in recent years including wound repair, tissue healing, antimicrobicidal properties, lymphangiogenesis, tumour metastasization and maintenance of blood vessel integrity.

Congenital platelet disorders are often part of a syndrome. Patients with Wiskott–Aldrich syndrome have small platelets in association with eczema and recurrent infections. Other congenital platelet disorders, such as MYH9-related disorders, can present with deafness or cataracts while skeletal deformities and oculocutaneous albinism are common in other syndromic presentations.

Blood film morphology can provide important clues about the causes of thrombocytopenia (Figure 65.5). Fragmented red cells (schistocytes) increase the possibility of microangiopathic haemolytic anaemia, where an altered vessel wall and fibrin formation in the blood vessels shred the erythrocytes and consume platelets. Thrombotic thrombocytopenia purpura, haemolytic uremic syndrome and disseminated intravascular coagulation can all present with thrombocytopenia. Dysplastic red or white cells should raise the suspicion of myelodysplasia which can be confirmed by bone marrow examination and cytogenetic analysis. It is important to exclude in vitro platelet agglutination as a cause for apparent thrombocytopenia. This can be an anticoagulant (EDTA)-dependent phenomenon so a repeat sample should be examined using citrate anticoagulant. Rarely, platelet satellitism where the platelets clump round the neutrophils, can cause artefactual thrombocytopenia.

Anaemia in Low-income Countries

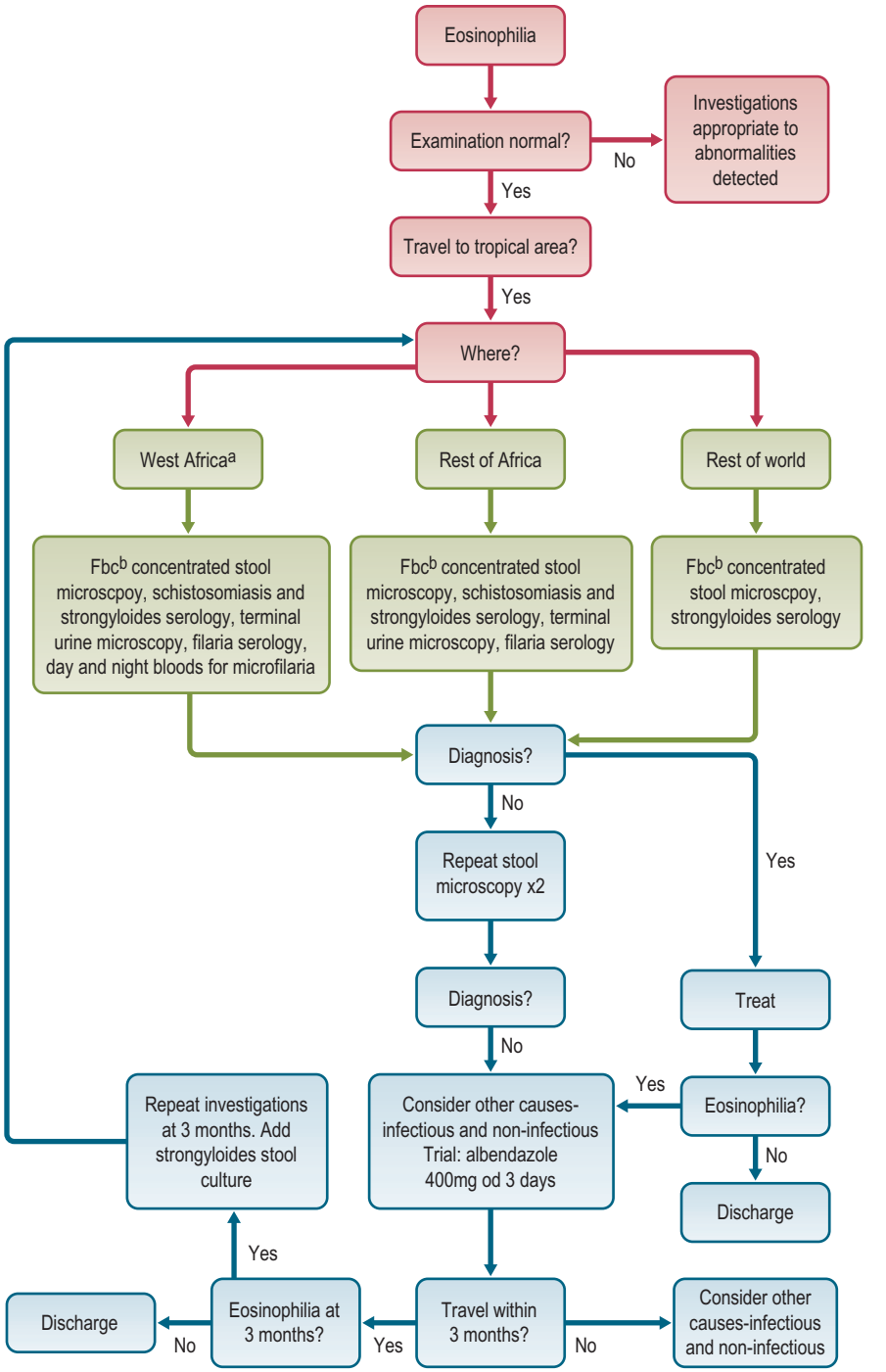
Anaemia affects nearly two billion people globally with a much higher prevalence in developing countries compared with more wealthy nations (43% vs 9%).[8] The continents of Africa (highest prevalence) and Asia (greatest absolute burden) account for more than 85% of the anaemic population. Anaemia burden is highest among children and women of reproductive age. Anaemia contributes to more than 115 000 maternal deaths and 591 000 perinatal deaths globally per year.[9]

WHO have defined anaemia according to various haemoglobin concentrations (Table 65.2)[10] but the appropriateness of these thresholds has been questioned because there are wide variations in haemoglobin concentration among people of different races.[11] The prevalence of anaemia can be a useful indicator of public health status of a nation because:

- The prevalence of anaemia is objective and quantifiable
- Anaemia is a major complication of several infections, including malaria, HIV, tuberculosis, and the neglected tropical diseases, which are among the commonest problems in most tropical countries
- Anaemia can be measured even in the most remote areas and devices have been developed which are cheap and reliable in different climate settings

TABLE 65.2 Haemoglobin Concentration Thresholds Used to Define Anaemia in Subjects Living at Sea Level According to the World Health Organization Guidelines

Age or Gender Group	Haemoglobin Threshold (g/L)
Children (6 months to under 5 years)	110
Children (5 years to under 12 years)	115
Children (12 years to under 15 years)	120
Non-pregnant women (15 years and over)	120
Pregnant women	110
Men (15 years and over)	130



a - West/Central African countries: Benin, Congo, Gabon, Ghana, Guinea, Guinea Bissau, Cote d'Ivoire, Nigeria, Togo, Burkina Faso, Gambia, Liberia, Mali, Mauritania, Equatorial Guinea, Senegal, Sierra Leone, Central African Repulbic, Cameroon, Niger, Chad
b - Fbc: Full blood count

Figure 65.4 Scheme for investigation of individuals with eosinophilia. *(From Checkley AM, Chiodini PL, Dockrell DH, Bates I, Thwaites GE, Booth HL, Brown M, Wright SG, Grant AD, Mabey DC, Whitty CJ, Sanderson F; British Infection Society and Hospital for Tropical Diseases. Eosinophilia in returning travellers and migrants from the tropics: UK recommendations for investigation and initial management. J Infect. 2010 Jan;60(1):1-20. Copyright Elsevier 2010.)*

- The incidence of anaemia changes in a predictable fashion with alterations in disease burden
- The prevalence of anaemia can be used to assess whether an intervention has reached the poorest communities.

Haemoglobin concentration of <90 g/L has been recommended for disease surveillance in high-prevalence countries where changes in haemoglobin are used for monitoring the impact of interventions.[11]

Anaemia in tropical countries (Box 65.3) is often due to infections but chronic health problems, such as diabetes and chronic respiratory disease, and cancer and related complications are increasing as causes partly due to lifestyle changes.

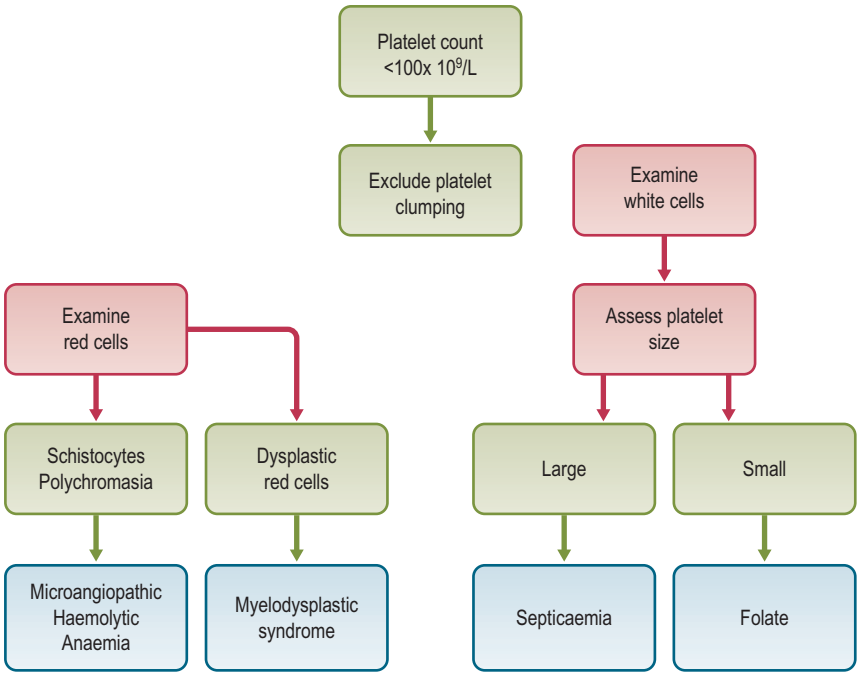


Figure 65.5 Scheme for investigation of patients with thrombocytopenia.

CLINICAL EVALUATION OF ANAEMIA

The clinical symptoms and signs of anaemia vary and depend on the cause and the speed of onset. A rapid drop in haemoglobin is much more likely to cause symptoms of anaemia than chronic anaemia. Slowly developing anaemia allows time for the body to compensate for the drop in haemoglobin content. For this reason the haemoglobin level can drop to extremely low levels before symptoms develop. Anaemia presents with symptoms such as exertional breathlessness, palpitations and in some cases, syncopal attacks. Patients with chronic anaemia may also have a multitude of nonspecific symptoms including poor concentration, decreased work performance and easy exhaustion (Table 65.3).

A thorough history and clinical examination may provide clues about the cause of anaemia but further investigations are often necessary to confirm the diagnosis and guide treatment. However, in many resource-poor settings, access to routine biochemical and haematological testing is scarce, so much reliance is placed on clinical examination. The international guidelines for the Integrated Management of Childhood Illness recommend that a diagnosis of anaemia in sick children is based on the assessment of palmar pallor. For pregnant women, symptoms of fatigue and dyspnoea, combined with signs of conjunctival and palmar pallor, and increased respiratory rate suggest anaemia. However, making a diagnosis of anaemia based on clinical assessment alone is unreliable unless the anaemia is severe.[12] No specific anatomical site is particularly accurate for the prediction of anaemia[11] though sensitivity may be increased by using multiple sites.[12]

BOX 65.3 CLASSIFICATION OF ANAEMIA IN TROPICAL COUNTRIES

NUTRITIONAL DEFICIENCIES

- Very common – Iron deficiency
- Common – Deficiencies of vitamins A, B_{12}, and folate
- Possibly common – Deficiencies of micronutrients like copper and vitamins C and E

INFECTIONS

- Malaria
- HIV
- Tuberculosis
- Hookworm infection
- Schistosomiasis
- Trichuriasis

HAEMOGLOBINOPATHIES

- Sickle cell disease
- Thalassemia
- Enzyme deficiencies (e.g. G6PD deficiency)

CHRONIC DISEASES

- Diabetes
- Chronic kidney disease due to various causes
- Chronic respiratory illnesses (e.g. chronic bronchitis, bronchiectasis)

CANCER

In many cases, there will be more than one of these conditions coexisting in the same individual. An adequate response to the treatment of anaemia requires management of ALL the contributory factors.

HAEMOGLOBIN MEASUREMENT FOR DETECTING ANAEMIA

Most central laboratories in low-income countries have automated haematology analysers and several manual methods exist for assessment of haemoglobin concentration, which are suitable for rural areas where there is no mains electricity (e.g. Haemoglobin Colour Scale; HemoCue technique).[13–15]

Haemoglobin Colour Scale[16]

Principle. The colour of a finger-prick blood sample, soaked into special chromatography paper, is compared with

TABLE 65.3 Long-Term Clinical Effects of Anaemia in Different Population Groups

Pregnant females	Increased risk of maternal morbidity Intrauterine growth retardation Increased risk of prematurity and lower birth weight Increased fetal and neonatal mortality Postpartum depression Poor maternal/infant behavioural interactions Impaired lactation
Infants and children	Cognitive defects up to two decades after iron deficiency in infancy Poor psychomotor development Decreased attentiveness, shorter attention span Poorer academic achievement in school-age children who developed iron deficiency in early childhood Breath-holding spells Increased risk of severe morbidity from malaria Increased risk of upper respiratory tract infections
All ages	Impaired physical performance Poor concentration and memory Increased irritability Poor appetite (mucositis, hypochlorhydria, oesophageal webs) worsening the nutritional status Suboptimal response to iodine in populations with endemic goitre Increased risk of chronic lead poisoning in high-lead environments Increased risk of restless legs syndrome Cardiac hypertrophy Poor fracture healing

The major cause of anaemia in most of these cases is iron deficiency. Some of the effects have been described in individuals with iron deficiency without obvious features of anaemia.

high-quality digital examples of known haemoglobin concentration. The colours are represented in 20 g/L increments from 40 g/L to 140 g/L. This method is inexpensive, does not depend on skilled scientists, is durable in dusty, hot, dry and humid conditions and is probably better than clinical diagnosis for detecting mild and moderate degrees of anaemia. The disadvantages are that it requires specific chromatography paper and good natural light and it cannot detect changes in haemoglobin less than 10 g/L.

Hemocue

This is a small battery- or mains-operated machine, which uses a drop of blood in a plastic cuvette to produce a direct read-out of haemoglobin in a few seconds. It is simple to use, produces accurate and consistent results to one decimal place and it has an in-built quality-checking mechanism. The HemoCue Hb-301 has been specifically designed for tropical conditions and operates in temperatures up to 50°C, in dusty and humid conditions. However the recurrent costs associated with disposable plastic cuvettes mean there is little opportunity for cost-saving with high-volume workloads.

PRINCIPLES OF MANAGEMENT OF ANAEMIA (Box 65.4)

Anaemia in Infants and Children

The iron status of an infant is directly proportional to its body mass and blood volume, both of which are reflections of intrauterine growth. Thus, low birth weight and prematurity are both associated with iron depletion in the postnatal period. Several interventions have been suggested to improve infantile iron deficiency, including:[17–19]

- Delayed cord clamping at delivery; the short delay of 2–3 minutes allows a small but important amount of blood to continue to flow to the foetus from the placenta
- Improvement of infant feeding practices
- Prevention and treatment of infectious diseases
- Interventions to prevent low birth weight, such as maternal nutritional supplementation, the control of infections and chronic health problems in pregnancy.

Anaemia in young children can be due to increased nutrition requirements during periods of rapid growth; these requirements may be up to 10 times higher per kilogram of body weight than that of an adult male. In addition, infant and toddler diets often lack bio-available iron. A case–control study of preschool children in Malawi with severe anaemia (haemoglobin concentration, <50 g/L) identified bacteraemia, malaria, hookworm, HIV infections and deficiencies of vitamins A and B_{12} as the commonest causes of anaemia. Lack of folate and iron were uncommon. In low-income countries multiple interdependent causes of anaemia often operate in one individual so rectifying a single factor is unlikely to make a big impact on resolving anaemia. Interventions which are useful in preventing anaemia in younger children include micronutrient supplementation (food fortification), de-worming, prevention and treatment of infectious diseases, school nutrition programmes and community-based nutrition promotion.

Anaemia in Pregnant Women

WHO defines anaemia of pregnancy as a haemoglobin level less than 110 g/L, or haematocrit less than 33%, at any time during pregnancy. About one-fifth of maternal mortality is attributable to anaemia in pregnancy[20] and anaemia affects nearly half of all pregnant women worldwide. Maternal anaemia is associated with many factors that might also be causally associated with mortality including poverty, infections and inadequate health-seeking behaviour. Globally, the most important cause of anaemia in pregnancy is iron deficiency although hookworm, malaria, HIV infection, and deficiencies in folate and other micronutrients may contribute. Pregnancy-associated complications, including septicaemia, pre-eclampsia and other obstetric problems can precipitate anaemia.[21] It is important to note that a diagnosis of iron deficiency in pregnancy which relies on ferritin measurements may be misleading because of

BOX 65.4 PRINCIPLES OF MANAGEMENT OF ANAEMIA

- Education about the significance of anaemia and its prevention in local community, wider society and nationwide
- Manage haemoglobinopathies adequately
- Improved dietary intake (quality and quantity)
- Fortification of staple foods
- Iron and folic acid supplementation to high-risk groups[a]
- Early diagnosis and treatment of nutritional deficiencies
- Infection control
  - Treatment of infections (malaria, helminths)
  - Prevention of infections (hygiene, vaccinations)

[a]Target pre-school children, adolescent females, women of reproductive age, pregnant women, postpartum lactating women

the physiological increase in ferritin levels during the 3rd trimester.

There are three intervention strategies recommended by WHO to prevent anaemia in pregnancy:

1. Weekly iron and folic acid supplementation in women of reproductive age[22]
2. Daily iron and folic acid supplementation during pregnancy
3. Presumptive treatment of hookworm infection during pregnancy in areas where hookworm infection is known to be endemic.[23]

Several factors may interfere with the efficacy of these interventions. Under-participation in antenatal care may be common due to factors such as geographic distance, low motivation and poor interpersonal skills of health staff, poor quality of supplies and facilities, insufficient supply of iron and folic acid pills and womens' poor understanding about the daily use of supplements, especially in the face of common side effects.[23] In sub-Saharan Africa, the acute shortage and high turnover of health workers, and lack of time have also been shown to contribute to ineffective antenatal measures for reducing anaemia.[24] Interestingly, a study from Bangladesh showed that the first 20 pills (whether taken on a daily basis or less frequently) yielded most of the benefit for raising haemoglobin levels, which suggests that currently recommended doses may be higher than necessary to achieve optimal outcomes, except when anaemia is very severe.[25]

Anaemia Due to Iron Deficiency

The global burden of iron deficiency has been estimated from anaemia prevalence surveys, which include many different causes of anaemia so data may be unreliable as they are often not based on proven cases of iron deficiency. WHO estimates that globally 41% of women and 27% of pre-school children are affected by iron-deficiency anaemia, making it number 15 of selected risk factors for preventable death and disability worldwide.[20]

Iron deficiency begins in childhood, worsens during adolescence in girls and is aggravated during pregnancy. Poor iron stores at birth, low iron content of breast milk and low dietary iron intake throughout infancy and childhood result in high prevalence of anaemia in childhood. Anaemia is exacerbated by increased requirements during adolescence and iron loss from menstruation and is often compounded by the lack of adequate nutrition. The situation is worsened by pregnancy when iron requirement is approximately two times higher than in a non-pregnant state.

Iron deficiency should not be considered a diagnosis but a secondary outcome due to an underlying medical condition. Although it may be a physiological response to rapid growth or increased requirements during childhood and pregnancy, it still requires treatment due to potential deleterious consequences. Many of the chronic effects of iron deficiency may develop before the clinical and laboratory evidence of anaemia becomes apparent. The biochemical evidence for iron deficiency occurs in several steps.[26] Initially, iron stores in the bone marrow are depleted as reflected by a decreased serum ferritin. The total iron-binding capacity then starts to rise, while the serum iron saturation begins to fall before microcytosis and a drop in haemoglobin ensue. There have been attempts to identify this early iron deficiency before anaemia develops in order to improve neurological and psychomotor functions in children and work performance in adults through widespread iron supplementation. However, there are concerns that iron excess may promote infections, especially in malarious areas.

A range of laboratory investigations are usually necessary if iron deficiency is suspected (Table 65.4)[27–30] because once the diagnosis is confirmed, a search for the precise cause is necessary. A systematic approach to the investigation of iron deficiency (see below) is required based on an understanding of alterations in the iron absorption and transport cycle.

- Deficient intake (cow's milk has poor iron content and can cause gut blood loss in some infants)
- Inadequate absorption
  - *Helicobacter pylori*
  - Antacid therapy or high gastric pH (gastric acid assists in increasing solubility of inorganic iron)
  - Cereals or vegetables with high phytates (bind iron avidly)
  - Loss or dysfunction of gastrointestinal system – gastrectomy, ileal surgery, inflammatory bowel disease, coeliac disease, malabsorption syndromes
  - Cobalt or lead ingestion (share the iron absorption pathways)
- Increased demand – pregnancy, young children and adolescence, increased erythropoietic states
- Blood loss (gastrointestinal system, genitourinary system, lungs as with pulmonary haemosiderosis)
- Rare defects of haem biosynthesis and iron transport.

Iron-deficient individuals may have no symptoms. Excessive fatigue and other nonspecific signs of anaemia become more pronounced as anaemia develops. Consumption of unusual 'foods' such as ice and paint or 'pica' only occurs in a minority of individuals. Physical examination may reveal stomatitis, glossitis, koilonychia (spoon-shaped nails) and hair loss. Oesophageal webs have been described in the Plummer–Vinson syndrome but are rare and may respond to iron replacement. Since iron is important in neuromuscular development, several features of anaemia described in Table 65.3 may be related to iron deficiency.

Treatment of iron deficiency is with dietary modifications and oral or parenteral iron.[31] Blood transfusions should be reserved for those with severe symptoms especially if the anaemia developed rapidly. Haemoglobin levels alone should not be considered as a criterion for transfusion since very low levels (e.g. 10–30 g/L) may be appropriately treated with oral iron if anaemia has developed slowly. Intravenous iron should only be considered in cases of poor response or intolerance to oral iron.

Cereals, poultry and green leafy vegetables, contain non-haem iron, which is often poorly absorbed. If dietary history suggests a deficiency, diet with foods rich in haem iron, such as red meat or liver should be recommended if social and religious customs and financial status allow, ideally with a drink containing vitamin C to facilitate iron absorption. Absorption is also facilitated by taking supplements on an empty stomach although side effects of dyspepsia may not always allow this strategy. Heavy tea intake can interfere with iron absorption and should be avoided. Multivitamin or dietary supplements containing calcium, zinc or copper can also interfere with iron absorption. Absorption may be delayed by tetracyclines, milk and soft drinks. Since acid is necessary for iron absorption, antacids may account for a poor response to oral iron.

Iron is usually prescribed as a daily dose of 150–200 mg of elemental iron, commonly ferrous sulphate, 1 tablet three times

TABLE 65.4 Tests to Confirm or Exclude Iron Deficiency

Mean cell volume	Useful as a diagnostic clue but not confirmatory Can also be low in thalassaemia, sideroblastic anaemia and rarely lead poisoning Can be falsely normal in the presence of iron deficiency in older people or with coexistent megaloblastic anaemia Anaemia of chronic disease can occasionally cause microcytosis
Serum ferritin	The most useful laboratory measure of iron status Low value is diagnostic in the presence of anaemia Very high values (>100 µg/L) usually exclude iron deficiency' Being an acute-phase protein, it increases in inflammatory conditions, and certain malignancies, making it unreliable Also increased in tissue damage especially of the liver Levels are falsely decreased in vitamin C deficiency and hypothyroidism
Erythrocyte zinc protoporphyrin	An intermediate in haem biosynthesis and elevated concentrations indicate interrupted haem synthesis due to iron deficiency when zinc is incorporated in place of iron Can be measured on a drop of blood with a portable haematofluorometer Small sample size makes it very useful as a screening test in field surveys, particularly in children, and pregnant women where inflammatory states may not co-exist Red cells should be washed before measurement (serum bilirubin and fluorescent compounds like some drugs can give falsely high values) although not often done Lead poisoning can give falsely high values Rarely acute myeloid leukaemia and sideroblastic anaemia give slightly high values Useful in that it is not increased in thalassaemias WHO recommends normal level >70 µmol/mol haem
Iron studies	Serum iron concentration represents the iron entering and leaving the circulation. Its range varies widely with age, circadian rhythm, infections and iron ingestion Total iron binding capacity measures iron bound to transferrin. Raised levels are suggestive of iron deficiency Transferrin saturation is the ratio of serum iron and the TIBC expressed as a percentage – It is probably more useful in detecting iron overload rather than low levels.
Reticulocyte haemoglobin content	Sensitive indicator that falls within days of onset of iron-deficiency Reduced levels shown to be predictor of iron deficiency especially in the setting of renal insufficiency False normal values can occur when MCV is increased or in thalassaemia
Serum transferrin receptor	Receptors shed by iron-hungry erythropoietic cells Increased in iron deficiency It is not increased in inflammatory conditions May be upregulated by increased erythropoiesis (haemolytic diseases) giving falsely high values – serum transferrin receptor to ferritin ratio has been suggested in these cases
Bone marrow examination with special iron staining (Perl's)	Absence of stainable iron in a sample that contains particles can establish the diagnosis without other laboratory tests A simultaneous control specimen containing stainable iron should also be assessed Useful in differentiating from anaemia of chronic disorders or α-thalassaemia or milder forms of thalassaemia Can help in identifying the sideroblastic anaemias (ring sideroblasts with Perls stain), and some forms of congenital dyserythropoietic anaemia which can also cause microcytosis.

An improvement in haemoglobin and clinical symptoms with iron replacement is probably the simplest way to diagnose iron deficiency. Peripheral smear may help by demonstrating pencil cells, anisopoikilocytosis and high platelet number in cases of blood loss.

daily. The dose in children is 3–6 mg/kg per day split into divided doses. Assuming good compliance and absorption, this should result in an increase in haemoglobin within 4 weeks. Once the haemoglobin is normalized, iron should be continued for 3 months to replenish the iron stores. The major problem with oral iron is upper gastrointestinal side-effects, which can be dose-dependent. A reduction in the dose or change in the formulation to gluconate or fumarate or even liquid forms, may be successful. Liquid iron preparations may stain the teeth and should therefore be taken through a straw. Oral iron can also cause constipation or diarrhoea which is not dose-dependent. Parenteral iron is best given intravenously because intramuscular iron is painful and has been associated with development of soft tissue sarcomas.[32] High-molecular-weight iron dextran carries a low but significant risk of anaphylaxis, but the newer formulations including low-molecular-weight iron dextran, iron sucrose, ferumoxytol and iron gluconate have minimal risks.

Anaemia Due to Vitamin B_{12} Deficiency

Vitamin B_{12} or cobalamin deficiency is a well-recognized cause of macrocytic anaemia (Box 65.5). Although some microorganisms can synthesize cobalamin, humans need to obtain this essential vitamin from foods, mainly meat, poultry and dairy products. Vitamin B_{12} is an essential co-factor in DNA synthesis, serving as a co-factor in two key biochemical processes involving methylmalonic acid and homocysteine as precursors. Consequently vitamin B_{12} deficiency can interfere with DNA synthesis. Clinical manifestations include haematological (megaloblastic anaemia and pancytopenia), and neuropsychiatric disorders (paraesthesia, peripheral neuropathy, psychosis and dementia) and an increased risk of cardiovascular disease because of hyperhomocystinaemia.[32–34]

A systematic approach to the investigation of vitamin B_{12} deficiency requires an understanding of the absorption cycle.[35] Ingested vitamin B_{12} is broken down in the acidic environment of the stomach. It binds to R-binders in gastric secretions and saliva which stabilize the vitamin B_{12}. In the alkaline environment of the small intestine, vitamin B_{12} is released from R-binders to bind to intrinsic factor, synthesized in the gastric parietal cells. This vitamin B_{12}-intrinsic factor complex is absorbed from the terminal ileum. Recently, an alternative absorption system independent of intrinsic factor and the terminal ileum has been postulated which provides a rationale for

BOX 65.5 CAUSES OF VITAMIN B_{12} DEFICIENCY

REDUCED DIETARY INTAKE

- Strict vegetarians (no dairy products or eggs)
- Malnutrition
- Older individuals with poor diet (and on antacids for dyspepsia)
- Alcoholics

UNSUITABLE GASTRIC ENVIRONMENT FOR ABSORPTION

- Food-cobalamin malabsorption – probably the commonest cause; seen in older age; develops due to a decreased ability to separate cobalamin from food protein due to decreased gastric acidity
- Decreased stomach acid – atrophic gastritis, antacids (proton-pump inhibitors, H2 antagonists)
- Gastric resection

UNSUITABLE INTESTINAL ENVIRONMENT FOR ABSORPTION

- Pancreatic insufficiency (inability to transfer cobalamin from R-binders to intrinsic factor)
- Zollinger–Ellison syndrome (insufficient alkalinization in the duodenum to neutralize excess acid)
- Bacterial overgrowth due to blind-loop syndromes
- Fish tapeworm, *Diphyllobothrium latum*, competes with the host for cobalamin
- Ileal resection or bypass
- Intestinal malabsorption caused by tropical sprue, coeliac disease, Crohn's disease, or malignant infiltration of the small intestinal wall
- Medications (cholestyramine, metformin, colchicine)

DEFICIENCY OF INTRINSIC FACTOR (IF)

- Pernicious anaemia (begins after 40), increased risk of gastric carcinoma and carcinoid tumours
- Rare congenital disorders, e.g. Imerslund–Grasbeck syndrome.

increasingly popular oral replacement therapies. Once absorbed, vitamin B_{12} binds to transcobalamin II to be transported around the body.

The diagnosis of vitamin B_{12} deficiency is based on the measurement of serum vitamin levels in a patient with clinical evidence of deficiency. A note of caution is that folic acid deficiency can cause falsely low serum vitamin B_{12} levels. Diagnostic clues for vitamin B_{12} deficiency include marked macrocytosis (often >130 fl), neutrophil nuclear hypersegmentation and oval macrocytes in the peripheral blood film. Blood tests may demonstrate increased lactate dehydrogenase and low haptoglobin levels due to haemolysis within the bone marrow. The cause of the macrocytosis can be confirmed by bone marrow examination which reveals a megaloblastic picture. Although macrocytic anaemia is a typical feature of vitamin B_{12} deficiency, it can be absent in older individuals who may only have neuropsychiatric features. Measurements of methylmalonic acid and homocysteine levels, two markers which are very sensitive for detecting B_{12} deficiency, have shown that vitamin B_{12} deficiency can occur with normal haemoglobin levels and without macrocytosis.[36]

Pernicious anaemia is probably the commonest cause of vitamin B_{12} deficiency. The presence of parietal cell or intrinsic factor antibodies supports a diagnosis of pernicious anaemia.[33–36] Schilling tests are rarely performed because of the unavailability of the radio-labelled vitamin B_{12} and the difficulty in interpreting the results in the presence of renal insufficiency.

The treatment of vitamin B_{12} deficiency can be by the oral or parenteral route.[37] Increasing evidence suggests that oral supplementation may be adequate even in the presence of malabsorption or pernicious anaemia.[38,39] The recommended initial oral replacement dosage is 1–2 mg but higher doses may be needed for malabsorption or pernicious anaemia.[40] For patients with severe anaemia and/or neurological disease, daily or alternate day intramuscular injections should be initiated for the first 2–4 weeks before reverting to the maintenance three-monthly dose. Reticulocytosis is an early marker of response to treatment and is noticeable within 1–2 weeks.

Anaemia Due to Folic Acid Deficiency

Folic acid deficiency causes similar haematological manifestations to vitamin B_{12} deficiency though neuropsychiatric manifestations are less common. The ability of nerve tissue to concentrate folate to levels five times greater than those in the plasma has been suggested as a reason for the absence of neuropathy in folate deficiency. Folic acid deficiency is associated with fetal neural tube defects, and possibly with an increase in atherosclerosis and arteriovenous thrombosis, dementia and colonic cancer. Dietary folic acid is present in the form of polyglutamates, which are converted to folate monoglutamates by the enzyme folate conjugase in the intestinal brush border, prior to absorption. The monoglutamates function as a carbon transporter and are essential for DNA biosynthesis.

Folate is found in green vegetables and fruits and deficiency can result from decreased intake, impaired absorption and increased utilization, although the commonest cause is dietary insufficiency.[41] In some wealthy countries, cereals have been fortified with folic acid to successfully prevent vitamin deficiency. However folate deficiency continues to be a problem in less wealthy countries and particularly among children and pregnant women.[42,43] Exclusive feeding of goat's milk to infants can lead to folate deficiency. Other causes include alcoholism, excessive cooking of vegetables, and malabsorption (e.g. abnormalities of the small bowel). Increased demand for folic acid occurs in pregnancy because the growing foetus has a high avidity for folate. For this reason, folate supplementation has been widely recognized as an essential part of routine antenatal care to reduce the risks of neural tube defects. High folate utilization also occurs in haemolytic anaemias such as sickle cell disease due to high red cell turnover and exfoliative dermatitis. Several drugs, including sulfasalazine, trimethoprim, methotrexate, pyrimethamine and phenytoin, can also interfere with folate metabolism.

Folate-deficient individuals develop a macrocytic anaemia with peripheral blood and bone marrow findings similar to that found in vitamin B_{12} deficiency.[32] Diagnosis of folate deficiency is confirmed by the presence of low serum folate. Red cell folate levels decrease more slowly than serum levels during the 120-day turnover of the red cells. Red cell folate levels may be a better indicator of tissue folate levels than serum folate, although red cell folate can be more expensive and falsely low in vitamin B_{12} deficiency.[45,44]

Treatment of folate deficiency is with oral folate (5 mg daily) which is sufficient even in malabsorptive states. It is crucial that any co-existing vitamin B_{12} deficiency is ruled out before initiating folic acid therapy, otherwise the neurological manifestations of B_{12} deficiency may deteriorate rapidly. It is also important

that the underlying cause of folate deficiency is identified and treated.

Anaemia Due to Vitamin A Deficiency

Vitamin A is important in erythropoiesis, iron metabolism (enhances iron absorption and its release from stores to the bone marrow) and for decreasing the risk of infections.[45] Vitamin A deficiency is a major public health problem in low-income countries, with an estimated 200 million preschool children affected.[47] Pregnant women and women of childbearing age also constitute high-risk groups for vitamin A deficiency.[46] Vitamin A given to Thai school children with conjunctival xerosis led to a significant increase in haemoglobin level[47] and in anaemic school children in Tanzania, vitamin A supplementation produced a marked increase in haemoglobin which was enhanced by co-administration of iron.[48] Vitamin A can also improve anaemia in pregnant women, depending on the local prevalence of deficiency[49–52] though the response may be sub-optimal in pregnant women infected with HIV.[53]

Anaemia Due to Copper Deficiency

Copper is a trace element necessary for normal haematopoiesis and myelopoiesis. Anaemia in copper deficiency is due to decreased activity of the copper-dependent enzymes, hephaestin, ceruloplasmin and cytochrome C oxidase. These are important in ferrous–ferric iron conversions and their decrease leads to abnormalities in iron absorption and its incorporation into the haemoglobin molecule. Acquired copper deficiency occurs with malnutrition and gastrointestinal malabsorption syndromes. Coeliac disease, cystic fibrosis and individuals who have had gastrectomy or surgery resulting in 'short bowel' are also at risk. Copper deficiency has also been described in persons ingesting excessive amounts of zinc-containing supplements and those who have swallowed zinc-containing coins.[54,55]

Anaemia related to copper deficiency is normocytic or macrocytic and can be associated with neutropenia; thrombocytopenia is rare. Bone marrow findings are characteristic with cytoplasmic vacuolization of both erythroid and myeloid precursor cells with ringed sideroblasts and an unusual finding of iron granules in plasma cells. These findings may be misdiagnosed as myelodysplastic neoplasm.

Measurement of serum copper levels is helpful in confirming the diagnosis although the test is fairly insensitive. Since almost complete haematological recovery can occur with copper replacement, this may be a useful diagnostic test. Oral copper supplements can be started with 8 mg of elemental copper a day slowly decreasing over the next few weeks to 2 mg until a good response is noted.

Anaemia and Zinc

Although low zinc levels do not cause anaemia they have been linked to growth retardation, heightened susceptibility to infection and male hypogonadism in relation to sickle cell disease.[56] Zinc deficiency has been described in nearly half of children and 70% of adults with sickle cell disease possibly due to increased loss of zinc in the urine and high cell turnover with decreased dietary intake.[57] In contrast zinc excess can cause anaemia through interference with copper absorption by sequestering it in the gut lumen. For this reason, zinc compounds have been used to treat Wilson's disease which is characterized by copper excess.

Anaemia Associated with Neglected Tropical Diseases

The neglected tropical diseases are a group of infections which are endemic in developing countries. Several of these neglected tropical diseases cause anaemia and many can be managed using inexpensive interventions to treat the underlying parasitic infections.[14] The mechanisms of anaemia in these conditions are predominantly blood loss from the gastrointestinal or genitourinary tracts but also poor nutrition, bone marrow suppression, inflammation, hypersplenism and haemolysis.[58]

Anaemia is a common consequence of infections with soil-transmitted helminths or schistosoma with a strong correlation between haemoglobin level and worm load or faecal egg count. Even mild infections can lead to anaemia.[59] Polyparasitism (i.e. infection with several parasites simultaneously) can be responsible for unresponsiveness of the anaemia to eradication of one organism.[60] Treatment of communities at high risk of soil-transmitted helminths improves growth and iron stores in children and reduces anaemia in pregnant women.[61]

The treatment of anaemia due to neglected tropical diseases depends on eradication of the parasite with drugs such as albendazole and praziquantel though anaemia resolution may be less successful if it is due to trichuriasis.[62–64] The addition of iron to anthelmintic treatment has met with variable success rates probably because there is associated anaemia related to inflammation. However it is still generally recommended that iron supplementation should be included with anthelmintic therapy in treatment programmes for neglected tropical diseases.[65–67]

Sickle Cell Disease

INTRODUCTION

Haemoglobin S (HbS) has a prevalence of 25–30% in many parts of Africa and also some areas in the Middle East (Figure 65.6). HbS tends to be common among ethnic groups that have traditionally had high exposure to *Plasmodium falciparum* malaria. In sub-Saharan Africa approximately 230 000 infants are born with sickle cell disease each year, mostly with HbSS. Sickle cell disease (SCD) is an autosomal recessive disorder characterized by production of an abnormal haemoglobin, sickle haemoglobin. Sickle haemoglobin (HbS) arises from a mutation in codon 6 of the β-globin gene resulting in replacement of the normal glutamic acid residue by a valine.[68] SCD is most commonly caused by the co-inheritance of two sickle cell genes (homozygous Hb SS disease) but patients who are heterozygous for HbS and for another haemoglobin mutation such as HbC (haemoglobin SC disease) or β-thalassaemia ($S\beta^0$ and $S\beta^+$) can also present with features of SCD.[69] SS disease and $S\beta^0$ disease are more severe than SC disease and $S\beta^+$ disease (Box 65.6).[70] SCD can affect multiple organs and its clinical course is punctuated by episodes of acute illness on a background of progressive organ damage, especially of the central nervous system and the lungs.[70]

HISTORY

The first description of SCD was in 1910 in an anaemic Grenadian dental student[71] and over the next 30 years it was

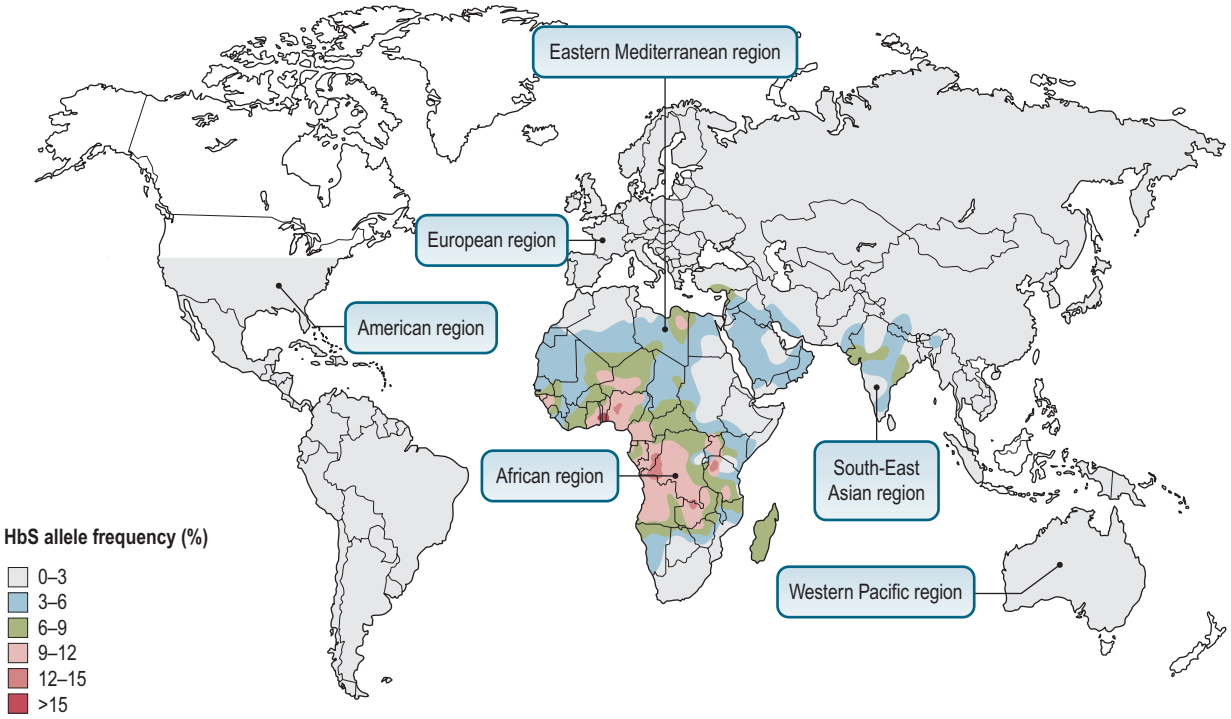


Figure 65.6 Distribution of the HbS allele. *(Rees DC, Williams TN, Gladwin MT. Sickle cell disease. Lancet 2010; 376: 2018–31. Copyright Elsevier 2010.)*

discovered hypoxia led to red cell sickling[72] and that HbS could be identified by its pattern of migration on electrophoresis.[73]

PATHOPHYSIOLOGY (Figure 65.7)

SCD arises from the tendency of HbS to polymerize in hypoxic states. This phenomenon occurs where there is deoxygenation and is due to the binding between β1 and β2 chains of two haemoglobin molecules, a property unique to haemoglobin variants that have the Glu-6-Val substitution.[74] The polymerized haemoglobin fills the erythrocyte and deforms its architecture and flexibility to form a sickle shape. This alteration in the structure promotes cellular dehydration,[70,75,76] Upon reoxygenation, the polymers dissolve thus reversing the sickling process. However repeated sickling and unsickling eventually causes irreversible changes,[77] so early management to avoid repeated crises is important to prevent disease progression.

Polymerization, and therefore the clinical features of SCD, are influenced by three main factors[78]; hypoxia, the intracellular HbS concentration and the co-existence of other genetic haemoglobin abnormalities (e.g. α-thalassaemia or hereditary persistence of fetal haemoglobin–haemoglobin F).[79] Sickled red cells lead to vaso-occlusion and haemolysis due to the entrapment of sickled erythrocytes in the microvasculature and upregulation of adhesion receptors.[76,80,81] White blood cells contribute to this process by providing an inflammatory

BOX 65.6 CLINICAL VARIETIES OF SICKLE CELL DISEASE BASED ON THE CO-EXISTING MUTATIONS IN HAEMOGLOBIN

SEVERE

- HbSS
- HbS/β^0-thalassaemia
- Severe HbS/β^+-thalassaemia
- HbS/OArab
- HbS/D Punjab
- HbS/C Harlem

MODERATE

- HbS/C
- Moderate HbS/β^+-thalassaemia
- HbA/S Oman

MILD SICKLE-CELL DISEASE

- Mild HbS/β^{++}-thalassaemia
- HbS/E.

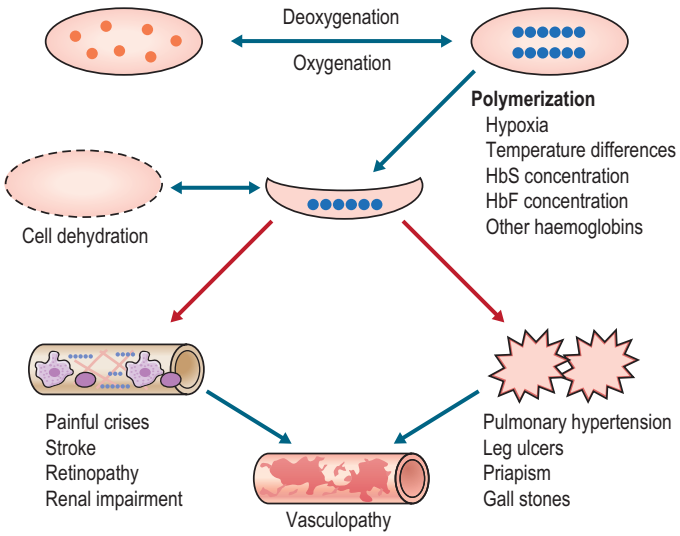


Figure 65.7 Pathological consequences of sickle cell disease.

environment. Activation of platelets and the coagulation system also contribute to the vaso-occlusion in SCD.[82–86]

CLINICAL FEATURES

Infants with SCD are protected during the first few months of life by the high levels of haemoglobin F in the red cells. Anaemia usually develops by 3 months. At all ages, chronic haemolysis of abnormal red cells means that SCD is associated with steady state haemoglobin levels of 60–80 g/L. Although any organ can be affected by SCD and complications can occur at any age, certain features tend to predominate in different age groups (Box 65.7).

Painful Crises

Pain is the hallmark of SCD[87] and four different patterns of pain have been described with SCD each with different underlying mechanisms:[88]

- Vaso-occlusive (acute and intermittent)
- Pain from bone and tissue necrosis (chronic)
- Neuroplasticity (chronic, neuropathic) – functional brain changes
- Opioid-induced hyperalgesia (acute or chronic).

Painful crises often start in young children as dactylitis or hand–foot syndrome, in which painful swelling of the hands and feet results from the inflammation of metacarpal and metatarsal periosteum. These crises are the result of vaso-occlusion of the bone marrow causing bone infarction and release of mediators that activate pain receptors.[82] The number, severity and frequency of painful episodes vary widely in individuals. Half may never have any episodes whereas about 3% may need hospital admission up to 6 times a year.[89] More than three pain episodes requiring hospitalization per year is associated with increased mortality among patients over 20 years old. In under-resourced settings, hospital visits underestimate the frequency of pain since many do not seek medical help.[90] Exposure to cold, fever, menstruation, alcohol intake and dehydration can precipitate pain crises. Unlike acute pain crises, chronic pain in SCD usually has an identifiable basis such as femoral head necrosis, osteoarthritis or chronic skin ulcers.

BOX 65.7 CLINICAL COMPLICATIONS OF SCD AT DIFFERENT AGES

TODDLER (1–3 YEARS)

- Splenomegaly and splenic sequestration
- Increased infection rates – pneumonia and meningitis due to functional hyposplenism
- Dactylitis

CHILDHOOD

- Painful crises
- Stroke
- Acute chest syndrome
- Osteonecrosis

ADOLESCENCE

- Painful crises
- Stroke
- Priapism
- Delay in sexual development
- Psychosocial problems

ADULTS

- Painful crises
- Pulmonary hypertension
- Renal insufficiency
- Osteonecrosis
- Retinopathy
- Leg ulcers.

BOX 65.8 CAUSES OF ANAEMIA IN SICKLE CELL DISEASE

- Chronic haemolysis
- Acute splenic or hepatic sequestration
- Red cell aplasia
- Chronic renal impairment
- Folic acid or iron deficiency
- Transfusion reactions from alloimmunization
- Hyperhaemolysis in patients with severe infection.

Anaemia

Sickle erythrocytes have an average life span of 17 days and anaemia can be due to several causes (Box 65.8). Red cell haemolysis causes anaemia and gall stones and can cause fatigue out of proportion to the anaemia.[91,92] There are suggestions that patients with low haemoglobin concentrations and high haemolytic rates are more likely to develop vascular problems compared with those with higher haemoglobin concentrations.

Splenic sequestration with a sudden rapid drop in haemoglobin occurs in those who have not yet developed autosplenectomy so it can occur in young children with HbSS and adults with HbSC disease or sickle cell-β^+-thalassaemia. Treatment may require blood transfusion and in rare cases, sequestration can be fatal. Splenectomy may be needed for recurrent severe sequestration. Parents can be taught to feel their infant's abdomen for an enlarging spleen and report to hospital if there is a sudden increase in spleen size. Red cell aplasia can develop due to secondary parvovirus infection which has a predilection for erythroid progenitors. Alloimmunization is common in SCD patients who have had frequent transfusions so, if possible, extended red cell phenotyping should be undertaken. Hyperhaemolytic crisis is suspected when there is sudden exacerbation of anaemia with increased reticulocytosis and bilirubin level.

Infections

Infectious complications of SCD are a major cause of morbidity and mortality, even with adequate vaccination and prophylactic antibiotic regimens. This propensity to infection is related to impaired splenic function although tissue ischaemia, especially in the lungs and renal system, can contribute. Hyposplenism is demonstrable in the peripheral blood film by the presence of Howell–Jolly bodies. Most children with SCD have undergone autosplenectomy by the age of 5 years and therefore have increased risk of infection from encapsulated microorganisms.[93] Typical infectious complications include pneumococcal sepsis, *Neisseria* meningitis, osteomyelitis caused by *Salmonella* species, urinary tract infections and pyelonephritis due to *Escherichia coli*. Anatomical abnormalities such as renal papillary necrosis can predispose to urinary complications which may require long-term antibiotics.

Acute Chest Syndrome

Acute chest syndrome (ACS) is defined as a new pulmonary infiltrate on the chest radiograph combined with one or more

BOX 65.9 RISK FACTORS FOR ACUTE CHEST SYNDROME

- HbSS and HbS β^0-thalassaemia
- Lower HbF (Increase of HbF from 5–15% decreases risk by half)
- Chronic hypoxia (low nocturnal oxygen saturation)
- Bronchospasm due to asthma
- Winter months
- Smoking
- Postoperative states
- High morphine doses during pain crises
- HLA DRB1*130101haplotype
- ET-1 T8002 allele.

There is a lower risk of ACS with Arab-Indian haplotype (higher HbF levels) compared with the African haplotypes.

manifestations such as fever, cough, sputum production, tachypnoea, dyspnoea or new-onset hypoxia.[94] ACS is the most common cause of death in SCD patients and a frequent cause of hospitalization, second only to painful crisis. Mortality in patients with ACS in a wealthy country setting is 1% in children and 4.3% in adults.[95] The peak incidence for ACS is 2–4 years of age and gradually declines to 8.8 per 100 patient-years in subjects older than 20 years.[96,97]

Fever and cough are more common in children with ACS and chest pain and dyspnoea are more common in adults.[96] ACS is often preceded by febrile pulmonary infection in children and by vaso-occlusive pain crisis and lung infarction in adults. It is important to note that although tachypnoea, wheezing and features of chest infection may be identified, a third of the patients may have a normal physical examination. More than one-third of patients with ACS are hypoxaemic (oxygen saturation <90%).[98] Chest radiography is essential although infiltrates may lag behind clinical symptoms by up to 3 days. Repeat chest X-rays are recommended if there is a strong clinical suspicion of ACS. Bilateral infiltrates or involvement of multiple lobes may predict a poorer prognosis.

Risk factors for ACS (Box 65.9) include fat embolus which can be confirmed by finding stainable fat in pulmonary macrophages.[99] Chronic complications such as pulmonary hypertension occur in as many as 60% of patients and do not appear to be associated with prior episodes of ACS. High serum phospholipase A2, and the surrogate marker C-reactive protein, have been noted in patients admitted with vaso-occlusive crisis 24–48 hours before the development of ACS.[100,101]

Stroke

Neurological complications occur in at least 25% of patients with SCD and SCD is one of the most common causes of stroke in children.[102,103] In SCD, the risk of having a first stroke is 11% by the age of 20, 15% by age 30 years and 24% by age 45 years. Both thrombotic and haemorrhagic strokes occur, although the former is more common in children and those over 30 years of age, whereas the latter is more common between the ages of 20 and 30 years.[108] This age-specific pattern may be related to the higher cerebral flow rates in early childhood. Although the prevalence of clinically overt stroke is of the order of 11%, clinically silent infarction, detectable by magnetic resonance scans, affect nearly double this number by the age of 20. Silent infarcts are associated with cognitive impairment and the majority of these children require lifelong specialist care.[104] Cerebral thrombosis, which accounts for 70–80% of all strokes in SCD, results from large-vessel occlusion whereas silent infarcts are the result of microvascular occlusion or thrombosis or hypoxia secondary to large-vessel disease. In a third of SCD patients, major-vessel stenosis is accompanied by collateral vessels that appear as 'puffs of smoke' (*moyamoya*) on angiography. Risk factors for ischaemic strokes in SCD include increased cerebral blood flow velocity, previous silent infarcts, nocturnal hypoxaemia, severe anaemia, acute chest syndrome and elevated systolic blood pressure. An elevated leukocyte count is a risk factor for haemorrhagic stroke.[105–108]

DIAGNOSIS

Often the family history and clinical findings clearly point towards a diagnosis of SCD and during an acute crisis, abundant sickled red cells can be seen on a blood film. White cell counts are higher than normal in SCD disease, particularly in patients under age 10 years. The presence of sickle haemoglobin in different sickle syndromes (e.g. HbAS, HbSS, HbSC) (Table 65.5) can be confirmed by a simple sickle slide or solubility test. Haemoglobin electrophoresis will distinguish between many of these variants but high-performance liquid chromatography and iso-electric focusing are preferred for a definitive diagnosis.

TABLE 65.5 Sickle Cell Syndromes

	Hb (g/L)	MCV (fl)	Reticulocyte (%)	HbS	HbA	Others
Sickle cell disease (β^S/β^S)	80–90	70–90	6–12	>85	0	HbA2 3–3.8; HbF 2–20
Sickle cell trait (β^A/β^S)	130–150	75–90	Normal	30–40	60–70	HbA2 2.5; HbF <1
Sickle thalassemia (β^S/β^+)	80–120	65–75	4	70–90	5–30	HbA2 3.5–6; HbF 1–15
Sickle thalassemia (β^S/β^0)	70–110	60–90	4	80–95	0	HbA2 3.5–6; HbF 1–15
Sickle-HPFH	110–140	80–90	2	70–80	0	HbA2 1–3; HbF 20–30
Sickle-HbC (β^S/β^C)	80–130	75–90	4	50	0	HbA2 normal; HbF 1–7

In individuals with sickle cell trait, depending on the presence or absence of α globins, the Hb levels, MCV, and the percentages of HbS and A can vary. For example, if the genotype is –/–α, then the HB will be around 8 with MCV in the 50s and HbS and HBA demonstrating lower and higher values, respectively. Hb, haemoglobin; MCV, mean cell volume; HPFH, hereditary persistence of fetal haemoglobin

BOX 65.10 MANAGEMENT OF COMPLICATIONS OF SICKLE CELL DISEASE

RENAL IMPAIRMENT

- Inability to maximally concentrate urine (hyposthenuria) in response to water deprivation is an early finding
- Renal tubular acidosis
- Increased urinary tract infections
- Glomerular hyperfiltration, increased creatinine secretion, and a very low serum creatinine are characteristic of young patients with sickle cell anaemia, so renal dysfunction can be present even with normal serum creatinine values
- Microalbuminuria is common in childhood and up to 20% of adults develop nephrotic-range protein loss
- Gross haematuria can develop due to microthrombin in renal vessels, renal medullary carcinoma, and nocturnal enuresis
- Treatment is based on the early use of hydroxycarbamide and angiotensin-converting enzyme inhibitors in children with clinically significant albuminuria.

PULMONARY HYPERTENSION

- Noted in up to 60% of SCD cases
- No relationship to acute chest syndrome (different pathophysiology)
- Mortality risk with even mild pulmonary hypertension is high
- Regular blood transfusions and long-term anticoagulation have been tried
- Hydroxycarbamide may decrease the risk
- Prostacycline analogues (epoprostenol, and iloprost), endothelin-1 receptor antagonists (bosentan), phosphodiesterase inhibitors (including sildenafil), and calcium channel blockers are being evaluated.

PRIAPISM

- Brief but recurrent (stuttering); may occasionally last for many hours and can lead to impotence
- Usually ischaemic, or low-flow, priapism
- Patients should be educated to seek medical attention if more than 2 hours duration
- Detumescence within 12 hours is necessary to retain potency
- Intravenous hydration and analgesia initially with consideration for α-adrenergic agonists (etilefrine or phenylephrine)
- Penile aspiration and irrigation with saline and α-adrenergic agents or shunting may be required in severe cases in combination with an exchange transfusion.

Haemoglobin mass spectrometry and DNA analysis are being increasingly used.

Antenatal screening is available to women in some countries to help to identify couples who are at risk of having a baby with SCD. Community acceptance of reproductive genetic services however depends on the effectiveness of education and counselling. The use of prophylactic penicillin and the provision of comprehensive medical care during the first 5 years of life have reduced mortality related to SCD from 25% to less than 3%.[109]

MANAGEMENT (Box 65.10)

Individuals with SCD are best managed by a multidisciplinary team as they may require a variety of specialist inputs including haematology, ophthalmology, nephrology, obstetrics, orthopaedics and physiotherapy. The cornerstones of SCD therapy are disease modification and prompt and effective management of crises. Severe pain crises generally require intravenous fluids and adequate, often opiate, analgesia (Box 65.11), while disease modification is based on interventions to increase HbF levels. In steady state it is usual practice to give sickle cell patients folate supplements (1–5 mg/day) because their high rates of haemopoiesis put them at risk of deficiency. SCD is associated with functional asplenia so patients should also receive prophylactic oral penicillin (250 mg twice a day) and vaccinations against encapsulated organisms.

Hydroxycarbamide

Hydroxycarbamide is the main agent used to increase HbF (Box 65.12) and is associated with significant reductions in acute pain crises, hospitalization rate, time to first and second pain crises, episodes of acute chest syndrome, and the need for transfusions and the number of units transfused.[110] Other beneficial effects of hydroxycarbamide, which are independent of the increase in HbF, include reduced neutrophil count, increased cellular water content, decreased HbS concentration, changing expression of adhesion molecules and nitric oxide generation.[111] Hydroxycarbamide may also be an alternative to frequent blood transfusions for the prevention of recurrent stroke in children as it can lower transcranial Doppler velocities.[112,113] Under-use of this cheap, effective drug is related to concerns about leukaemogenicity but this has not been shown to be a problem when used for a non-malignant condition like SCD.

Blood Transfusions (Box 65.13)

The two main approaches to transfusion[74] in SCD are simple top-up transfusion and exchange transfusion. Target haemoglobin level in SCD therapy is 100 g/L or a haematocrit of 30%; higher target levels are associated with hyperviscosity and

BOX 65.11 MANAGEMENT OF PAIN IN PATIENTS WITH SICKLE CELL DISEASE

- Assess pain intensity
- Choose the analgesic, dosage, and route of administration
- Paracetamol and hydration should be considered in all patients
- Oral, sustained-release morphine is as good as intravenous morphine infusion in children and young adults
- Manage mild pain with rest, hydration, and weak opioids (such as codeine). Admit patients in whom pain that does not subside promptly or require opioid treatment; fever, pallor, or signs of respiratory compromise; a low likelihood of receiving appropriate care at home
- Pain management should be individualized and dosing should take into account prior pain management and use of opioids
- The pain pathway should be targeted at different points with different agents, avoiding toxicity with any one class
- Always look for a cause, e.g. infection, dehydration, etc.
- Education about avoiding exposure to precipitants
- Be empathetic, reassuring, and supportive
- Benzodiazepines may be helpful to reduce anxiety
- Re-examine the patient often to ensure adequate pain relief, to assess sedation and respiratory rate (to avoid opioid overdose). In assessing patient responses to conventional doses of analgesia, it must be remembered that those with sickle cell disease metabolize narcotics rapidly
- Re-search for evidence of any complications such as acute chest syndrome or anaemia
- Always look for a cause, e.g. infection.

BOX 65.12 HYDROXYCARBAMIDE USE IN PATIENTS WITH SICKLE CELL DISEASE

BEFORE COMMENCEMENT

- Blood counts, red cell indices, HbF level, serum chemistries, pregnancy test

PATIENT EXCLUSION CRITERIA

- Regular transfusion regimen
- Abnormal liver function tests
- Inability to attend hospital for regular follow-up

PATIENT ELIGIBILITY

Patients (HbSS or $S\beta^0$-thalassemia, not HbSC) with a severe clinical course as:

- Three admissions with painful crisis within 1 year *or*
- Frequent days of pain at home, leading to a lot of time off work *or*
- Recurrent acute chest syndrome.

The following predict a more severe clinical course and are additional reasons to consider offering hydroxyurea: Hb <70 g/L, WBC >15 × 10^9/L, HbF <6% and renal insufficiency due to SCD.

DOSE AND MONITORING

- Start at 10–15 mg/kg per day (to the nearest 500 mg/day)
- If no or poor response, increase dose by increments of 5 mg/kg per day every 4 weeks (max: 30 mg/kg per day). Most good responses require about 1–2 g/day in adults
- Monitor FBC, HbF%, and reticulocytes every 1 or 2 weeks initially, then every 4 weeks when on a stable dose
- Monitor biochemistry profile (hydroxyurea has renal excretion and hepatic toxicity).

GOALS OF TREATMENT

- Less pain
- Persistent increase in HbF (usually measured every 6–8 weeks) or mean cell volume
- Persistent increase in haematocrit if severely anaemic
- Decrease in LDH
- Acceptable toxicity.

Improvement in symptoms and blood parameters may take 3–4 months of therapy, but can be seen after approximately 6 weeks. If the reticulocyte count is less than expected for the degree of anaemia, erythropoietin deficiency should be considered.

worsening of complications. In exchange transfusion, the aim is to achieve an HbS% of <30%. Complications of transfusion in SCD include alloimmunization,[114] delayed haemolytic transfusion reactions and iron overload. The high rates of red cell antibody formation (30%) noted in wealthy countries are due to minor blood group incompatibilities between the recipient and the blood donor who is often of a different ethnicity. Leukocyte reduction of transfused blood, routine ABO, Rh and Kell matching for all patients and extended phenotype matching for those with alloantibodies may be useful for reducing transfusion reactions.

Management of Acute Chest Syndrome

Treatment for ACS is predominantly supportive and includes adequate pain relief, antibiotics (e.g. a macrolide with a cephalosporin), continuous pulse oximetry and delivery of supplemental oxygen to patients with hypoxaemia. Incentive spirometry can prevent atelectasis and infiltrates[115] and blood transfusion is indicated when a patient develops respiratory distress, a clinically significant fall in the haematocrit or signs of multi-organ failure.[116] Both simple transfusion and exchange transfusions have been used and neither appears to be superior. A short course of steroids may attenuate ACS but it may also increase the risk of re-hospitalization.[117] Bronchodilators may help patients with wheezing[118] but inhaled nitric oxide has not shown any clear benefits.[119] Since coagulation activation is important in the pathophysiology of acute chest syndrome, treatment with low-molecular-weight heparin may reduce clinical complications.[120]

Management of Stroke

Transcranial Doppler measurement of cerebral blood flow has been a major step forwards in identifying individuals with an increased risk of ischaemic stroke. A value more than 200 cm/second imparts a 40% risk of stroke within the next 3 years.[121] Regular blood transfusions can reduce the incidence of stroke in children.[105] Due to a high recurrence of stroke (60%) on stopping transfusions, continuation of transfusions should be guided by transcranial Doppler measurements.[122,123] Once a stroke has developed, the best therapeutic strategy is exchange transfusion which probably needs to be done monthly.[70,73] Neurosurgical re-vascularization should be considered for moyamoya-like syndromes when new strokes occur despite transfusion.

HAEMOGLOBIN SICKLE CELL DISEASE

Haemoglobin SC results from the co-inheritance of HbS and HbC and has its highest prevalence in West Africa. Clinical features and disease management are similar to those of HbSS disease but splenomegaly, splenic infarcts and splenic sequestration may occur into adulthood. Proliferative retinopathy necessitates regular ophthalmic review in those aged over 10 years. Compared with HbSS, anaemia is less marked in Hb SC (8–140 g/L) and there are fewer sickle cells and more target cells on the blood film. The diagnosis can be confirmed by haemoglobin electrophoresis, HPLC or iso-electric focussing.

BOX 65.13 BLOOD TRANSFUSIONS IN SICKLE CELL DISEASE

INDICATIONS FOR ACUTE TRANSFUSIONS

- Acute exacerbation of anaemia
- Acute chest syndrome
- Stroke or acute neurological deficit
- Multiorgan failure
- Preoperative management

INDICATIONS FOR LONG-TERM TRANSFUSIONS

- Primary and secondary stroke prevention
- Recurrent acute chest syndrome not helped by hydroxycarbamide
- Recurrent complications
- Occasionally in complicated pregnancy

SPECIAL CONSIDERATIONS

- Aim in all cases to reduce HbS level to <30%
- Exchange transfusions may be considered in cases of stroke, acute chest syndrome not responding to top-up transfusion and major surgeries
- Target haemoglobin concentration of 100 g/L may be considered in cases of organ failure and surgery.

SICKLE CELL TRAIT

Individuals with sickle cell trait (Hb AS) have 10-fold protection against severe malaria compared to individuals with normal haemoglobin (HbAA) probably due to both innate and immune-mediated mechanisms. Individuals with sickle cell trait (HbAS) are generally asymptomatic and they have a normal haemoglobin and normal life expectancy. Uncommonly, complications such as poor perfusion of the renal papillae and increased bacteruria may occur.[124] The blood film is generally normal and the diagnosis can be confirmed by haemoglobin electrophoresis, HPLC or iso-electric focusing.

Thalassaemia

HISTORY

The original descriptions of thalassaemia originated from areas round the Mediterranean and the term derives from the Greek *thalassos* (sea) and *haima* (blood).[125–127]

EPIDEMIOLOGY

Thalassaemia is one of the most common single gene disorders and approximately 5–7% of the global population are carriers. α^+-Thalassaemia occurs throughout the tropics, whereas α^0-thalassaemia, which is responsible for haemoglobin Bart's hydrops fetalis, is concentrated predominantly in South-east Asia and to a lesser extent around the Mediterranean.[128,129] β-Thalassaemia is common in the Mediterranean countries, parts of Africa, throughout the Middle East, the Indian subcontinent and South-east Asia. Haemoglobin E prevalence is highest in Cambodia, Laos and Thailand and can reach 50–60% with lower prevalence rates in Indonesia, Malaysia, Singapore and Vietnam.

MOLECULAR ABNORMALITIES

β-*Thalassaemia*

β-Thalassaemia is an inherited quantitative deficiency of β-globin chains which are required to make normal adult haemoglobin.[130] More than 200 mutations have been associated with the development of β-thalassaemia (a complete list is available at the Globin Gene Server website, at: http://globin.cse.psu.edu) and they affect protein synthesis[130,131] leading to reduced (designated β^+) or absent (designated β^0) production of the β-globin chains. The clinical severity of thalassaemia can be lessened by co-existing haemoglobin abnormalities such as the co-inheritance of α-thalassaemia and increased production of haemoglobin F.[132,133]

α-*Thalassaemia*

Normal α-globin synthesis is regulated by duplicate α-globin genes on chromosome 16. The genotype is usually represented as αα/αα and α-thalassaemia usually results from deletion of one or both α-genes. Occasionally point mutations in critical regions of the α-genes may cause non-deletional α-thalassaemia (α^T).[130] Mutations can completely abolish expression of the α-genes (i.e. α^0-thalassaemia) or partially down-regulate expression (α^+-thalassaemia).[130] Both α^0 and α^+ thalassaemias can occur in the heterozygous or homozygous state or as a compound α^0/α^+ heterozygote form (Table 65.6). Underproduction of α-globin chains due to three or four gene deletions gives rise to excess γ (fetal) or β (adult) globin chains which form tetramers, called Hb Bart's (fetal) or HbH (adult).[134] Rare forms of α-thalassaemia occur in association with other conditions such as mental retardation and myelodysplastic/leukaemia syndrome.[135,136]

TABLE 65.6 Classification of α-Thalassaemia

	Genotype	Designation
α-thalassaemia-2 trait	–α/αα	α^+/α
α-thalassaemia-1 trait	–α/–α	α^+/α^+
	αα/–	α/α^0
Hb H disease	–α/–	α^+/α^0
Hb Barts hydrops fetalis	–/–	α^0/α^0

PATHOPHYSIOLOGY

β-*Thalassaemia* (Figure 65.8)

Thalassaemias[131,137,138] cause an imbalance of α- and β-globin chain synthesis. In homozygous β-thalassaemia, excess α-chains precipitate in the red cell precursors and up to 75% of cells are destroyed in the bone marrow resulting in ineffective erythropoiesis and a shortened red cell survival. The red cells released from the bone marrow contain abnormal α-chains and these inclusions promote destruction of the cells by the spleen leading to clinical symptoms and signs of haemolysis. In heterozygotes, the α-chain excess and the degree of inadequate erythropoiesis is much less than in homozygous β-thalassaemia. HbF production normally tails off within a few months of birth but in β-thalassaemia HbF production can continue into adulthood. The effect of increased HbF production is to prevent precipitation of the excess globin chains and consequent ineffective erythropoiesis. However HbF has a high oxygen affinity, which can lead to increased erythropoietin production and thus, increased bone marrow expansion.

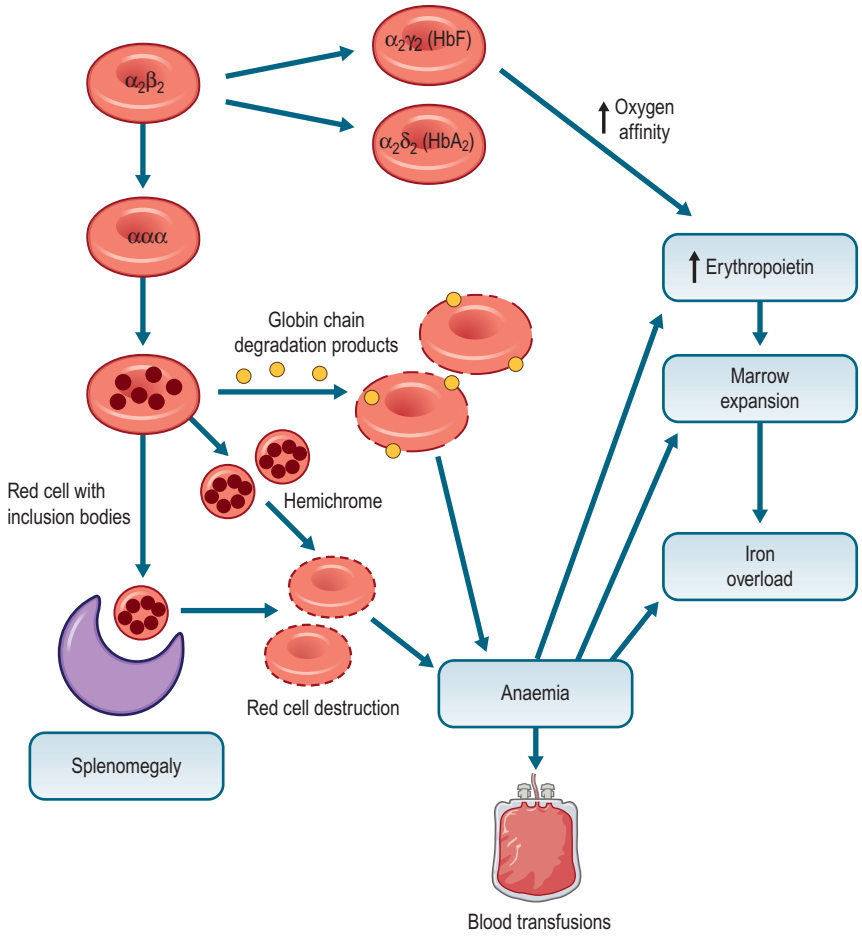
α-*Thalassaemia*

The pathophysiology of α-thalassaemia, and hence the clinical manifestations, is quite different from β-thalassaemia. The excess non-α-globin chains form soluble tetramers rather than precipitates so there is only minimal ineffective erythropoiesis. The only clinical abnormality in those with HbH may be splenomegaly secondary to increased work load from destruction of red cells containing inclusions. Rarely anaemia may be severe enough to require blood transfusions. The clinical manifestations of Hb Barts are the result of its very high oxygen affinity which causes severe anaemia, intrauterine hypoxia, increased capillary permeability, severe erythroblastosis with hepatosplenomegaly and cardiac failure. The grossly hydropic infant inevitably dies around the time of delivery.

CLINICAL FEATURES

β-*Thalassaemia*

β-Thalassaemia is categorized according to the clinical severity of the condition rather than the underlying genetic abnormality. The level of dependency on transfusions is used to



In homozygous β-thalassemia, β-globin synthesis is markedly reduced or absent. The excess α-chains cannot form a tetramer but form a precipitate in the red cell precursors leading to intra-medullary destruction of these cells. This destructive process of the red cell membrane occurs from the formation of α-chain hemichromes (shown as red cell inclusions) and degradation products of the excess α-chains. The red cells which may be released from the bone marrow are destroyed by the spleen leading to clinical symptoms and signs of haemolysis. Since only the β-chain is affected in these individuals, the synthesis of HbF and HbA_2 continues unabated. These haemoglobins have very high oxygen affinity, which can lead to increased erythropoietin production and thus, increased bone marrow expansion

Figure 65.8 Pathophysiological consequences of β-thalassaemia.

divide β-thalassaemia into thalassaemia major (transfusion-dependent), thalassaemia intermedia (able to maintain adequate haemoglobin without transfusions or requiring less than 8 units/year) and thalassaemia minor (asymptomatic).[139] Infants with β-thalassaemia are protected from severe anaemia by the presence of haemoglobin F and are usually asymptomatic. Clinical manifestations of thalassaemia major depend on whether adequate blood transfusions are available and the stringency with which iron chelation is undertaken. Untreated patients with thalassaemia major will die in late infancy or early childhood from the effects of severe anaemia. Those who receive sporadic transfusions may survive longer but suffer from the secondary effects of anaemia, bony deformities and growth retardation.

Thalassaemia Major

The clinical features of β-thalassaemia major are divided into those resulting from anaemia, bony changes and iron overload.

Anaemia from defective erythropoeisis, decreased red cell survival and increased haemolysis in thalassaemia major leads to cardiac decompensation, failure to thrive and growth retardation in children. Splenomegaly, from the increased work load of culling red cells with inclusion bodies, can cause dilutional anaemia and a further drop in haemoglobin. Compensatory extra-medullary haematopoiesis can lead to hepatomegaly and occasionally vertebral compression and neurological defects. Haemolysis from increased red cell destruction is associated with gall stones in up to 20% of individuals with β-thalassaemia.[140]

Another consequence of accelerated haemolysis is the increased incidence of thromboembolism (4% in thalassaemia major and 10% with intermedia) from the exposure of negatively charged phospholipids on the red cell membrane and the generation of red cell and platelet microparticles.[141] Splenectomy with postoperative thrombocytosis is a risk factor for thrombosis especially if combined with endothelial oxidative stress from iron overload, or procoagulant co-morbid conditions such as diabetes mellitus, hormone therapy, thrombophilic mutations and atrial fibrillation.[142] Folate deficiency, hyperuricaemia and occasionally gout have been observed in thalassaemia major due to the high turnover of red cells.

The enhanced erythropoietic drive from anaemia in thalassaemia can lead to increased marrow expansion with

characteristic bossing of the skull and overgrowth of maxillary region, radiologically noted as 'hair on end' or 'sun-ray' appearance. Metatarsal and metacarpal bones are the first to expand so measurement of the metacarpal bones has been considered a good indicator for initiation of transfusion therapy.[143] Other skeletal deformities include shortening of long bones due to early epiphyseal fusion and overgrowth of the maxilla causing dental malocclusion. The marrow expansion can also lead to pathological fractures, early bone thinning and osteoporosis[144,145] while ineffective drainage of the sinuses and middle ear from skull bone overgrowth can cause chronic sinus and ear infections. Growth retardation is primarily the result of anaemia with contributions from iron overload, hypersplenism, deficiencies of thyroid and growth hormone, hypogonadism, zinc deficiency, chronic liver disease, malnutrition and psychosocial stress.[146]

Patients with β-thalassaemia have increased iron absorption mediated by reduced hepcidin and those who receive regular transfusions may also develop transfusion siderosis if they are inadequately chelated. The iron is deposited in the parenchymal tissues with a variety of clinical consequences (Box 65.14),[147–154] a process which may be modulated by variants in the haemochromatosis (HFE) gene.[155]

Thalassaemia Intermedia

Thalassaemia intermedia is characterized by haemoglobin concentrations of 70–100 g/L and children usually present at around 2–4 years of age with symptoms of anaemia, jaundice and hepatosplenomegaly.[156] There may also be skeletal changes such as expansion of the facial bones and obliteration of the maxillary sinuses.[157] Several molecular factors including: (a) coinheritance of α-thalassaemia; (b) hereditary persistence of haemoglobin F; (c) δβ-thalassaemia and (d) the specific Gγ Xmn1 polymorphism contribute to the 'conversion' of thalassaemia from major to intermedia type.[158]

In contrast to patients with thalassaemia major, iron loading in thalassaemia intermedia occurs mainly as a result of increased intestinal iron absorption rather than transfusion therapy. Ineffective erythropoiesis with resultant chronic anaemia and hypoxia can suppress hepcidin, the regulator of iron metabolism, leading to increased iron absorption.[158] The excess iron tends to accumulate in the liver rather than the heart.[159] Other clinical complications in thalassaemia intermedia include gallstones, extramedullary haemopoiesis leg ulcers, thromboembolic events and pulmonary hypertension, which is the major cause of heart failure in these individuals.[160] Although individuals with thalassaemia intermedia do not usually need regular blood transfusions, there is some evidence that complications, particularly later in life, may be less common in regularly transfused patients.[159]

α-Thalassaemias[130,134]

Carriers of α-thalassaemia (traits, with loss of 1 or 2 α genes) are usually asymptomatic and may only be detected through a routine blood count which shows mild to moderate microcytic, hypochromic anaemia. Antenatal counselling may be indicated if the mother has αα/– as there is a possibility that the fetus may be at risk of having haemoglobin Bart's.

Haemoglobin H disease occurs mainly in Asians and occasionally in the Mediterranean population. It is the result of deletion of three α genes (α–/–) and can produce anaemia varying from 30–130 g/L. There is usually associated splenomegaly, which may be massive, and growth retardation in children. Bony changes are unusual. Other complications include infections, leg ulcers, gall stones and acute haemolysis in response to drugs and infections. The severity of the clinical features is related to the molecular basis with non-deletional types of HbH disease more severely affected.

Haemoglobin Bart's (–/–) occurs almost exclusively in Asians, especially Chinese, Cambodian and Thai populations. An infant with Hb Bart's hydrops fetalis syndrome has pallor and gross oedema with signs of cardiac failure, marked hepatosplenomegaly and skeletal and cardiovascular deformities. There is often gross hypertrophy of the placenta. Many of the clinical manifestations of this condition can be explained by the

BOX 65.14 COMPLICATIONS FROM IRON OVERLOAD IN PATIENTS WITH THALASSAEMIA

LIVER

- Earliest organ to be affected
- Liver fibrosis and cirrhosis are the commonest manifestations
- Fibrosis correlates with age, transfusion frequency, liver iron concentration (assessed by Ishak score) and transfusion-transmitted hepatitis C infection (genotype 1b)
- The prevalence of cirrhosis ranges from 10% to 20%
- 1–5% are hepatitis B surface antigen-positive (higher in Asia and South-east Asia)
- Detection techniques include transient elastography, magnetic resonance imaging and liver biopsy.

HEART

- 22% have a cardiac problem
- Heart failure and arrhythmias are the commonest manifestations
- Pulmonary hypertension may also be seen (more common in thalassaemia intermedia)
- Magnetic resonance imaging useful in the diagnosis of cardiac problems especially cardiac failure. Cardiac T2* values <10 ms associated with significantly high failure rates
- Myocardial fibrosis diagnosed by MRI more often in Italian patients who have higher prevalence of hepatitis C virus antibodies and associated myocarditis.

ENDOCRINE GLANDS

- Hypogonadism is the most frequent complication in patients with prevalence over 50% in both males and females. It is usually hypogonadotrophic suggesting iron damage to the anterior pituitary or hypothalamus. The features range from total absence of sexual development to delayed puberty. In females with normal menstrual function, fertility is normal with the ovarian function preserved in most although secondary amenorrhoea can develop. Damage of the ovaries is rare and is more likely to appear in older women (around 30) because of high vascular activity on the ovaries at this age. Secondary hypogonadism is common (50%) in older men. Serum ferritin >2000 ng/mL is a risk factor.
- Hypothyroidism is the second most common endocrine disorder (about 20%) although many of them may have the subclinical variety. Most commonly hypothyroidism is of the primary type with secondary, central hypothyroidism increasingly being diagnosed in recent years.
- The prevalence of diabetes mellitus is around 5% with the mean age of diagnosis being 18 years. Impaired glucose tolerance occurs first with microvascular damage like retinal changes being less common than the conventional form. Chronic hepatitis C infection can precipitate the onset of diabetes. Impaired glucose tolerance usually responds to oral hypoglycaemics although insulin therapy can be difficult due to difficult glycaemic control.

BOX 65.15 A STEPWISE APPROACH TO DIAGNOSIS OF THALASSAEMIAS

FAMILY HISTORY OF HAEMOLYTIC DISEASE OR THALASSAEMIA

- Ethnic background can be helpful in considering the type of thalassaemia
- Age of onset can aid in determining the severity and need for blood transfusions
- Development of the child can be useful to know the likely complications
- Late-onset complications including heart, liver and endocrine effects is also helpful.

CLINICAL EXAMINATION

- Anaemia
- Haemolysis
- Bone changes
- Splenomegaly
- Endocrine assessment.

INVESTIGATIONS

- Blood count – severe anaemia with thalassaemia major; in thalassaemia minor or trait; the mean cell volume is decreased disproportionately to the haemoglobin while the mean haemoglobin concentration is markedly reduced (20–22 pg)
- Blood film – Microcytic, hypochromic red cells; Target cells, polychromasia; Basophilic stippling; Nucleated red cells (very high levels after splenectomy); Poikilocytes in non-splenectomized patients
- Haemoglobin electrophoresis at alkaline and acidic pH – haemoglobin on a membrane is subjected to charge gradient which separates them and can be identified by special stains for haem or protein
- High-performance liquid chromatography – this procedure which separates components by their adsorption onto a negatively charged stationary phase on a chromatography column followed by elution to detect and quantify haemoglobins A, A2 and F and variants
- Isoelectric focussing – the haemoglobins are separated in a polyacrylamide or cellulose acetate gel containing molecules with different isoelectric values (when they do not have a net charge) and are identified based on comparisons with the known variants after staining.

very high affinity for oxygen for haemoglobin Bart's. The infants very often die in utero, usually after the 1st trimester due to protection from haemoglobin Portland, or shortly after birth. The morphological abnormalities of severe microcytosis and hypochromia differentiate this condition from haemolytic disease of the newborn.

DIAGNOSIS (Box 65.15)

β-Thalassaemia major, haemoglobin H disease and haemoglobin Bart's are easily diagnosed using clinical findings and basic laboratory techniques. However, the diagnosis of β-thalassaemia trait and β-thalassaemia intermedia is complex and requires considerable expertise. The haemoglobin profile varies across the spectrum of β-thalassaemia syndromes. HbF levels are increased, varying from around 10% in the more mild forms, to 100% in homozygous patients who are unable to make any HbA ($\alpha\alpha\beta\beta$). Levels of HbA2 can vary from normal to 7%. Reticulocytosis occurs but is 2–8% lower than would be expected for the extreme erythroid hyperplasia reflecting intramedullary erythroid precursor destruction. Osmotic fragility is reduced, sometimes strikingly so since in some cases the red blood cells do not haemolyse even in distilled water.[161] For this reason, if sophisticated tests are not available, osmotic fragility can be used as a screening test for thalassaemia trait. Serum zinc levels may be low and this may be related to abnormal growth.[162] Vitamin C levels may also be low due to its increased conversion to oxalic acid in the presence of iron overload.[163] Care may be needed if folic acid is commenced on a background of bone marrow failure due to folate deficiency as it may precipitate painful erythropoietic crises.[164]

MANAGEMENT

A comprehensive management plan for patients with thalassaemia may involve transfusion therapy, iron chelation, splenectomy, prevention or early treatment of complications and stem cell transplant.

Transfusion Therapy

The mainstay of treatment for the severe forms of thalassaemia is blood transfusion with the aim of reducing anaemia and erythropoietic drive. However, in many low-income settings blood supplies are inadequate and many thalassaemic patients are chronically under-transfused (Table 65.7).[165] Transfusion frequency should be guided by clinical symptoms and signs such as poor growth and facial or other bone abnormalities, and should take into account any potential disease-modifying comorbidities.[156] Although the decision to transfuse should not be based purely on haemoglobin levels, a value of <70 g/L is often used as a trigger for regular transfusions.

To prevent alloimmunization, extended red cell antigen typing for C, E and Kell in addition to ABO and Rh(D) typing should be carried out prior to the first transfusion, and before each transfusion, full cross-match and screening for new antibodies should be undertaken.[166] The risk of alloimmunization appears to be greater in patients who begin transfusion therapy after the first few years of life.[128] Development of alloantibodies and autoantibodies may result in increased transfusion requirements or haemolysis. Use of leukodepletion techniques can result in less alloimmunization and fewer febrile transfusion reactions. Since storage of red cells in anticoagulant solutions may decrease their efficacy, the use of blood that has been stored for less than 7–10 days may be beneficial for patients who require frequent transfusions. The use of 1st-degree relatives as blood donors should be discouraged, especially if the patient is a candidate for stem cell transplant.

Patients with thalassaemia major need lifelong regular blood transfusions, 15 mL/kg per month or 1–2 units of blood every 2–5 weeks, to maintain the pre-transfusion haemoglobin level above 90–105 g/L. The clinical benefits of this regular transfusion programme include normal growth, suppression of erythropoiesis and bone marrow expansion, reduced hepatosplenomegaly and an overall sense of wellbeing, which allows normal age-appropriate activities. A higher target pre-transfusion haemoglobin level of 110–120 g/L may be necessary for patients with heart disease or other medical conditions and for those patients who do not achieve adequate suppression of bone marrow activity at the lower haemoglobin level. Shorter intervals between transfusions may reduce overall blood requirements but need to be balanced against the patient's work or school schedule and other lifestyle issues.

TABLE 65.7 Estimated Reach of Treatment for β-Thalassaemia in Each WHO Region

WHO Region	Estimated Annual Births β-Thalassaemias		Transfusion				Adequate Iron Chelation		Inadequate or No Iron Chelation	
	Total	Transfusion-Dependent	Annual No. Starting Transfusion	% of Transfusion-Dependent Patients Transfused	Annual Deaths Because Not Transfused	No. of Known Patients	% with Chelation	No. with Chelation	No. of Patients	Annual Deaths Due to Iron Overload
African	1386	1278	35	2.7	1243	–	–	–	–	–
American	341	255	134	52.4	121	2750	58	1604	1146	57
Eastern Mediterranean	9914	9053	1610	17.8	7 443	39 700	27	10 818	28 882	1444
European	1019	920	140	15.5	780	16 230	91	14 754	1476	74
South-east Asian	20 420	9 983	962	9.6	9021	35 500	19	6 621	28 879	1444
Western Pacific	7 538	4 022	108	2.7	3914	3450	44	1504	1946	97
World	40 618	25 511	2 989	11.7	22 522	97 630	39	37 866	59 764	2988

The initiation of regular transfusion therapy for severe thalassaemia usually occurs in the first 2 years of life. Some patients with thalassaemia intermedia who only need sporadic transfusions in the first two decades of life may later need regular transfusions because of a falling haemoglobin level or the development of serious complications. Haemoglobin should be monitored to assess the rate of fall in the haemoglobin level between transfusions and this can be used to indicate the frequency of transfusions. Exchange transfusions have been tried as a way of reducing iron loading and are associated with a reduction in blood requirements by about one-third.

Iron Chelation Therapy (Table 65.8)

Since each unit of red cells can contain up to 200 mg of iron, cumulative iron burden is an inevitable consequence of a long-term transfusion programme. In addition there is increased iron absorption from the gut (0.3–0.6 mg/kg per day) as a response to severe anaemia and down-regulation of hepcidin. Iron chelation therapy[167,168] has improved survival rates for thalassaemic patients, and prevented hepatic fibrosis and iron-induced cardiac disease; most patients who are compliant with chelation therapy have normal growth and sexual development. Iron chelators (Box 65.16) are usually initiated in children over 2 years who have received 10 units of blood and/or have a steady-state serum ferritin level above 1000 ng/mL on at least two occasions. This level of iron overload typically occurs after 1–2 years of transfusions. Desferrioxamine is started at 25–30 mg/kg per day in these children initially, to avoid toxicity due to over chelation.

Splenectomy

Marked splenomegaly, often treated with splenectomy, was common in thalassaemia patients before the advent of regular transfusion programmes. Severe haemolysis in thalassaemia is related to a hyperactive spleen, which aggravates anaemia and can increase transfusion requirements. Although early

TABLE 65.8 Features of Currently Available Iron Chelators

	Deferoxamine	Deferiprone	Deferasirox
Chelating properties	Hexadentate binds iron in a 1-to-1 complex	Bidentate binds iron in a 3-to-1 complex	Tridentate binds iron in a 2-to-1 complex
Half-life	8–10 min	2–4 hours	12–18 hours
Excretion of iron removed	50–70% in the stool, remainder in the urine. vary with level of iron overload, dose, and erythropoietic activity	Predominantly in the urine (90%)	Predominantly (90%) faecal
Removal of iron from the liver	Very good	Good but at higher doses may be very good	Very good
Removal of iron from the heart	Mainly with 24 hour intravenous infusion	Higher than standard deferoxamine	As deferiprone
Dose	30–60 mg/kg	75–100 mg/kg	20–40 mg/kg/day
Frequency	Subcutaneous or intravenous 8–12 h, 5–7 days/week	Oral three times daily	Oral once daily
Adverse effects	1. Most common – induration at the site of infusion. 2. Aggressive chelation with lower iron levels may cause ototoxicity (bilateral high-frequency hearing loss) and visual toxicity (loss of night and colour vision, retinal atrophy, and cataract) – baseline/annual checks and adjusting the dose to ferritin level are advised 3. Growth plate deformities or cartilage dysplasia 4. Rare but serious – *Yersinia* and mucormycosis infections presenting as colitis, abdominal abscess	1. Nausea and vomiting in 33% of patients; usually resolve 2. Arthropathy with arthralgias and joint effusions in 15% 3. Agranulocytosis occurs in 1% of patients 4. Mild neutropenia in approximately 8%	1. Rare reports of fulminant hepatic failure – liver function tests every 2 weeks for 1 month after starting therapy and then monthly 2. Elevations in serum creatinine in 1/3 – kidney function monitored monthly

BOX 65.16 NEWER TREATMENTS AVAILABLE FOR THALASSAEMIA

INDUCTION OF FETAL HAEMOGLOBIN SYNTHESIS (HBF)

- Hydroxyurea – helpful in some patients with β-thalassaemia intermedia, but not as effective in thalassaemia major
- Histone deacetylase inhibitors – derivatives of butyric acid; intermittent pulses with hydroxycarbamide has been tried
- Kit ligand
- Decitabine
- Knockdown of BCL11A (regulator of γ-globin expression)
- Erythropoietin.

ANTIOXIDANTS

- Vitamins C and E
- Fermented papaya preparations.

GENE THERAPY

- Successful in β-thalassaemia animal models using a retroviral vector transferring the human β-globin gene sequence and its promoter region into mice stem cells
- β-Globin gene transfer into progenitor hematopoietic cells of humans is also being studied
- Other molecular approaches being tried include using different mutations of stop codons and aberrant splicing.

transfusion therapy can avert splenomegaly, hypersplenism still can develop, usually in children between 5 and 10 years of age. In these individuals, splenectomy can limit the complications from extramedullary hematopoiesis. Splenectomy should be considered when the annual transfusion requirement reaches 200–250 mL red blood cells/kg per year and usually results in a halving of the transfusion requirements.

Splenectomy complications include opportunistic infections with encapsulated organisms. Patients should therefore receive appropriate vaccinations preoperatively and should be advised to seek medical advice at the first sign of infection. It is advisable to delay splenectomy until patients are at least 5 years old because of the increased risk of overwhelming sepsis below this age. Thalassaemia patients can develop thromboembolic complications and pulmonary hypertension after splenectomy so partial splenectomy and splenic embolization have been attempted to minimize these complications but have not been studied in large trials.

Management of Complications

Iron overload can occur in any organ in thalassaemia patients but particularly affects the heart, liver, the endocrine system, the bone and occasionally the pancreas and lungs. Iron overload needs to be detected early and treated to prevent long-term damage. Annual assessment of the iron loading of the liver and heart can be achieved using non-invasive methods such as magnetic resonance scanning to detect early changes. Children should have regular growth and endocrine assessments and appropriate investigations should be carried out if there are any signs of developmental delay or hormonal deficiencies. Osteoporosis is increasingly being recognized and should be prevented by ensuring adequate dietary calcium intake and sun exposure. Vitamin supplementation with folic acid, zinc, vitamin E and vitamin C may be useful although the combination of vitamin C and desferrioxamine carries a risk of cardiac toxicity.

Stem Cell Transplant

Allogeneic stem cell transplant[169,170] is currently the only means of curing thalassaemia. The outcome in carefully selected patients, measured by overall event-free survival, is around 90% with a transplant-related mortality of 3%. Hepatomegaly, liver fibrosis, and inadequate iron chelation therapy predict a poor outcome. The best results from transplant have been obtained with HLA-matched siblings. Umbilical cord blood is a useful source of stem cells for young children. Other potential treatment options for thalassaemia are outlined in Box 65.16.[171–174]

Prevention of Thalassaemia

Prevention of severe thalassaemia births by prenatal diagnosis and termination of pregnancies has been successful in countries with a high prevalence of thalassaemia.[175] Early identification of couples at risk and culturally sensitive genetic counselling facilitate decision-making for termination or continuation of pregnancy. The mean corpuscular haemoglobin (MCH) is used to screen for the presence of thalassaemia using a cut-off of less than 27 pg. Rarely, silent β-thalassaemia mutation may present with an MCV over 27 pg and should be considered in those with a positive family history. At-risk couples should be referred for detailed counselling on the options for prenatal diagnosis. These include chorionic villous sampling or amniocentesis, which are used to obtain fetal DNA samples for genetic analysis. Polymerase chain reactions and precise hybridization assays to detect single point mutations using very small DNA samples have also been developed. A less invasive and less risky option is to isolate fetal DNA circulating in the maternal blood for genetic analysis. Pre-implantation genetic diagnosis is a newer technique where DNA from the blastomere is used for genetic diagnosis. Ultrasound can be used from the 2nd trimester for fetuses suspected of having α-thalassaemia to detect signs of hydrops fetalis and enlarged placenta (Figure 65.9).[175,176]

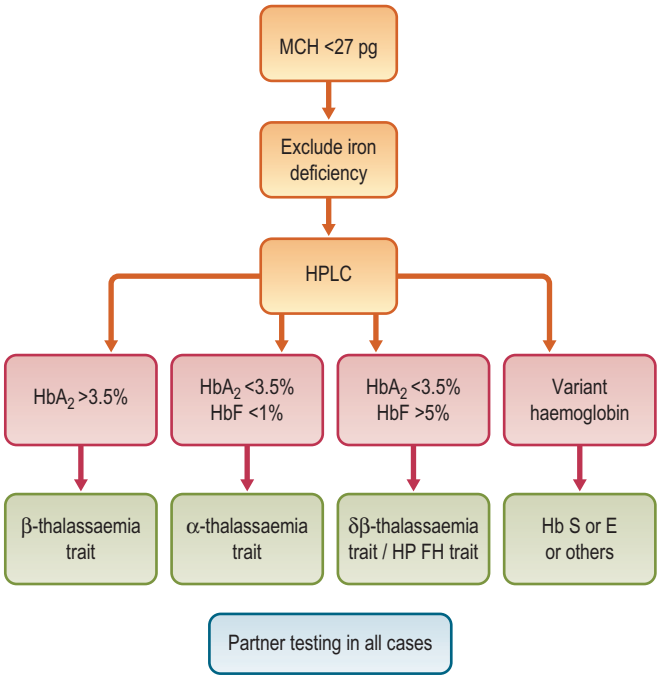


Figure 65.9 Prevention of thalassaemia births using prenatal diagnosis.

HAEMOGLOBIN E DISEASE

Hb E is caused by a substitution of glutamic acid by lysine at codon 26 of the β-globin gene.[177] This causes reduced synthesis of the β-E chain and leads to a thalassaemia phenotype. Hb E β-thalassaemia affects at least a million people worldwide and is an important health problem particularly in the Indian subcontinent and South-east Asia. In some areas, it has replaced β-thalassaemia as the most common thalassaemia disorder. The frequency of HbE reaches 60% in many regions of Thailand, Laos and Cambodia with estimates of at least 100 000 new cases of HbE β-thalassaemia expected in the next few decades in Thailand alone. The natural history of HbE thalassaemia is highly variable; some patients are asymptomatic (e.g. heterozygotes, HbE 20–30% or homozygotes HbE, 80–90%) while others (e.g. HbE with β-thalassaemia) may be transfusion-dependent.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

PATHOPHYSIOLOGY

Glucose-6-phosphate dehydrogenase (G6PD) deficiency was originally recognized through its association with haemolysis related to eating fava beans ('favism') and primaquine ingestion.[178] G6PD deficiency is the most common enzyme defect in humans and is present in about 400 million people worldwide (Figure 65.10).[179,180] It is an X-linked, hereditary defect caused by mutations in the G6PD gene. G6PD is an enzyme that catalyses the first reaction in the pentose phosphate pathway, to produce NADPH, which is an important antioxidant used to preserve the reduced form of glutathione.[178,181] Reduced glutathione acts as a scavenger for oxidative metabolites thereby protecting red cells. Red cells lack any other source of NADPH and are solely dependent on the pentose phosphate pathway so G6PD deficiency leaves these cells with no defence against oxidative damage. Oxidative damage results in denatured haemoglobin aggregates which form Heinz bodies (denatured haemoglobin precipitates). These damaged cells bind to the membrane cytoskeleton resulting in decreased cellular deformability, and are also destroyed in the spleen, resulting in haemolysis. The level of enzyme activity is higher in young erythrocytes than in more mature cells so older cells are more susceptible to haemolysis.

EPIDEMIOLOGY AND CLASSIFICATION

The global distribution of G6PD deficiency mirrors that of malaria, and where malaria has historically been prevalent, and it provides a degree of protection against malaria.[181,182] The different variants of G6PD deficiency are classified according to the severity of the enzyme deficiency and resulting haemolysis.[183]

- Class I – Severely deficient with chronic non-spherocytic haemolytic anaemia as the clinical manifestation
- Class II – Severely deficient with acute haemolytic anaemia as the clinical manifestation
- Class III – Moderately deficient (10–60% enzyme activity)
- Class IV – Normal (60–150% enzyme activity)
- Class V – Increased activity (>150% enzyme activity).

G6PD enzyme variants can be distinguished by their electrophoretic mobility.[184] G6PD B, the wild-type enzyme, and G6PD A^+, a common variant in populations of African descent, demonstrate normal enzyme activity and are not associated with haemolysis. G6PD A^- is the most common variant associated with mild to moderate haemolysis with approximately 10–25%

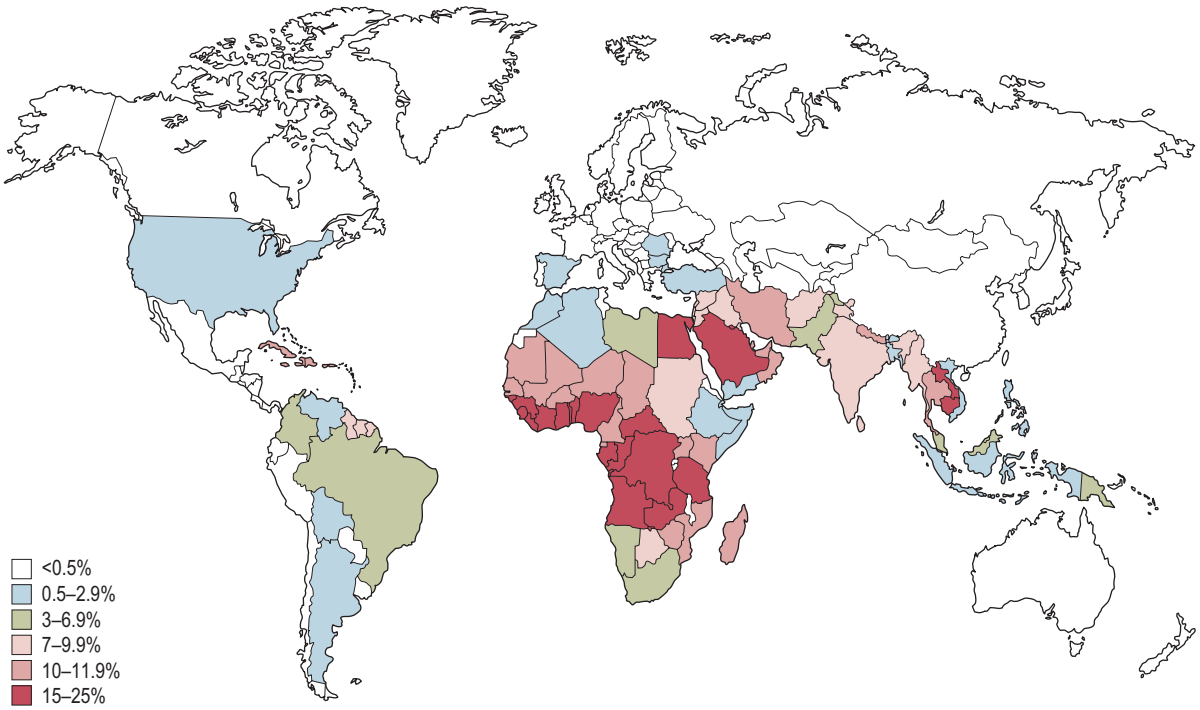


Figure 65.10 Distribution of glucose-6-phosphate dehydrogenase deficiency. *(From WHO working group. Glucose-6-phosphate dehydrogenase deficiency. Bull World Health Organ 1989; 67: 601–11.)*

of Africans carrying this variant. G6PD Mediterranean, present in all countries surrounding the Mediterranean Sea, Middle East, India and Indonesia, has the same electrophoretic mobility as G6PD B but the enzyme synthesis and catalytic activity are reduced. In several populations, G6PD A^- and G6PD Mediterranean co-exist.

CLINICAL FEATURES

The clinical manifestations of G6PD deficiency can be classified into: (i) asymptomatic; (ii) acute haemolytic anaemia; (iii) favism; (iv) neonatal jaundice; and (v) chronic non-spherocytic haemolytic anaemia.

Acute Haemolytic Anaemia

Acute haemolytic anaemia in G6PD deficiency can be secondary to infection (e.g. pneumonia, hepatitis A and B, and typhoid fever) or oxidant drugs, or may be precipitated by diabetic ketoacidosis, myocardial infarction and strenuous physical exercise.[185,186] A list of the drugs which may cause haemolysis in G6PD-deficient individuals (Table 65.9)[187] can be obtained from: http://www.g6pd.org/favism/english/index.mv. A drug which is deemed to be safe for some G6PD-deficient individuals may cause haemolysis in others due to the heterogeneity of the underlying genetic variants. Haemolysis typically occurs within 1–3 days after commencing the drug and can produce intense haemoglobinuria. Fortunately, the disorder is self-limiting and most patients do not develop renal impairment or anaemia requiring transfusion. The spontaneous recovery reflects replacement of the older, enzyme-deficient red cells by younger reticulocytes which can withstand oxidative injury.[186] If the precipitating cause has been removed the haemoglobin begins to recover after 8–10 days. Acute renal failure due to acute tubular necrosis and tubular obstruction by haemoglobin casts can develop as a complication of haemolysis in G6PD deficiency. This occurs more often in adults than children and may require haemodialysis.

Favism

This occurs predominantly in boys aged 1–5 years in Mediterranean countries, but it has also been observed in the Middle East, Asia and North Africa. Both intravascular and extravascular haemolysis, occasionally severe enough to cause renal impairment, can occur after eating fresh or cooked fava beans, and favism has been reported in breastfed babies of mothers who have eaten fava beans.[179] Divicine and isouramil have been implicated as the toxic components of fava beans.[188]

Neonatal Jaundice

This occurs in one-third of male babies in areas where G6PD deficiency is common and is likely due to G6PD deficiency.[179] It presents 1–4 days after birth and can lead to kernicterus.[189,190] Maternal exposure to oxidant drugs, and even naphthalene-camphor mothballs, can precipitate haemolysis in affected babies. Breast-feeding mothers should therefore be warned to avoid offending drugs, umbilical potions containing fava, triple dye or menthol, and should not apply henna to the skin or use clothes that have been stored in naphthalene.[190] Premature infants and babies who have co-inherited the mutation for Gilbert's syndrome are at particular risk. Phototherapy and exchange transfusion therapy may be required to reduce the level of unconjugated bilirubin. The diagnosis may be easily missed so assessment of G6PD status should be undertaken for any jaundiced infant whose family history or ethnic or geographic origin suggest the likelihood of G6PD deficiency, and in infants who respond poorly to phototherapy.[191]

Congenital Non-spherocytic Haemolytic Anaemia

This is an unusual manifestation of G6PD deficiency and usually presents in childhood.[179,184] There may be a history of severe neonatal jaundice, episodic or worsening anaemia which requires blood transfusions, and complications from gallstones. Although these individuals usually have a well-compensated anaemia, and require transfusions only for exacerbations, rarely some may become transfusion-dependent. Antioxidants such as vitamin E and selenium may be of benefit in some cases. The haemolysis does not resolve following splenectomy. Folic acid supplementation is necessary to support the increased compensatory erythropoiesis.

DIAGNOSIS

The diagnosis of G6PD deficiency is usually suspected when neonatal jaundice occurs in an area where G6PD deficiency is

TABLE 65.9 Drugs Which May Cause Haemolysis in G6PD-Deficient Individuals

	Definite Haemolysis	Possible Haemolysis	Doubtful Haemolysis
Antimalarials	Primaquine Pamaquine	Chloroquine	Mepacrine Quinine
Sulfonamides	Sulfanilamide Sulfacetamide Sulfapyridine Sulfamethoxazole	Sulfadimidine Sulfasalazine Glibenclamide	Aldesulfone Sulfadiazine Sulfisoxazole
Sulfones	Dapsone		
Nitrofurantoin	Nitrofurantoin		
Antipyretic or analgesic	Acetanilide	Aspirin	Paracetamol Phenacetin
Other drugs	Nalidixic acid Niridazole Methylthionium Phenazopyridine Co-trimoxazole	Ciprofloxacin Chloramphenicol Vitamin K analogues Ascorbic acid Mesalazine	Aminosalicylic acid Doxorubicin Probenecid Dimercaprol
Other chemicals	Naphthalene 2,4,6-trinitrotoluene	Acalypha indica extract	

common or when an episode of non-immune haemolytic anaemia occurs in association with an infection or drug. The appearance of the red cells on the blood film is characteristic because denatured haemoglobin concentrates in one area within the cell creating 'helmet' or 'bite' cells.[192] Denatured haemoglobin precipitates in peripheral red blood cells as Heinz bodies which can be detected by staining with methyl violet. Definitive diagnosis of G6PD deficiency is by quantitative spectrophotometric analysis of the rate of NADPH production. Point of care tests for G6PD deficiency are being developed but have not yet been validated for routine use. Measuring enzyme activity during an episode of acute haemolysis is not helpful since reticulocytosis, which is a feature of acute haemolysis, produces a false-negative result because of the high enzyme levels in younger erythrocytes.[179,186]

MANAGEMENT

The most effective management strategy for G6PD deficiency is to prevent haemolysis by avoiding triggering agents like infections, drugs and fava beans. For the milder variants (e.g. Class III and IV), drugs known to trigger haemolysis may be given to individuals with G6PD deficiency if the benefits outweigh the risks and the blood count is closely monitored (e.g. use of low-dose primaquine for individuals with G6PD A-variant). Screening programmes have been established in some Mediterranean and other populations where G6PD deficiency is prevalent.[193]

Haematological Complications of Malaria (see Chapter 43)

MALARIAL ANAEMIA

Pathophysiology

The pathophysiology of anaemia in malaria is multi-factorial and influenced by the age of the individual and their anti-malarial immune status. Anaemia mechanisms in malaria involve:

- Haemolysis with increased red cell destruction of both infected and bystander erythrocytes
- Dyserythropoiesis
- Hypersplenism
- Haemolysis
- Co-existent conditions which can cause anaemia.

Haemolysis is more common in non-immune individuals with acute malaria, whereas dyserythropoiesis is the predominant mechanism for anaemia in recurrent falciparum malaria.[207,194] Haemolysis is the result of red cell phagocytosis by the reticuloendothelial system and is triggered by damage to the red cell membranes and exposure of abnormal surface antigens on their surface.[195–198] Ten uninfected red cells are removed from the circulation for each infected red cell destroyed,[199] possibly related to loss of red cell complement regulatory proteins and increased levels of circulating immune complexes.[200] This may partly explain the persistent or worsening anaemia following parasite clearance and the poor correlation between parasitaemia and the severity of anaemia noted in some studies.[207] An increased incidence of anaemia has been noted in malaria vaccine trials possibly due to enhanced clearance of uninfected red blood cells.[201]

Decreased erythropoeisis with abnormalities in red cell precursors and reticulocytopenia is found consistently on examination of bone marrow from malaria-infected patients.[202] The decreased erythropoiesis is due to many factors including low levels of TNF-α, high levels of interleukin-10, abnormalities of erythropoietin, a decrease in burst colony forming units, cytokine-induced suppression of red cell production and the inhibitory effect of the malarial pigment haemozoin.[203–206]

Epidemiology

Malaria-related anaemia is most commonly seen in children and pregnant women. The prevalence of malarial anaemia in sub-Saharan Africa in children is 30–90% and in pregnant women it is 60–80%.[207] The highest prevalence is in infants and children less than 3 years of age. Infants may acquire malaria through the placenta.[208,209]

Individuals living in malarious areas may have multiple reasons for anaemia such as bacteraemia, hookworm infections and vitamin A deficiency[208] making it difficult to assign anaemia solely to malaria. However, animal studies and the fact that anaemia improves with anti-malarial treatment suggest a direct relationship between malaria infection and anaemia.[210,211] For example, in Tanzanian children about 60% of anaemic episodes were thought to be caused by malaria.[212]

WHO defines severe anaemia attributable to malaria as: (i) haemoglobin concentration <50 g/L or haematocrit <15%; (ii) parasitaemia with >10 000 parasites/μL of blood and (iii) normocytic blood film (to exclude other common causes of anaemia).[213] However, aspects of this definition have been criticized because blood films are not examined routinely and parasite density varies with endemicity and age.[207] Although traditionally it is *P. falciparum* that has been associated with the most severe malaria-related anaemia, *P. vivax* is also a major risk factor for severe anaemia especially in young children or those with chronic and recurrent infections. *P. vivax* anaemia is associated with recurrent bouts of haemolysis of predominantly uninfected erythrocytes with increased fragility.[214]

Clinical Features

Symptoms of malarial anaemia can vary from negligible to profound depending on the degree of anaemia and the rapidity of onset. Splenomegaly is a common feature of malarial anaemia because of the role of the spleen in the removal of both infected and uninfected red cells.[215] Blackwater fever, characterized by intense intravascular haemolysis with haemoglobinuria and occasionally renal failure in a patient with malaria, may be related to underlying glucose-6-phosphate deficiency.[216,217] Factors such as poor nutrition, deficiencies of vitamins and micronutrients, bacteraemia, and hookworm or HIV infection may co-exist with malaria and contribute to anaemia[209] so non-malarial causes of anaemia should be considered in patients whose anaemia does not respond to malaria treatment.

Management and Prevention

The management of severe malarial anaemia involves supportive care and treatment of the malaria and any other underlying conditions. Recovery from malaria-associated anaemia can be slow, taking 6 weeks or even longer if there are episodes of re-infection.[212] In children, blood transfusion is usually reserved for those with haemoglobin levels of less than 40 g/L (<50 g/L if there are complications such as respiratory distress[207]). There

have been some concerns about a possible increased risk of infection associated with iron supplementation for children in malarious areas[218,219] but current recommendations advocate that where iron deficiency and malaria are common, iron supplements should not be withheld and appropriate anti-malarial treatment or prevention should also be offered.[220]

The best way to prevent malarial anaemia is to prevent malaria infection by avoiding mosquito bites (e.g. through the use of bed nets) or through chemoprophylaxis. Malaria chemoprophylaxis during infancy can reduce both malaria and anaemia.[221] Children who have been hospitalized with severe malarial anaemia may benefit from intermittent preventive malarial therapy after discharge to prevent recurrence of anaemia.[222] Daily co-trimoxazole prophylaxis which is used for HIV-infected individuals has been shown to reduce malaria parasitaemia and anaemia.[223]

THROMBOCYTOPENIA IN MALARIA

The normal platelet life span of 7–10 days is reduced to less than 4 days in malaria infection.[224] Several factors are responsible for thrombocytopenia in malaria infection, the most common being increased platelet activation and aggregation (Figure 65.11).[225] Platelet activation is by parasitized red cells which express surface tissue factor and initiate coagulation and platelet aggregation. The resultant activated endothelium binds platelets and sequesters them in vascular beds including in the cerebral vasculature.[226,234] These platelets facilitate the adhesion

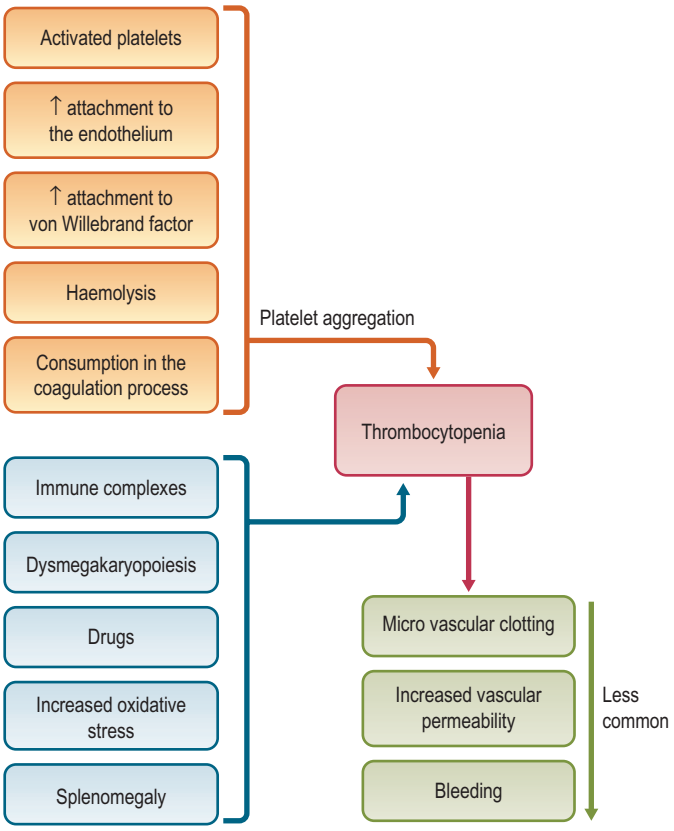


Figure 65.11 Factors associated with thrombocytopenia in malaria infection. The more significant mechanisms are given in bold. The mechanisms described in the top half cause thrombocytopenia by platelet aggregation, which is the major consequence on platelets.

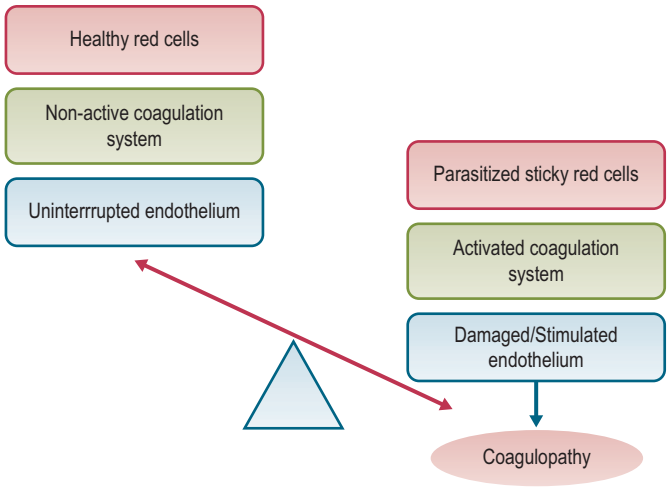


Figure 65.12 Coagulopathy induced by malaria infection.

of parasitized red cells[227] and the release of von Willebrand factor multimers which cause widespread platelet aggregation leading to thrombocytopenia[228,84,231] Platelet synthesis by the bone marrow is relatively well maintained during infection[231,229] but antiplatelet antibodies, immune complexes and splenomegaly all contribute to thrombocytopenia.[230]

Thrombocytopenia occurs in 60–90% of individuals infected with malaria irrespective of the species of plasmodium.[214,231] Thrombocytopenia in febrile patients in an endemic area increases the probability of malaria by a factor of 5[232] and in individuals returning from tropical countries with a fever, thrombocytopenia is highly specific for malaria infection.[233] Profound thrombocytopenia is unusual and malaria-associated thrombocytopenia is rarely associated with haemorrhagic manifestations.[234]

The clinical consequences of platelet aggregation and endothelial binding are primarily microvascular ischaemia. This may manifest as renal impairment, cerebral ischaemia, and occlusion of retinal vasculature or even in some cases, skin necrosis. Bleeding is unlikely, although in severe thrombocytopenia, petechiae or purpura may develop which denotes extravasation of red cells into the subcutaneous tissue.[235] Continued platelet activation and consumption can exacerbate bleeding and decreased circulating platelets are associated with increased vascular leakage and the development of oedema.[236] Platelet transfusions are rarely required because the platelet count generally rises rapidly on treating the underlying malaria.

COAGULOPATHY IN MALARIA

Coagulopathy is a disturbance of the whole coagulation system involving not just coagulation factors but platelets, anticoagulant factors, fibrinolytic system and, in the case of malaria, the parasitized red cells and the vascular endothelium. Parasitized red cells induce expression of tissue factor on endothelial cells and monocytes, release of microparticles, cytokine release and platelet clumping, all of which initiate blood coagulation and tilt the balance towards the pro-coagulant state (Figure 65.12).[234,237–242] Anticoagulant factors are severely depleted in malaria. Protein C and antithrombin levels are inversely correlated with severity of falciparum malaria and return to normal with treatment of the malaria.[245]

Coagulopathy in malaria infection is unusual, occurring in less than 5% of cases. It appears to be most common in adults with cerebral malaria who may present with gastrointestinal bleeding[243] or with microvascular ischaemia in the brain, kidneys, retina and occasionally, the dermal vasculature.[244] Prolongation of prothrombin time and activated partial thromboplastin time only occur in 4–8% of patients with *P. falciparum* infection and coagulopathy does not appear to be a feature of *P. vivax* infection.[245] Since coagulation factors need to be depleted to less than 20% of normal to prolong the clotting times, these tests can be normal despite active coagulopathy.

Management of coagulopathy aims to restore the balance between pro- and anticoagulant processes. This is complex and requires input from a coagulation specialist and ideally, access to plasma, heparin and factor concentrates and a well-equipped coagulation laboratory.

Haematological Complications of HIV Infection (see Chapter 10)

ANAEMIA

Anaemia is very common in HIV-infected individuals occurring in up to 20% at initial presentation and about 70% at some stage during their disease.[246] Thirty-seven percent of patients with clinical AIDS have a 1-year incidence of anaemia (haemoglobin <100 g/L)[246] and high rates of anaemia persist despite combination anti retroviral treatment (ART).[247] Anaemia is directly related to mortality in HIV infection and is independent of other risk factors including CD4 count.[248]

There are multiple reasons for anaemia in HIV-infected patients (Box 65.17), which often co-exist in individual patients. Bone marrow infection by mycobacteria species, *Histoplasma*, *Cryptococcus* and *Penicillium marneffei* can all decrease red cell production[249] and can be detected by bone marrow examination and cultures. Parvovirus has a predilection for the erythroid progenitor cells and can cause severe anaemia in HIV-infected patients. Serological tests for parvovirus are unhelpful in HIV-infected patients and viral polymerase chain reaction is needed to confirm the diagnosis.[250] The likelihood of parvovirus-induced anaemia increases with the severity of anaemia and has been found in 31% of individuals with HIV and haemoglobin less than 70 g/L.[251] Haemophagocytosis occurs in HIV infections and may be secondary to co-infection with mycobacteria, cytomegalovirus, Epstein–Barr or other herpesviruses.

Poor nutrition due to socioeconomic reasons, HIV-related anorexia, malabsorption from conditions affecting the gastrointestinal tract, and achlorhydria may contribute to anaemia. Haemolytic anaemia occurs secondary to drugs or concomitant glucose-6 phosphate dehydrogenase deficiency and because reticulocytopenia is common in those with HIV infection, reticulocyte counts cannot be used to exclude haemolysis. Although the direct Coombs test may be positive in patients with HIV infection, autoimmune haemolysis is not a common cause of anaemia. A reduction in red cell precursors has also been noted in children in Africa with severe anaemia.[252]

Treatment of HIV-related anaemia should focus on starting ART and eliminating any other factors, such as infections or vitamin deficiencies, which may contribute to the anaemia. In wealthy countries ART has been shown to reduce anaemia prevalence from 65% to 53% within 6 months of starting treatment, and to 46% after a year.[253,247] Although transfusions may be required in severe life-threatening cases of anaemia, aggressive transfusion therapy has been associated with fatal pulmonary emboli due to accelerated haemolysis and disseminated intravascular coagulation.[254]

In those who do not respond to ART, erythropoietin may be considered since reduced responsiveness to this hormone and antierythropoietin antibodies have been noted in HIV patients. Erythropoietin is particularly useful in individuals whose erythropoietin levels are less than 500 IU/L[255] because in addition to increasing the haemoglobin it can also improve the quality of life.[256] Erythropoietin may take several weeks to achieve full effect and patients should be replete in haematinics. Erythropoietin can very rarely be associated with thrombosis or pure red cell aplasia.

BOX 65.17 CAUSES OF ANAEMIA IN HIV INFECTION

INFECTIONS
- Mycobacteria (tuberculosis or atypical forms)
- Parvovirus
- Opportunistic viruses – cytomegalovirus
- Histoplasma capsulatum
- Malaria
- HIV itself

MALIGNANT INFILTRATION OF THE BONE MARROW
- Lymphoma
- Other malignancies

HAEMOLYSIS
- Drug-induced
- Autoimmune haemolysis
- Microangiopathic haemolysis

INSUFFICIENT NUTRIENTS
- Iron
- Vitamin deficiencies (folate, B_{12}, A)

GASTROINTESTINAL BLEEDING
- Gastritis (e.g. *Candida*)
- Gastric and duodenal ulcers
- Intestinal Kaposi's sarcoma or lymphoma
- Viral infections such as cytomegalovirus

DRUGS
- Bone marrow suppression (e.g. ganciclovir)
- Glucose-6-phosphate dehydrogenase deficiency haemolysis (e.g. Dapsone)

HAEMOPHAGOCYTOSIS
- Infection related

HYPERSPLENISM

ANAEMIA OF CHRONIC DISEASE

CO-EXISTENT HAEMOGLOBINOPATHIES

HYPOGONADISM.

THROMBOCYTOPENIA

Thrombocytopenia is a common finding in HIV-infected patients and it may be the initial manifestation of HIV infection in as many as 10% of patients. Data from wealthy countries demonstrate platelet counts less than 150×10^9/L in 11% of patients, and less than 50×10^9/L in 1.5%. Overall the 1-year

incidence of moderate thrombocytopenia ($<50 \times 10^9$/L) is 3.7%, though this is higher in those with clinical AIDS (8.7%).[257,258] Thrombocytopenia is more common in those who abuse drugs, have opportunistic infections and malignant disorders of the bone marrow (e.g. lymphoma), and it may also be a side-effect of therapeutic drugs.[259]

The most common cause of thrombocytopenia in HIV infection is immune thrombocytopenia which may be associated with hepatitis C co-infection, and produces decreased platelet survival, particularly at CD4 counts below 200/μL. The anti-platelet antibodies, immune complexes and cross-reacting antibodies to HIV envelope proteins and platelets, which occur in HIV-associated thrombocytopenia[259,260] may also contribute to generation of reactive oxygen species.[261] Platelet production can also be affected in HIV infection and may explain the high levels of thrombopoietin that have been documented in HIV-related thrombocytopenia.[262]

Some cases of HIV-related thrombocytopenia may undergo spontaneous remission so treatment of thrombocytopenia is usually only initiated if it is associated with bleeding, which is unusual.[259] The first line of treatment involves antiretroviral therapy with the aim of achieving undetectable plasma HIV viraemia.[263,264] Any drugs that may be associated with causing thrombocytopenia should be withdrawn and opportunistic infections or secondary malignancies treated. The treatment of immune thrombocytopenia is the same as in non-HIV cases and options include a short course of steroids, intravenous immunoglobulin (short-lived response), anti-D, interferon-α or splenectomy.

THROMBOTIC THROMBOCYTOPENIC PURPURA

Although there are multiple causes of thrombocytopenia in HIV-positive individuals, one of the most devastating is the thrombotic microangiopathy of thrombotic thrombocytopenic purpura (TTP). This is because the combination of haemolytic anaemia and microthrombi has a very poor prognosis. Symptoms are nonspecific and may include fever, headache, bleeding and changes in consciousness. If TTP is suspected, an urgent blood film should be requested and the combination of thrombocytopenia with red cell fragmentation is highly suggestive of TTP. TTP associated with HIV infection was more frequent before the introduction of ART and is more common if adherence to treatment is poor or resistance to therapy has developed.[265] TTP is thought to be due to endothelial damage, but unlike the situation in non-HIV-infected individuals, low levels of ADAMTS-13 are not a useful predictor of outcome.[266]

Treatment of TTP involves plasma exchange, and although refractoriness may occur, this can be corrected by ART in some cases.[266] If ART is administered in these cases it is important to maintain adherence throughout the period of plasma exchange. If apheresis facilities are limited, plasma infusions alone (30 mL/kg per day) may also produce a response.[267] ART should also be administered immediately after plasma exchange to minimize drug removal. Patients with a viral load of less than 500 000 copies/mL generally require fewer plasma exchanges for remission than those with a higher load.[265] Survival of patients with HIV-associated TTP in the pre-ART era was rarely longer than 2 years, even with plasma exchange and steroid treatment, but for patients who are compliant with ART the mortality is around 4%.[268,269]

HIV-RELATED LYMPHOMA

Non-Hodgkin's lymphoma (NHL) was noted to be associated with HIV infection early in the epidemic and is an AIDS-defining illness.[270] The incidence of NHL is up to 200 times greater in HIV-infected adults than in those who are not infected, and it is responsible for nearly one-sixth of the deaths attributable to AIDS. Since the introduction of HAART, the incidence of all types of NHL has decreased by approximately 30–50%[271,272] and the outcome of HIV-infected patients with lymphoma has improved. In the setting of clinical trials, the 60% 1-year survival rate is comparable to those without HIV infection.[273] The incidence of Hodgkin's lymphoma has increased in the post-HAART era, possibly due to immune reconstitution and increased CD4 cells.[274,275] Evidence of Epstein-Barr virus (EBV) infection can be found in virtually all cases of Hodgkin's disease.[276]

HIV-related lymphomas (Box 65.18)[277] (see also Lymphomas, below), are broadly divided into systemic lymphomas (80%) and primary central nervous system lymphomas.[278] The incidence of highly aggressive lymphomas, either Burkitt's lymphoma (approx. 25%) or diffuse large B-cell lymphoma (approx. 75%), is much higher in HIV-infected patients than in those without infection.[279] Although T-cell lymphomas are uncommon in HIV disease (1%), there has been an increase in recent years. The incidence of primary central nervous system lymphoma in HIV-affected individuals is 2–6% and it is 1000 times more common than in the general population.[280]

The pathogenesis of NHL in HIV infection is related to the inadequate host immune responses to viruses with oncogenic potential, predominantly EBV and human herpesvirus 8 (HHV8)/Kaposi's sarcoma-associated herpesvirus. This allows unregulated lymphoid growth and an accumulation of genetic abnormalities in B cells.[272] Markers of B-cell activation such as serum immunoglobulins and free light chains, and CD4 cell count have been suggested as predictive markers for the development of NHL in HIV infection.[281,282]

Extranodal and leptomeningeal involvement, and B-symptoms occur in the majority of HIV-infected patients with NHL and the bone marrow is commonly involved. The most common extranodal site to be involved is the

BOX 65.18 LYMPHOMAS ASSOCIATED WITH HIV INFECTION

LYMPHOMAS ALSO OCCURRING IN IMMUNOCOMPETENT PATIENTS

- Diffuse large B-cell lymphoma
- Burkitt's lymphoma
- Extranodal marginal zone B-cell lymphoma of mucosa associated
- Mucosa-associated lymphoid-tissue (MALT) lymphoma
- Peripheral T-cell lymphoma

LYMPHOMAS OCCURRING MORE SPECIFICALLY IN HIV+ PATIENTS

- Primary effusion lymphoma
- Plasmablastic lymphoma of the oral cavity type

LYMPHOMAS ALSO OCCURRING IN OTHER IMMUNODEFICIENCY STATES

- Polymorphic B-cell lymphoma
- 'Post-transplant lymphoproliferative disorder (PTLD)-like'.

gastrointestinal tract, often the stomach or the perianal region.[283] Hepatic involvement, seen in a quarter of cases, is associated with a particularly poor prognosis. CNS disease may be asymptomatic so diagnostic lumbar puncture may be required.[284] HIV-related lymphomas frequently present with poor prognostic features such as elevated serum lactate dehydrogenase levels.[285,286] Older age, lowest nadir CD4 cell counts prior to NHL diagnosis, developing NHL while on ART, and cumulative HIV viraemia are also poor prognostic features.[282] A formal prognostic scoring system has been developed which takes into account the CD4 count (<100 cells/μL).[287]

Some types of HIV-related lymphoma are associated with characteristic clinical and laboratory features. Primary effusion lymphoma is an aggressive lymphoma characterized by effusions in serosal cavities in the absence of any other tumour masses.[288,289] It is strongly associated with HHV8 infection and the virus can be identified in the nuclei of the malignant cells. Plasmablastic lymphoma mainly affects the oral cavity and the mucosa of the jaw and is typically associated with Epstein–Barr virus.[290]

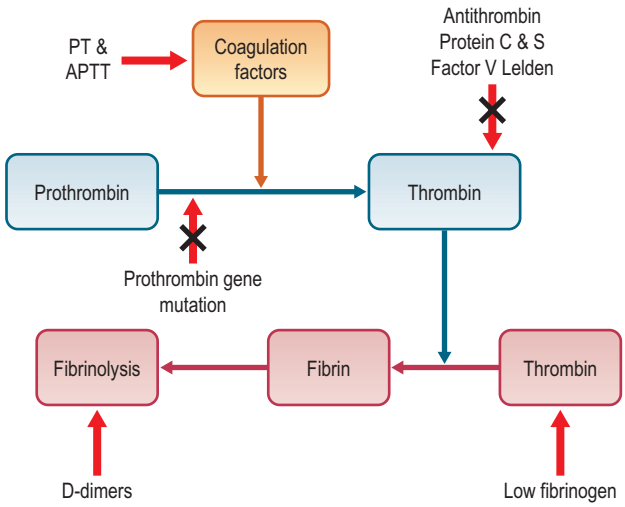
Histological examination of biopsied tissue is necessary to confirm the diagnosis and type of lymphoma. Diagnostic difficulties may arise because HIV-related hyperplasia in lymph node biopsies may be confused with lymphoma, the histological appearance of HIV-related lymphomas may be different from those of non-infected individuals[291] and many opportunistic pathogens may mimic the appearances of NHL, or co-exist with it, and will need to be identified or excluded before making a diagnosis of lymphoma.

Prior to the widespread use of ART, conventional lymphoma chemotherapy resulted in considerable toxicity, increased opportunistic infections and high mortality. ART has facilitated the use of conventional doses of chemotherapy in conjunction with haematopoietic growth factor support. This has markedly improved the outcome of patients with HIV-related lymphomas who now have overall response rates of 60%.[292] The concomitant use of ART and chemotherapy is therefore recommended, especially in those with CD4 counts of less than 100/μL. Anti-CD20 antibody is now included in treatment regimens for NHL, and studies that include patients with HIV-related lymphomas all report favourable outcomes.[293,294] Some antiretroviral agents such as zidovudine are best avoided in combination with chemotherapy, because it adds to the myelosuppression of chemotherapy. Didanosine may worsen the peripheral neuropathy caused by taxanes and vinca alkaloids. HIV-infected patients undergoing chemotherapy should receive adequate anti-infective prophylaxis due to the high risk of opportunistic infections such as pneumocystis, herpes simplex and zoster and candida. Consolidation chemotherapy and stem cell transplant have been used successfully in relapsed HIV-related lymphomas.

Abnormalities of Coagulation

PATHOPHYSIOLOGY

Haemostasis is maintained by interactions between vessel walls, platelets and a balance between pro- and anticoagulant factors. Although the process of haemostasis is usually considered to occur in a stepwise fashion, in vivo the steps happen virtually simultaneously. Activation of the lining of the endothelium by trauma, cancer cells or cytokines triggers vasoconstriction,



The tests for each pathway is given with arrows corresponding to each box

Figure 65.13 Critical processes in clot formation.

which immediately limits the amount of blood loss. Exposure of the subendothelial space releases factors such as von Willebrand factor multimers which bind to platelets and initiate platelet adhesion to the endothelium. The adherent platelets release their granules and attract more platelets, which in combination with fibrinogen, form an aggregate. The activated platelets also attract coagulation factors thereby promoting the clotting process. The critical parts of clot formation are the conversion of prothrombin to thrombin and the thrombin-facilitated conversion of fibrinogen to fibrin (Figure 65.13). Haemostatic control mechanisms operate throughout the clotting process to prevent excessive clot formation and involve proteins C and S, and anti-thrombin and antifibrinolytic systems. Any alteration in these regulatory pathways can lead to either bleeding or thrombotic complications.

Bleeding can result from:

- Inadequate vasoconstriction, due to vascular problems which can be acquired (e.g. viral haemorrhagic fevers or immune vasculitis) or congenital (e.g. collagen vascular disorders)
- Qualitative or quantitative abnormality of von Willebrand factor causing von Willebrand's disease
- Decreased number or function of platelets which can be either acquired (e.g. aspirin, NSAIDs) or congenital (e.g. platelet function defects)
- Qualitative (e.g. caused by inhibitors to coagulation factors, commonly factor VIII) or quantitative (e.g. haemophilia) abnormality of coagulation factors
- Increased fibrinolysis (e.g. viral haemorrhagic fevers, snake bites).

ACQUIRED BLEEDING DISORDERS

Acquired bleeding disorders are commonly caused by vitamin K deficiency, disseminated intravascular coagulation (DIC) or platelet disorders (Box 65.19) but may sometimes be due to acquired inhibitors of coagulation factors. The initial laboratory tests in a patient with excessive bleeding should therefore include a platelet count, clotting screen (prothrombin time (PT) and activated partial thromboplastin time (aPTT)), and

BOX 65.19 ACQUIRED BLEEDING DISORDERS

VITAMIN K DEFICIENCY

- Dietary deficiency or malabsorption
- Systemic illness (e.g. liver disease)
- Haemorrhagic disease of newborn

DISSEMINATED INTRAVASCULAR COAGULATION

- Viral and bacterial infections
- Obstetric disorders (e.g. septic abortion, placental abruption)
- Shock (e.g. trauma, surgical, burns)
- Envenomation

PLATELET DISORDERS

- Infections (e.g. malaria, dengue)
- Hypersplenism
- Immune (e.g. ITP, drugs, HIV)
- Others (e.g. cyclical, congenital, cytotoxic or non-steroidal drugs).

fibrinogen levels, which may be helpful in cases of excessive fibrinolysis (Table 65.10). A difficult venepuncture can cause in vitro activation of the clotting system resulting in a shortened PT or aPTT. Similar findings may occur in chronic DIC due to in vivo activation. The PT and aPTT are not necessarily good predictors of the bleeding risk because some clotting disorders associated with thrombosis (e.g. anti-phospholipid antibodies) can prolong the aPTT. A shortened aPTT can be associated with marked elevation of factor VIII levels (e.g. pregnancy) and may be a predictor of deep vein thrombosis. A prolonged thrombin time is caused by quantitative or qualitative fibrinogen deficiency, heparin and fibrin degradation products. Reptilase time is helpful to distinguish between fibrinogen abnormalities (prolonged reptilase time) and heparin therapy (normal reptilase time).

Vitamin K Deficiency

Deficiency of vitamin K can be due to poor diet, small bowel disease or bile flow obstruction. Clotting factors (II, VII, IX and X) are dependent on vitamin K which is a fat-soluble vitamin. Vitamin K deficiency therefore causes prolongation of the PT and APTT. In newborn infants, vitamin-K-dependent clotting factors can drop precipitously within a couple of days of birth. This causes haemorrhagic disease of the newborn which particularly affects infants that are premature, exclusively breast fed or have been exposed to drugs for tuberculosis, convulsions or anticoagulation in utero. These babies develop bleeding into the skin and gut, or bleeding from the umbilical stump or circumcision.

Vitamin K deficiency will respond to intravenous vitamin K (10 mg/day for 3 days orally or by intravenous injection) and in severe bleeding the clotting abnormality can be treated with fresh frozen plasma. Haemorrhagic disease of the newborn can be prevented with 1 mg of intramuscular vitamin K given at delivery.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is characterized by activation of haemostasis with widespread fibrin formation, activation of fibrinolysis and consumption of platelets and clotting factors. It may be precipitated by tissue injury, obstetric complications, malignancies and infections and is a serious condition with a high mortality. Patients present with spontaneous bruising or excessive bleeding from minor wounds such as venepuncture sites, and they may also have signs of complications such as renal failure, acute respiratory distress syndrome and microangiopathic haemolytic anaemia. DIC is associated with a combination of depleted clotting factors (i.e. prolonged PT and APTT), a falling platelet count, red cell fragments on the blood film, raised D-dimers or fibrin degradation products, and reduced fibrinogen levels. Management of disseminated intravascular coagulation includes treating or removing the underlying cause, and correcting the haemostatic abnormalities with combinations of platelets, cryoprecipitate and fresh frozen plasma.

Acquired Platelet Disorders

Although bleeding due to thrombocytopenia is unusual unless the platelet counts falls below 10–20 $\times$ 10^9/L, bleeding may occur with a normal platelet count and normal clotting screening tests (i.e. PT and aPTT) if platelet functions are impaired (e.g. myelodysplastic syndromes). Platelet transfusions are generally not required unless there is active bleeding or prior to surgery.

Idiopathic Thrombocytopenic Purpura. Idiopathic thrombocytopenic purpura is due to immune destruction of platelets. It is usually primary but can be associated with conditions such as lymphomas and infections including HIV. It may present incidentally or with petechiae, bruising or bleeding from the nose or gums, especially if the platelet count is less than 20 $\times$

TABLE 65.10 Interpretation of Clotting Tests

PT	aPTT	Plt	Condition
N	N	N	Common – Normal haemostasis, vascular abnormalities[a] Rare – Platelet dysfunction, dysfibrinogenaemia, mild coagulation factor defect[b] Extremely rare – Factor XIII deficiency, alpha 2 antiplasmin deficiency
Long	N	N	Common – Early oral anticoagulation, early vitamin K deficiency Rare – Factor VII deficiency
N	Long	N	Common – Antiphospholipid antibody, Heparin, Factors VIII, IX, XI, XII, deficiency, vonWillebrand's disease Rare – inhibitors to the above factors
Long	Long	N	Common – Vitamin K deficiency[c], oral anticoagulants[c] Rare – Factors V, VII, X and II deficiency
Long	Long	N	Heparin[d], liver disease, fibrinogen deficiency, hyperfibrinolysis
Long	Long	Low	DIC, acute liver disease

Plt, Platelet count; N, normal; DIC, disseminated intravascular coagulation.
[a]Vascular abnormalities include scurvy, Cushing's disease and Ehlers Danlos.
[b]A mild coagulation defect below the detection of the routine tests or which has been masked by the administration of blood products (e.g. mild factor VIII deficiency; some cases of von Willebrand's disease).
[c]PT is relatively more prolonged than aPTT.
[d]TT is extremely sensitive to heparin and a normal reptilase time is useful to confirm the presence of heparin.

10^9/L. Spontaneous recovery occurs less commonly in adults than in children. It is important to exclude other causes of thrombocytopenia such as drugs, DIC or sepsis. The diagnosis can be suspected from a bone marrow examination which shows increased numbers of platelet precursors. Treatment with prednisolone (0.25–0.5 mg/kg) is usually only necessary if there is bleeding or excessive bruising and the dose should be reduced slowly once the platelet count improves. Second-line treatments include immunosuppressive agents and danazol. Splenectomy may also be beneficial but carries an increased risk of infection. Platelet transfusions or intravenous gammaglobulin can temporarily increase the platelet count in an emergency or prior to surgical procedures.

INHERITED BLEEDING DISORDERS

Inherited bleeding disorders can be classified broadly into coagulation factor deficiencies (e.g. factor VIII and factor IX deficiencies), von Willebrand's disease and platelet disorders. The frequency of genes for inherited bleeding disorders is the same throughout the world. Haemophilia A has a prevalence of about 10/10 000, von Willebrand's disease of >10/10 000 and haemophilia B of <0.1/10 000. These conditions occur more frequently among populations where consanguineous marriage is common and where prenatal diagnostic facilities are unavailable.

In general, individuals with inherited coagulation factor deficiencies present with soft tissue bleeds such as haemarthroses or intramuscular bleeds. Those with platelet disorders or von Willebrand's disease tend to present with mucosal bleeds, however severe (type III) von Willebrand's disease can present with severe soft tissue bleeds. Many of these conditions are diagnosed following excessive and uncontrolled bleeding after trauma or surgical procedures. Menorrhagia and delayed severe postpartum haemorrhage may be presenting features of bleeding disorders, particularly von Willebrand's disease or hypothyroidism, which can cause decreased synthesis of von Willebrand factor. Some inherited platelet function disorders are associated with characteristic syndromes (e.g. oculocutaneous albinism or skeletal defects) which may provide a clue to the diagnosis.

Early recognition of symptoms by clinicians, teachers and the public is important so that early treatment can be established. Patients with inherited bleeding disorders are usually managed with blood products (Box 65.20) or chemotherapy designed to reduce bleeding and associated complications.[295,296,298,299] Clotting factor concentrates may be imported or produced locally by fractionation of plasma and are included in the WHO list of essential medicines.[297,298] One international unit (IU) of FVIII clotting factor concentrate per capita is recommended as the minimum requirement for countries wishing to achieve optimal survival for their haemophilia population but only about 25% of the estimated 400 000 people in the world with haemophilia receive adequate treatment. Management of patients with bleeding disorders relies on a well-equipped and quality assessed laboratory for accurate diagnosis and monitoring of treatment and access to plasma and components for replacement therapy. Appropriate support services such as physiotherapy, orthopaedics and counselling should also be available. In many countries inherited bleeding disorders are associated with stigma, which is particularly directed against the mothers of affected children,[297] so educational interventions are an important intervention.

BOX 65.20 PRINCIPLES OF MANAGEMENT OF HAEMOPHILIA AND RELATED CONDITIONS IN LOW-INCOME SETTINGS

EDUCATION

- For the individual
- For the family
- For the healthcare providers

DIAGNOSIS

- Local laboratories
- Central laboratories to ensure quality control and provide training

ANCILLARY TREATMENTS

- Soft tissue bleeds – PRICE: Protection, Rest, Ice packs, Compression and Elevation (avoid compression in children who may not be able to report adverse symptoms like paresthesiae)
- Mucosal bleed – tranexamic acid mouthwashes (better than tablets)
- Regular physiotherapy

DEFINITIVE TREATMENT

Early factor replacement for soft tissue bleeds may limit prolonged product requirement and long-term damage

- Musculoskeletal bleeds – 5–15 U/kg daily until resolution of symptoms
- Serious bleeds (e.g. intracranial haemorrhage) – 30–40 U/kg for at least 3–5 days
- Major surgery – target level of 100% maintained for 3 days followed by decrease by 20–30% every 3 days
- Minor surgery – target level of 40–60% levels with further decrease over the next few days

DRUG THERAPY

- Desmopressin (DDAVP)
- Danazol
- Oestrogens in von Willebrand's disease.

Desmopressin (DDAVP) is a relatively inexpensive drug that increases FVIII levels and vWF activity within 30 minutes of administration. It is useful in mild haemophilia and mild von Willebrand's disease.[299] The major side effects are headaches and hyponatraemia so fluid intake should be restricted to 1.5 L/day. Tranexamic acid mouthwashes may be helpful for oral mucosal bleeding. Danazol can increase both factor VIII and IX levels within 5–7 days[300] and has therefore been recommended for patients with recurrent haemarthrosis or with central nervous system bleeding which both carry a high risk of recurrence.

THROMBOEMBOLISM

Most thromboembolic episodes are single events and may be associated with precipitating events or underlying risk factors. Thrombophilia is the clinical state of hypercoagulability and should be suspected in patients who have a strong family history of thrombosis, or who have recurrent or unusual thromboses.

Increasing affluence and consequent lifestyle changes mean that the prevalence of thromboembolism is rising in some low- and middle-income countries. Risk factors such as sedentary work, obesity, excessive alcohol intake, smoking and additional cardiovascular risk factors are compounded by other

conditions that are associated with thrombosis such as HIV infection, and chronic infections including tuberculosis[301,302] and helminth-induced eosinophilic myocarditis.[303] African Americans are more likely to be diagnosed with pulmonary embolism rather than deep-vein thrombosis compared to other racial groups[304] and African patients with thrombosis tend to be younger than those reported in literature[305] with higher mortality rates (around 28%) possibly due to late presentation and poor access to health facilities. Asian populations[306–308] seem to have a lower prevalence of symptomatic venous thrombosis compared to African Americans.[304]

Very little is known about the prevalence of prothrombotic factors such as mutations of the prothrombin gene or deficiencies of antithrombin, protein C and protein S in tropical countries, although high rates of factor V Leiden, a risk factor for venous thrombosis, have been described in Tunisia.[309,310] Lupus anticoagulant and anti-phospholipid syndrome, which are associated with increased thrombosis risk, are increased in Afro-Caribbean populations, especially in the presence of HIV, and have also been described in Nigerian women with pre-eclampsia.[311,312]

The management of venous thrombosis is initially with heparin and then with warfarin for 3–6 months. Compliance may be difficult in low-resource settings because of the requirement for regular monitoring of warfarin. It is therefore important to try to prevent thromboses by removing any underlying risk factors and by treating individuals at risk of thrombosis with a short course of prophylactic heparin to cover procedures known to be associated with thrombosis risk.

Thrombophilia

This can present as venous or arterial thromboembolism and it may be inherited (e.g. deficiencies of thrombin, protein S or protein C) or acquired (e.g. antiphospholipids). The patient's personal and family history, and the results of clinical and imaging examinations to confirm thrombosis, may suggest the diagnosis. The laboratory tests needed to determine the cause and classify the type of thrombophilia, and their interpretation, are complex, so patients with recurrent or unusual thromboses should be referred to a specialist centre.

Haematological Malignancies in the Tropics

Haematological malignancies are predominantly leukaemias, lymphomas and myelomas. Some of the general approaches for managing these conditions in low-income countries are outlined in Box 65.21[313] but definitive treatment should be undertaken by a specialist haematology unit.

LEUKAEMIAS

Clinical Features

Leukaemias can be broadly classified as acute or chronic, and lymphoid or myeloid. The presenting symptoms and signs are related to the disturbed blood cell production from the bone marrow due to the effects of the malignant cell clone (Box 65.22). Acute leukaemias are characterized by rapid progression and poor prognosis if left untreated whereas chronic leukaemias generally follow a much slower course.

BOX 65.21 MEASURES WHICH MAY BE ADOPTED TO IMPROVE CARE OF PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES IN AN UNDER-RESOURCED SETTINGS

- Mobilization of the community (especially parents and families) to raise awareness among local councils and government bodies about the treatability of the cancers and benefits from curing them
- Find an external partner unit locally, nationally or internationally which is already well-established and willing to help but will not dictate terms
- Improvement of supportive care facilities, especially protection from those with infectious diseases
- Development of a safe and reliable blood transfusion service
- Provision of subsidized travel, and satellite clinics to lessen the burden
- Development of appropriate protocols for each disease entity which is locally practicable with minimum cost and maximum efficacy
- Development of medical, nursing and paramedical expertise in the diseases to be treated – initially by offering visiting fellowships and in the long term for the trained individuals to arrange regional and local teaching programmes
- Formation of a cooperative group bringing together all the professionals involved in the speciality within a country or region to share expertise and develop training programmes.

Diagnosis

Acute and chronic leukaemias are usually associated with a high white cell count but acute leukaemias can present with normal or even sub-normal white cell counts. Morphology of peripheral blood and bone marrow specimens is crucial to confirm the diagnosis. This is particularly important in the case of acute leukaemia in children which may be mistaken for an acute viral infection. Staining methods including Sudan black B, myeloperoxidase and nonspecific esterase are important to distinguish between the different subtypes of acute myeloid and lymphoid leukaemias and therefore to guide treatment.

Management

Acute Myeloid Leukaemia (AML). Prevalence of this increases with age and the success rate with chemotherapy protocols is not high even in the most sophisticated centres. Neutropenia and myelosuppression requiring intensive blood component support occur during chemotherapy[314] and bone marrow transplantation offers the best option for cure for patients who relapse. Management of AML is therefore complex and expensive. Hydroxycarbamide or subcutaneous cytarabine may be used as a palliative treatment.

Acute Promyelocytic Leukaemia (AML Subtype M3). This must be distinguished from other types of acute myeloid leukaemia because it has a high cure rate with early treatment. It predominantly affects young adults and it has a high incidence in certain ethnic groups especially those of Latin American descent.[315] A treatment protocol which includes all-transretinoic acid with combination chemotherapy has been developed which is feasible in low-income countries.[315,315] Another regimen based on intravenous arsenic trioxide has been developed in India,[316,317] which has an 86% response rate with good disease-free and overall survival.

BOX 65.22 CLINICAL FEATURES OF LEUKAEMIAS

ACUTE LEUKAEMIAS

- Fatigue and cardiac symptoms from anaemia
- Bleeding from thrombocytopenia
- Increased risk of infections despite a higher number but dysfunctional white cells
- Lymphadenopathy and hepatosplenomegaly occur with ALL although lymphadenopathy may be observed in the monocytic variety of AML
- Blindness due to hyperviscosity from hyperleukocytosis
- Tumour lysis syndrome due to spontaneous cell lysis presents as renal failure
- Pustules or pyogenic infections of the skin from minor wounds
- Bleeding gums are a characteristic feature of acute monocytic leukaemia
- Disseminated intravascular coagulation can occur with acute promyelocytic leukaemia
- Gout can arise from breakdown of the excess white cells and release of uric acid
- Oral aphthous ulceration is seen with severe neutropenia in both AML and ALL
- Granulocytic sarcoma or chloroma represent extramedullary deposits of leukaemic cells in any organ but mainly the skin. This may occur in the absence of peripheral blood involvement and is more common with chromosomal translocation (8; 21) of AML
- Central nervous system manifestations due to sludging of the cerebral circulation by the malignant cells or increased intracranial pressure due to ventricular blockade can occur. Monocytic myeloid leukaemia can also involve the meninges
- Intracranial haemorrhage can occur in ALL with very high white cell counts (>400 $\times$ 10^9/L)
- Bone pain and arthralgia can be a presenting feature of ALL in children in more than a quarter. These children may present with a limp or unwillingness to walk due to marrow infiltration by leukaemic cells. Rarely, they may have normal blood counts delaying the diagnosis of ALL
- Anterior mediastinal mass (thymus enlargement) can also occur in children and young adults with ALL which may present as superior venocaval obstruction
- Painless enlargement of scrotum is a sign of testicular leukaemia or hydrocele from lymphatic obstruction. Priapism can result from hyperleukocytosis rarely.

CHRONIC LEUKAEMIAS

- Most often asymptomatic and usually suspected on blood counts
- The chronicity of CML or CLL tends to cause gradual-onset symptoms since the patients get adjusted to the slowly developing anaemia
- Abdominal discomfort and early satiety are a feature of CML due to excessive splenomegaly compressing the stomach and reducing the luminal volume
- Sternal tenderness may be noted in CML
- Hyperleukocytosis in CML can occur more often than with AML or ALL due to the gradual increase in white cells. This can cause symptoms like hyperuricaemia and gout, tinnitus, priapism or central nervous system disturbances
- Left shoulder tip pain can arise from splenic infarction from the massive splenomegaly in CML
- CML can rarely present with features of thyrotoxicosis (heat intolerance, weight loss and excessive sweating) due to hyper-metabolism
- CLL is often associated with lymphadenopathy and rarely with mild to moderate splenomegaly.

ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia.

Acute Lymphoblastic Leukaemia (ALL). This is the most common type of leukaemia in children. It has a good prognosis when treated with modern chemotherapy protocols with cure rates in the best centres exceeding 80%.[318] In low-income countries, cure rates are much lower at around 35%[319] primarily because of failure to complete therapy and deaths caused by treatment. Considerable improvements in ALL outcomes have been achieved by twinning institutions in developing countries with specialist centres elsewhere in the country or internationally.[313] Measures that may improve outcomes focus on preventing abandonment of therapy (e.g. providing funding for transport, satellite clinics and support groups) and prompt treatment of infection.[320] Treatment in a dedicated paediatric oncology unit using a comprehensive multidisciplinary team approach and protocol-based therapy, is also associated with improved outcomes in resource-poor settings.[321]

Chronic Myeloid Leukaemia (CML). Management has been revolutionized by tyrosine kinase inhibitors (e.g. imatinib) which can produce complete remission in over 80% of cases. Once the diagnosis of CML is established, hydroxycarbamide can be used to reduce the white cell count, followed by treatment with a tyrosine kinase inhibitor. Manufacturers will provide the drug free of charge to patients in low-income countries with confirmed CML and generic forms of tyrosine kinase inhibitors are now becoming available.

Chronic Lymphocytic Leukaemia (CLL). This occurs predominantly in older people and usually presents with lymphadenopathy and recurrent infections. Treatment is with chlorambucil and prednisolone although aggressive forms require combination therapy with rituximab, fludarabine and cyclophosphamide. Treatment is generally not curative but the disease may be indolent and drugs may only be required if the patient has symptoms or if there is a risk of hyperviscosity from a very high lymphocyte count.

LYMPHOMAS

Epidemiology and Clinical Features

Approximately 30 000 cases of non-Hodgkin lymphoma (NHL) occur in the equatorial belt of Africa each year (Table 65.11).[322] There are marked geographical variations in prevalence but up to 50% are thought to be related to HIV infection.[322] Burkitt's lymphoma, a B-cell NHL, was originally described in children from Africa and has an estimated incidence of 30–70 per million. Lymphomas are broadly classified into Hodgkin's lymphoma and NHL; NHL are divided into B-cell, T-cell and NK-cell, and immunodeficiency-associated types.

The clinical presentation of lymphomas is characterized by enlargement of the lymphoid organs and subsequent compression of the adjacent structures, infiltration of organs by the malignant lymphoid cells and a dysfunctional immunological system which can manifest as immunosuppression or excessive but dysregulated immune activation associated with, for example, autoimmune conditions.

Diagnosis

The diagnosis and management of the various types of lymphomas are complicated and should be undertaken in a specialist

TABLE 65.11 Types of Lymphomas Identified from Selected Countries in Sub-Saharan Africa

	Paediatric And Adolescent Cases	Adult Patients
Type of non-Hodgkin's Lymphoma		
Precursor lymphoid neoplasms	3%	4.7%
Mature B-cell neoplasms	92.5%	91.3%
Burkitt	82%	9%
Diffuse large B-cell	7.5%	55%
Mature T-cell and NK cell neoplasms	2.2%	3%
Type of Hodgkin's Lymphoma		
Nodular lymphocyte predominant	5%	9.4%
Nodular sclerosing classical	37%	53%
Mixed cellularity classical	37%	31.2%
Lymphocyte-depleted classical	21%	3%
Lymphocyte-rich classical	O%	3%

centre. Diagnosis depends on clinical history and examination, radiological investigations to document the extent of disease, and morphology, immunohistochemistry and molecular studies on tissue samples to confirm the lymphoma subtype. Guidance on the diagnosis and treatment of lymphoma in settings where resources are limited includes recommendations about panels of immunostains and chemotherapy regimens that minimize the need for supportive care.[322] Tele-pathology, which involves transmitting histological images via the internet to experts overseas, may be helpful in certain circumstances though it is dependent on the quality of the histology preparations and the images of appropriate diagnostic regions in the sample.

Management

Treatment regimens for lymphomas differ according to the subtype but may involve chemotherapy and radiotherapy. High remission rates can be achieved in Burkitt's lymphoma with a combination of cyclophosphamide, vincristine and methotrexate and progressive disease can be managed with ifosfamide, mesna and cytosine arabinoside.[322,323]

ADULT T-CELL LEUKAEMIA-LYMPHOMA (ATLL)

Adult T-cell leukaemia-lymphoma (ATLL) is an uncommon lymphoid malignancy which occurs in patients infected with human T-lymphotropic virus type I (HTLV-I).[324] HTLV-1 is endemic in the Caribbean, western Africa, Peru and southern Japan. Less than 5% of those infected with HTLV-I develop ATLL and up to 30 years can elapse between the primary infection and the development of ATLL suggesting additional factors are needed for malignant transformation.[325]

ATLL presents acutely in approximately 60% of cases, although chronic forms have also been described.[326] The clinical presentation is with generalized lymphadenopathy in most cases and hepatosplenomegaly in over half.[324] ATLL is associated with a high risk of hypercalcaemia which occurs in more than two-thirds of patients during the course of their disease and may be associated with central nervous system disturbances and renal impairment. Lytic bone lesions occur as a para-neoplastic phenomenon due to production of parathormone-like peptides. As with other T-cell disorders, ATLL can involve the skin, producing, e.g. erythrodermic plaques.

The diagnosis of ATLL can be suspected from a high peripheral blood white blood cell count in combination with hypercalcaemia and characteristic lymphocytes with convoluted and hyperlobulated nuclei.[324] The diagnosis is confirmed by histological examination of a tissue (lymph node or bone marrow), immunophenotyping for specific cell markers and proof of HTLV infection, usually by serological methods.

Management of ATLL is primarily with combination chemotherapy with intrathecal prophylaxis.[327,328] A combination of zidovudine and interferon, as agents against HTLV, has also been tried with some success.[329] Hypercalcaemia and opportunistic infections should be sought and treated early in these patients. The high white cell count is associated with a significant risk of tumour lysis syndrome and should be prevented by adequate hydration and the judicious use of allopurinol and other urate-reducing agents.

MULTIPLE MYELOMA

Myeloma is a monoclonal proliferation of plasma cells and it particularly affects older people. Myeloma appears to be less common in Asian countries than elsewhere, although during the last 25 years, an almost four-fold increase in incidence of myeloma has occurred in Taiwan.[330] In the United States, the incidence of multiple myeloma in the black population is twice that of the white population.

Pathophysiology and Clinical Features

The abundant plasma cells infiltrate the bone marrow and interfere with normal haematopoiesis. This leads to anaemia, which is a presenting feature in 70% of individuals. Bony infiltration by the malignant plasma cells can produce osteoporosis, lytic lesions and pathological fractures in 60% of patients with myeloma. Involvement of the bones can lead to hypercalcaemia, which may be a presenting feature, and vertebral fracture leading to spinal cord compression. The malignant plasma cells produce a paraprotein which can cause renal impairment in 20–50% and hyperviscosity may ensue in 10% of patients if the paraprotein production is not controlled.

Management

Patients with myeloma may need a variety of supportive interventions including management of anaemia, renal failure, hypercalcaemia, hyperviscosity, infections and bone pains. Specific anti-myeloma treatment should be managed within a specialist unit and has undergone a radical change in the last decade with the use of thalidomide and its newer formulations, and the more expensive, proteasome inhibitors (e.g. bortzomib). Thalidomide is relatively safe and effective although somnolence and constipation can sometimes be troublesome. There is a risk of thrombosis with thalidomide especially at the initiation of therapy, and prophylaxis with heparin, warfarin or antiplatelet agents, depending on an assessment of the risk, may be warranted. Melphalan may also be useful, particularly if resources are limited and there is no specialist centre. However it is myelosuppressive, so regular monitoring of the blood count is essential.

Blood Transfusion

Maintaining an adequate blood supply is a major challenge for low-income countries. Only 39% of the global blood supply is donated in the poorest countries where 82% of the world's population lives.[331] Blood transfusion is a vital component of every country's health service. It can be a life-saving intervention for illnesses such as severe acute anaemia, but mistakes in the transfusion process can be life-threatening, either immediately or years later through transmission of infectious agents. Clinicians need to understand how blood is acquired and its risks and benefits, and to use it appropriately. Governments and transfusion services need to put measures in place to ensure that blood is safe for transfusion and that it reaches those who need it in a timely manner.

BLOOD TRANSFUSION AT THE NATIONAL LEVEL

Only 16% of member states meet all the World Health Organization's (WHO) recommendations for a national quality blood transfusion system.[331] At the national level the transfusion service should have a director, an advisory committee and clear transfusion policies and strategies (Table 65.12).[331] WHO recommend standardization of blood collection, testing and distribution. Although centralization of these services may offer the best guarantee of quality, it is often not practical in countries with poorly developed communications and transport infrastructure.

Two systems, centralized and hospital-based, exist in low-income countries for managing blood supply. In the centralized system, voluntary blood donors are recruited, screened and bled by regional centres and the blood collected is distributed to peripheral hospitals. Hospital-based systems are the predominant source of blood across sub-Saharan Africa. Hospital-based systems obtain blood predominantly from relatives of patients, and blood is screened and used within the local vicinity.[332]

TABLE 65.12 Components of National Strategies for Blood Safety

Essential Element	Supporting Strategy
Well-organized, nationally coordinated blood transfusion service	Government commitment; specific, adequate budget; implementation of national blood policy and plan; legislative and regulatory framework
Quality systems covering all aspects of activities	Organizational management; quality standards; documentation systems; staff training; quality assessments
Blood collection only from voluntary, non-remunerated donors	Effective donor recruitment programmes; stringent donor selection criteria; donor care programme
Quality assured testing of all donated blood	Testing for transfusion-transmissible infections; accurate blood group serology and compatibility testing procedures
Reduction in unnecessary use of blood	Use of appropriate component therapy; safe administration of blood and blood products

Blood from the centralized system costs at least three times as much per unit as that from a hospital-based system.[333] Although centralized systems can save costs through batching and bulk purchasing, the quality assurance processes and donor recruitment components are expensive and difficult to maintain without dependence on external funds. In hospital-based transfusion services, testing quality is variable and the families of patients bear the cost of finding blood donors.

SEPARATION OF WHOLE BLOOD INTO COMPONENTS

The vast majority of blood in low-income countries is transfused as whole blood. In high-income countries it is standard practice to optimize the use of each donation of blood by separating it into individual components but whether this approach is cost-effective in low-income countries, where indications for transfusion are different, is not known. These components, which may include plasma, platelets and cryoprecipitate, are prepared by centrifugation using a closed, sterile system and each component has different storage requirements. Plasma and cryoprecipitate are kept frozen, red cells are stored at 1–5°C, and platelets at 18–22°C with constant agitation. Recent evidence suggests that warm, fresh, whole blood may be better than component therapy for resuscitation of acidotic, hypothermic and coagulopathic trauma patients[334] and for patients needing massive transfusions.[335]

ENSURING SAFETY OF BLOOD FOR TRANSFUSION

Many infections can be transmitted through blood transfusions and transfusion of infected blood causes morbidity and mortality in the recipients, and has an economic and emotional impact on their families and communities. Those who become infected through blood transfusion are infectious to others and contribute to the spread of disease thereby increasing the burden on health services and reducing productive labour.

Selecting Low-risk Blood Donors

Strategies for recruiting blood donors have to provide blood for all who need it in a timely manner while ensuring that the blood is as safe as possible. The safest type of blood donor is one who donates regularly (i.e. repeat donors). WHO states that the safest source of blood is altruistic, voluntary, unpaid donors. Only 32% of WHO member states report having at least 90% of their blood supply from voluntary donors, and low-income countries have not been able to increase the recruitment of voluntary donors for several years.[331] Recent evidence from sub-Saharan Africa indicates that the focus on voluntary donors may be misplaced since first-time voluntary donors have a similar prevalence of transfusion-transmitted infections as family replacement donors.[336] In order to limit blood shortage and maintain constant blood supply in poorer countries, both voluntary and replacement donors should be accepted and encouraged to donate regularly. Mechanisms to convert family replacement donors into repeating voluntary donors have the potential to significantly increase blood donations in Africa. Political will and open-mindedness about ways to improve the supply and safety of blood are essential to promote more evidence-based approaches to blood transfusion practice in poorer countries.[337]

High-risk donors, such as commercial sex workers and their contacts, intravenous drug abusers, or those with an itinerant lifestyle such as traders, drivers and military personnel, should be deterred from donating.[338] Even in areas where HIV infection rates in the general population are high, donor deferral can be effective in excluding HIV-infected donors.[339] The whole donation process, including tests for HIV and other infections, should be explained to the donor before blood is collected and donors should have the option of knowing the results and receiving counselling. It is imperative that complete confidentiality is maintained throughout all procedures.

Screening for Transfusion-transmitted Infections

Infections with organisms such as HIV, hepatitis viruses, cytomegalovirus, syphilis, lyme borreliosis, malaria, babesiosis, American trypanosomiasis (Chagas disease) and toxoplasmosis can all be acquired through blood transfusions. Some 5–10% of HIV infections worldwide are thought to have been transmitted through the transfusion of infected blood and blood products. There have also been reports of transmission of variant Creutzfeldt–Jakob disease through blood transfusion and there is a theoretical risk of transmission of severe acute respiratory syndrome (SARS).[340,341] WHO recommends that all donated blood should be screened for HIV, hepatitis B and syphilis and, where feasible and appropriate, for hepatitis C, malaria and Chagas disease.

Malaria can be transmitted by blood transfusion and, depending on the local infection prevalence, 2–55% of blood donors in Africa screen positive for malaria.[342] However, there is very little evidence to suggest that these donors transmit malaria to transfusion recipients. Although WHO recommends screening donors in endemic areas for malaria, none of the screening methods that would be practical for transfusion services are sufficiently sensitive. Furthermore, in some countries with high malaria transmission, exclusion of parasitaemic donors could result in deferral rates exceeding 50% which would have a major impact on blood supply.[343] There is no evidence to support the widespread practice of routine treatment of transfusion recipients for malaria.

Fresh blood is potentially infectious for syphilis, but storage at 4°C for more than 5 days can inactivate *Treponema pallidum*. The high demand for blood in low-income countries means that blood is generally not stored for long enough to inactivate *T. pallidum* and syphilis seroconversion associated with transfusion has been reported from Africa.[344]

Globally, the prevalence of hepatitis C, HTLV-1 and -2 and Chagas disease is variable and the decision to introduce donor screening for these infections should be based on local assessments of the risks, benefits, feasibility and costs. Blood should not be separated into components if the residual risk of infection is high, as this will increase the number of potentially infected recipients. A unit of blood is usually stored until screening tests for infections have been completed. This means that potentially infected blood may be mixed up with units that have already been screened, and costly blood collection bags are wasted. Screening potential donors before venesecting a unit of blood may therefore be a more cost-effective way of ensuring safe blood.[345]

Tests for screening blood donors need to be highly sensitive, and infected blood should be rejected. Before informing the donor of the outcome, all positive results should be confirmed using a test with a high degree of specificity. Where blood donation is organized locally, the confirmatory test is often performed at a central laboratory, so there may be a delay in informing the donor of the result. There is evidence that nucleic acid amplification techniques (NAT) may be cost-effective in low-income countries where infection prevalence is high.[346]

CLINICAL USE OF BLOOD

Reasons for Transfusion in Low-income Countries

In wealthy countries, the majority of transfusions are carried out electively. By contrast, in poorer countries, and particularly those where the malaria transmission rate is high, most transfusions are given for life-threatening emergencies. In low-income countries, 50–80% of transfusions are administered to children, predominantly for malaria-related anaemia, and pregnant women. Transfusion can significantly reduce the mortality of children with severe anaemia within the first 2 days of hospital admission[347] and successful malaria control can reduce paediatric transfusion requirements.[348] In sub-Saharan Africa, 26% of in-hospital maternal deaths from severe bleeding were due to lack of blood for transfusion.[349] Other specialities which are significant users of blood are surgery, trauma, emergency medicine and general medicine.

Avoiding Unnecessary Transfusions

In low-income countries the most effective way to avoid transfusions is to reduce the prevalence of anaemia. More studies on the efficacy and cost of combinations of interventions including insecticide-treated bed nets, nutritional supplements and anthelmintic drugs to prevent anaemia are needed. When resources are very limited, governments may need to make some difficult decisions in order to achieve an equitable balance between investing in a transfusion service and public health measures to reduce anaemia.

Whether a patient needs a blood transfusion or not is ultimately a clinical decision. Emergency transfusions can be lifesaving for patients in whom anaemia has developed too quickly to allow physiological compensation, as in severe malaria-related anaemia in children, and sudden, severe obstetric bleeding. In contrast, if the anaemia has developed slowly, for example due to hookworm infestation or nutritional deficiency, patients can generally be managed conservatively by treating the cause of the anaemia and prescribing haematinic replacements. Iron supplements should be continued for at least 3 months after the haemoglobin has returned to normal, so that body stores can be replenished.

Clinical Guidelines. It is possible to avoid unnecessary transfusions by adhering to clinical transfusion guidelines. Most institutions have developed guidelines to help clinicians make rational decisions about the use of blood transfusions (Box 65.23)[344,350] and strict enforcement of transfusion protocols can significantly reduce avoidable transfusions.[351] The principles underlying most transfusion guidelines are similar and combine a clinical assessment of oxygenation, with haemoglobin measurement being used as a surrogate measure for intracellular oxygen concentration. Increasingly, transfusion guidelines are making use of evidence which shows that adequate oxygen delivery to the tissues can be achieved at haemoglobin levels that are significantly lower than the normal range.[352]

Implementation of transfusion guidelines is particularly difficult if clinicians do not have access to reliable haemoglobin

BOX 65.23 PRESCRIBING BLOOD: A CHECKLIST FOR CLINICIANS

Always ask yourself the following questions before prescribing blood or blood products for a patient:

1. What improvement in the patient's clinical condition am I aiming to achieve?
2. Can I minimize blood loss to reduce this patient's need for transfusion?
3. Are there any other treatments I should give before making the decision to transfuse, such as intravenous replacement fluids or oxygen?
4. What are the specific clinical or laboratory indications for transfusion in this patient?
5. What are the risks of transmitting HIV, hepatitis, syphilis or other infectious agents through the blood products that are available for this patient?
6. Do the benefits of transfusion outweigh the risks for this particular patient?
7. What other options are there if no blood is available in time?
8. Will a trained person monitor this patient and respond immediately if any acute transfusion reactions occur?
9. Have I recorded my decision and reasons for transfusion on the patient's chart and the blood request form?

Finally, if in doubt, ask yourself the following question:

If this blood were for me or my child, would I accept the transfusion under these circumstances?

measurements. When they doubt the haemoglobin result, clinicians rely entirely on clinical judgement to guide transfusion practice which can lead to significant numbers of inappropriate transfusions.[353] A lack of investment in the quality of a critical test, such as haemoglobin measurement, can waste significant resources downstream in the transfusion process, and unnecessarily expose recipients to the risk of transfusion-related infections.

Minimizing Surgical Blood Loss. Where blood is in short supply, it is particularly important to ensure that the best anaesthetic and surgical techniques are used, to minimize blood loss during surgery. Drugs which improve haemostasis or reduce fibrinolysis, such as aprotinin and cyklokapron, and fibrin sealants, can be effective in reducing perioperative blood loss. These drugs can therefore reduce the need for blood transfusion but they may be too expensive for use in low-income countries. A cost-effectiveness study of surgical bleeding in four sub-Saharan countries indicates that the antifibrinolytic, tranexamic acid, could save lives in countries with blood shortages, reduce healthcare costs and prevent transmission of infections.[354]

Preoperative Autologous Blood Deposit. Patients undergoing planned surgery who are likely to require a blood transfusion can have units of their own blood removed and stored in case they have significant intraoperative blood loss and need a transfusion. This process, known as preoperative autologous donation, can reduce the need for allogeneic transfusions by 46–74%[355] but it requires careful organization: the surgeon needs to predict how much blood will be required, the patient has to be fit enough to withstand removal of one or more units of blood over the weeks preceding the surgery and the surgery must take place within the shelf-life of the blood. As the blood has to be stored in the blood bank there is still a risk that the patient may receive blood which is not their own or that the blood may become infected with bacteria during the process.

Intraoperative Blood Salvage. This involves collecting blood lost during the operation and reinfusing it into the patient either during or after surgery. Although this technique is practical and safe, and reduces the need for donor blood by 27–53%,[355] it requires specialized equipment and training, and may be more expensive than routinely donated blood.[356]

Other Measures. Normal saline or intravenous replacement fluids can be used judiciously in acute blood loss, and in certain circumstances may be as effective as whole blood, red cells or plasma. Erythropoietin, which stimulates endogenous red cell production is well-established for use in chronic anaemias such as those due to renal failure, cancer and HIV infection but its delayed action makes it unsuitable for use in acute anaemias. Synthetic oxygen carriers, such as perfluorocarbons, are not yet routinely available.[357]

Haemoglobin Thresholds for Transfusion

In low-income countries, the recommended haemoglobin threshold for transfusions is often well below that which would be accepted in more wealthy countries. Randomized controlled studies in wealthy countries indicate that for most adults and children undergoing critical care, a haemoglobin threshold of 70 g/L for transfusion is safe[358] whereas paediatric blood transfusion protocols in sub-Saharan Africa often recommend transfusions for stable children only when the haemoglobin level is less than 40 g/L.[351] Complications such as cardiac failure or infection may necessitate transfusion at a higher haemoglobin level. Transfusion should be combined with adequate haematinic replacements and underlying conditions should be treated.[359] Early evidence suggests that intermittent preventive treatment with anti-malarials may reduce the high hospital readmission rates experienced by children post-transfusion.[360]

COMPLICATIONS OF BLOOD TRANSFUSION

Complications can occur immediately during transfusion, within a few hours of its completion, or be delayed for many years, as in the case of viral infections (Box 65.24).

BOX 65.24 COMPLICATIONS OF BLOOD TRANSFUSION

- Febrile non-haemolytic transfusion reactions. Haemolytic reactions include chills, headache, backache, dyspnoea, cyanosis, chest pain, tachycardia and hypotension
- Risk of severe bacterial infection and sepsis
- Transmission of viral infection (hepatitis B, HIV or hepatitis C)
- Transmission of blood-borne trypanosomes, filaria, malaria, etc.
- Cardiac failure
- Air embolism
- Transfusion-associated acute lung injury (TRALI) – a syndrome of acute respiratory distress, often associated with fever, non-cardiogenic pulmonary oedema, and hypotension, which may occur as often as 1 in 2000 transfusions
- Other risks: volume overload, iron overload (with multiple red blood cell transfusions), transfusion-associated graft-versus-host disease, anaphylactic reactions (in people with IgA deficiency), and acute haemolytic reactions (most commonly due to the administration of mismatched blood types).

Acute and Delayed Haemolysis Due to Red Cell Incompatibility

Transfusion of blood into a recipient who possesses antibodies to the donor's red cells can cause an acute, and occasionally fatal, intravascular haemolysis. This could occur, e.g. if group A cells are transfused into a group O recipient who has naturally occurring antibodies to group A cells. The profound haemolysis induces renal vasoconstriction and acute tubular necrosis. Treatment involves stopping the transfusion, cardiorespiratory support and inducing a brisk diuresis. In addition to abnormalities indicating renal failure, laboratory findings include haemoglobinuria and haemoglobinaemia. Proof of the diagnosis involves rechecking the whole transfusion process including all documentation stages, regrouping the donor and the recipient, and screening for antibodies on red cells with a direct antiglobulin test. These tests are usually available in any hospital laboratory capable of providing a transfusion service. Delayed haemolysis has a similar physiological basis to acute intravascular haemolysis but it tends to be less severe, it occurs 7–10 days after the transfusion and it is less likely to present as a clinical emergency.

Bacterial Contamination

Limited data from sub-Saharan Africa show rates of bacterial contamination in donated blood of around 9%[361,362] but the clinical consequences for transfusion recipients are unknown. Bacteria can enter the blood bag during venesection or if the bag is breached, e.g. when reducing the volume for a paediatric recipient or during component preparation. Gram-negative bacteria, including *Pseudomonas* and *Yersinia*, grow optimally at 4°C and infected blood may not necessarily appear abnormal to the naked eye. Reactions following infusion of infected blood are often due to endotoxins and may occur several hours after the transfusion has finished. Although these reactions are rare, they can be severe and fatal. If bacterial contamination is suspected, the transfusion should be stopped and samples from the patient and the blood bag sent to the laboratory for culture. Cardiorespiratory support may be needed and broad-spectrum antibiotics should be started immediately and continued until culture results are available.

Non-haemolytic Febrile Reactions

Non-haemolytic febrile reactions are episodes of fever and chills associated with transfusion and for which no other cause can be found. They are due to the recipient's antibodies reacting against antigens present on the donor's white cells or platelets. These reactions are most common in patients who have had transfusions in the past and have therefore been exposed to allo-antigens. Mild febrile reactions usually respond to simple antipyretics such as paracetamol. More severe reactions may be the first indication of a haemolytic transfusion reaction or bacterial contamination and should be investigated and managed accordingly.

Allergic Reactions

Allergic reactions are due to infusion of plasma proteins and manifestations include erythema, rash, pruritus, bronchospasm and anaphylaxis. The transfusion should be stopped and the patient treated with antihistamines. If the reaction is mild and the symptoms and signs completely disappear, the transfusion can be restarted. If this type of mild reaction occurs repeatedly with more than one unit of blood, the red cells can be washed before transfusion. This should only be done if absolutely necessary, as it carries the risk of introducing potentially fatal bacterial infection. Severe allergic reactions with evidence of systemic toxicity should be managed as acute anaphylaxis.

Circulatory Overload

Blood should always be transfused slowly to avoid overloading the circulation, unless the patient has active and severe bleeding. Fluid overload may be a particular problem when paediatric blood bags are not available, as children may be over-transfused due to miscalculation of the required volume, lack of accurate infusion devices or inadvertent administration of an adult-sized unit of blood.

Haemosiderosis

Four units of blood contain the equivalent amount of iron stored in bone marrow (approx. 1 g). Repeated transfusions for chronic haemolytic anaemia, as in thalassaemia major and sickle cell disease, lead to iron deposition in parenchymal cells. Eventually failure of the heart, liver and other organs supersedes. Adequate doses of iron chelators, such as injectable desferrioxamine or oral deferiprone, are able to maintain acceptable iron balance in patients with chronic anaemia who need regular transfusions.

Hypothermia

It is not usually necessary to warm blood unless large quantities are transfused rapidly. This may lower the temperature of the sino-atrial node to below 30°C at which point ventricular fibrillation can occur. If blood needs to be warmed, an electric blood warmer specifically designed for the purpose should be used. This keeps the temperature below 38°C and avoids the haemolysis associated with overheating blood.

Graft-Versus-Host Disease

Graft-versus-host disease occurs when donor lymphocytes engraft in an immune-suppressed recipient. The lymphocytes recognize the recipient's bone marrow as foreign and induce aplasia. Graft-versus-host disease is almost universally fatal and can be prevented by irradiating the donor blood, which inactivates the donor lymphocytes.

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