CHAPTER 5

GENERAL MEDICINE AND HAEMATOLOGY

Key points

1. This chapter covers selected medical disorders in which anaemia or cytopenias are important.

2. Blood transfusions should only be given if clinically indicated and not solely because an arbitrary threshold of haemoglobin or platelet concentration has been reached.

3. Transfusions should not be initiated if the patient is stable, physiologically adapted and the cytopenias are likely to improve with non-transfusion measures.

5.1 Introduction

This chapter covers many complex medical disorders whose management often requires blood transfusions. In patients with severe thalassaemia and sickle cell disorders, red cell transfusions together with medical management are essential for increasing survival. Bone marrow failure syndromes often require repeated administration of blood components, together with specialized interventions. For the bleeding disorders, recent advances in medical therapy can reduce the reliance on transfusions. Anaemia due to haematinic deficiencies and malaria, significant causes of morbidity in many parts of the world, can usually be managed without red cell transfusions. While newer drugs have transformed human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDs) into a chronic disease, blood transfusion remains an important cause of HIV transmission.

While the salient features of selected medical disorders are discussed in this chapter, these are not meant to replace guidelines or textbooks. The physiology of body fluids, anaemia and aspects of blood components and apheresis have been extensively reviewed in other chapters. These topics should be revisited as needed in addition to studying the sections in this chapter.

Learning outcomes

After reading this chapter, the reader will be able to understand the principles of diagnosis and management of major inherited and acquired haematological and general medical conditions which may require management including transfusion support.

5.2 Deficiency of haematinics

The commonest haematinic deficiencies encountered globally are of iron, vitamin B12 and folic acid. Examples of the various causes of these deficiencies are given in Table 5.1.

Table 5.1. Major causes of hematinic deficiencies

Hematinic	Iron	Vitamin B12	Folic acid
Dietary insufficiency	Vegetarian diet	Vegetarian diet	Poor diet
Increased requirement	Growth, pregnancy, menstrual loss	NA	Growth, pregnancy, chronic haemolytic anaemias, exfoliative skin diseases, some medications
Reduced absorption	Malabsorption syndromes	Pernicious anaemia (absent intrinsic factor), impaired absorption in terminal ileum, fish tapeworm, bariatric surgery	Malabsorption syndromes
Blood loss	Menstrual loss, uterine pathology Gastrointestinal bleeding	NA	NA

NA, not applicable.

Iron deficiency

Worldwide, half the cases of anaemia are due to iron deficiency, which causes microcytic, hypochromic anaemia, with low ferritin unless co-existing inflammation is present, in which case the ferritin may be within the normal range. In severe iron deficiency, koilonychia and cheilosis may be seen *(1)*.

Treatment of iron deficiency

The following aspects are important in treating iron deficiency:

- Treat the underlying cause.
- Hookworm infestation is a major cause of iron deficiency in many regions due to ongoing, low-grade gastrointestinal (GI) blood loss.
- In adult males and menopausal women, iron deficiency anaemia should lead to investigations of GI blood loss, especially malignancy.
- Other causes of microcytic hypochromic anaemia should be considered (for example, haemoglobinopathies (thalassaemias), inflammation and, rarely, sideroblastic anaemia).
- Oral and intravenous (IV) iron replacement should be administered as appropriate and tolerated by the patient.

Vitamin B12 and folate deficiency

Both vitamin B12 and folate deficiencies can cause megaloblastic anaemia characterized by macrocytosis and hypersegmented neutrophils. Patients with severe vitamin B12 deficiency can show associated neurological deficits.

Vitamin B12 has the following characteristics:

- It is present in non-vegetarian foods.
- The daily requirement is 2.5 µg.
- The body stores between 2 and 5 mg (adequate for 1–2 years).
- It is absorbed through the terminal ileum and requires gastric intrinsic factor.
- A very small amount (<1%) is passively absorbed throughout the GI mucosa.

Folic acid has the following characteristics:

- It is present in plant- and animal-derived foods and is destroyed by prolonged boiling.
- The daily requirement is 100–200 µg.
- The body stores 5–20 mg (adequate for 3 to 4 months only).

- Deficiency develops rapidly if there is fast cell turnover as in chronic haemolytic anaemia.
- It is absorbed through the upper small intestine.

Treatment of vitamin B12 and folate deficiency

Treatment should take into account the following:

- If the patient has symptomatic anaemia, neurological deficits (vitamin B12 deficiency), or when treating pregnant women or neonates, urgent replacement is recommended.
- Treatment may need to be indefinite.
- Do not give folic acid alone if there is concomitant vitamin B12 deficiency, as it might precipitate a neurological crisis due to vitamin B12 being diverted to haemopoiesis.
- Intramuscular (IM) or deep subcutaneous vitamin B12 and oral preparations are available as cyanocobalamin and hydroxycobalamin.
- Parenteral vitamin B12 is recommended initially (to overcome potential poor absorption).
- The typical adult parenteral vitamin B12 dose is 1000 µg once or twice a week until deficiency (and anaemia) is corrected, then once every 1 to 3 months for maintenance *(2, 3)*.
- Oral vitamin B12 can also be used in patients with malabsorption, at a dose of 1000– 2000 µg daily, as this allows passive absorption without the need for intrinsic factor or absorption at terminal ileum.
- Oral folic acid, 400 µg daily, is adequate for treating folate deficiency. For megaloblastic anaemia 5 mg a day (up to 15 mg in severe malabsorption) is recommended *(2, 3)*.

5.3 Haemolytic anaemias including glucose-6-phosphate dehydrogenase (G6PD) deficiency

Haemolytic anaemia (HA) is suspected when anaemia not related to blood loss, haematinic deficiency or bone marrow failure is seen in a patient with clinical and laboratory features of haemolysis and compensatory erythropoiesis.

In a classical presentation of HA, there is anaemia, jaundice, splenomegaly, reticulocytosis, unconjugated hyperbilirubinaemia, increased lactate dehydrogenase (LDH) and low haptoglobin. Most HAs are extravascular and splenomegaly is a feature of reticuloendothelial expansion. Aspects of clinical and laboratory features are shown in Table 5.2. HA is not a single disease, and each cause has protean manifestations.

Hereditary haemolytic anaemias

Hereditary haemolytic anaemias are classified as:

- membrane defects, for example, hereditary spherocytosis

- haemoglobin defects, for example, sickle cell disease and thalassaemia (discussed in section 5.6)
- enzyme deficiencies, for example, G6PD deficiency.

Acquired haemolytic anaemias

Acquired haemolytic anaemias can be classified as:

- immune-mediated, for example, autoimmune haemolytic anaemia (AIHA); or
- non-immune.

G6PD deficiency

- G6PD deficiency is an X-linked inherited disorder affecting red blood cells (RBCs) in which haemolysis is typically precipitated by an acquired factor.
- G6PD generates NADH and protects RBCs from oxidative injury.
- It is prevalent in regions where malaria was/is endemic.
- Variants of G6PD deficiency are seen.
- Clinical manifestations range from asymptomatic, episodic acute haemolysis to chronic haemolysis.
- Acute haemolysis is precipitated by certain foods (fava beans), drugs (primaquine) or infection.
- Haemolysis is both extravascular and intravascular.
- Peripheral blood smear shows microspherocytes, "bite" cells. Special stains show Heinz bodies.

Management principles

- In acute, severe HA, the rate of decline of haemoglobin and the patient's clinical status determines the management.
- A rapid fall in haemoglobin can be fatal and requires immediate intervention, including red cell transfusions and IV fluids. Consultation with blood bank and haematology experts is recommended.
- For acquired HA, if immune haemolysis is suspected, a direct antiglobulin test (DAT) (Coombs' test) should be performed. A positive result suggests immune-mediated haemolysis, like AIHA. Note that there is a high rate of positivity of DAT caused by antibodies that are unlikely to cause haemolysis.
- In chronic compensated HA, avoid transfusions when possible.
- Other tests should be directed by findings from patient history, examination and peripheral blood film (Table 5.2).

Specific treatment

- *G6PD deficiency*: remove offending agent (drugs, food), transfuse red cells if required for symptomatic anaemia. Transfused blood will not be haemolysed. Provide a list of drugs and foods to be avoided.
- *AIHA*: steroids, splenectomy, rituximab, immune suppression, treat underlying disease. Blood typing and crossmatching may be a challenge *(4)*.
- *Infection-related*: treat infection such as sepsis and malaria.
- *Acute intravascular haemolysis*: transfuse red cells if symptomatic, hydrate to reduce renal damage.
- *Supportive*: prescribe folic acid, avoid iron replacement (unless the patient is also iron deficient).

Table 5.2. Special features of haemolytic anaemia

Clinical feature	**Implications and conclusions**
Pallor, jaundice, splenomegaly	Triad suggestive of haemolytic anaemia, features nonspecific
History of blood transfusion in past 2– 4 weeks	May suggest acute or delayed haemolytic transfusion reaction
Recent fever, infection, medication	Haemolysis related to infection or drugs (immune-related, G6PD)
Laboratory finding	
Macrocytosis, reticulocytosis, polychromasia	Suggests compensatory erythropoiesis (these features also present after acute blood loss, or in response to haematinics)
Increased bilirubin (unconjugated) and LDH	Levels depend on severity of haemolysis
Haptoglobin reduced to absent	Low or unmeasurable levels in intravascular haemolysis
Haemoglobinaemia, haemoglobinuria, haemosiderinuria	Suggests intravascular haemolysis, can lead to renal failure. Causes: haemolytic transfusion reactions, G6PD deficiency, burns, severe sepsis, severe AIHA, falciparum malaria, traumatic (bongo drummers, march haemoglobinuria)
Spherocytes in blood film	Classically in AIHA and hereditary spherocytosis
Schistocytes in blood film	Traumatic haemolysis, thrombotic microangiopathy
Intracellular organisms	Malaria or other parasites
Sickle cells	Sickle cell disease
Hypochromic microcytic cells	Thalassaemias, iron deficiency
Bite cells and blister cells	Suggestive of oxidative haemolysis due to G6PD deficiency or oxidative medications
Target cells	Seen in thalassaemia and haemoglobinopathies

LDH, lactate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; AIHA, autoimmune haemolytic anaemia.

5.4 Malaria

Etiology

Malaria is caused by one of five species of plasmodium: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Transmission is mainly by the bite of an infected female *Anopheles* mosquito, but in rare cases, it may occur after transfusion of infected blood or transplacentally. In 2016, there were an estimated 216 million cases of malaria worldwide, with 90% in Africa, followed by South-East Asia.

Pathogenesis

The plasmodium life cycle takes place in two hosts:

- human: asexual cycle, termed schizogony.
- mosquito: sexual cycle in female *Anopheles* mosquitoes.

Clinical features

The incubation period of malaria varies from 9 to 40 days, depending on the species. The classical features are fever with chills and rigours, occurring in paroxysms. Severe malaria requires urgent intervention.

Diagnosis

Microscopic demonstration of the malarial parasite remains the gold standard. Thin and thick blood smears, stained with Giemsa, are required. A thick film is more sensitive than thin film, but not adequate to detect species or degree of parasitaemia. Microscopic diagnosis requires a trained operator.

Rapid diagnostic tests (RDTs), using finger-prick blood to detect antigens specific to the species of plasmodium have high sensitivity, but need quality control. These are particularly useful in areas where microscopy is not available. The RDTs are:

- histidine rich protein (HRP2): for *P. falciparum*;
- LDH: can be specific for *P. vivax* and *P. falciparum* or pan-malarial;
- aldolase: pan-malarial aldolase.

Management

The most important antimalarial drugs are listed in Table 5.3. The choice of antimalarial therapy is determined by the prevalent plasmodium species as well as the drug resistance patterns and is best summarized by the regional malaria control programme. For severe malaria, parenteral therapy is recommended. Various artemisinin-based combination therapies (ACT) are available. WHO-recommended fixed-dose combinations are preferred. For chloroquine-sensitive plasmodium species (for example, *P. vivax*), chloroquine can be used *(5)*.

Table 5.3. Drugs for the treatment of clinical malaria

Most effective agents for drug-sensitive plasmodium species	Artemisinin derivatives (artesunate, artemether, dihydroartemisinin), chloroquine, amodiaquine, mefloquine, quinine, lumefantrine
Synergistic lower efficacy drugs	Doxycycline, sulfonamides, pyrimethamine
Artemisinin-based combination therapies (ACT)	artesunate + amodiaquine; artemether + lumefantrine; artesunate + mefloquine; artesunate + sulfadoxine-pyrimethamine; dihydroartemisinin + piperaquine
Gametocidal and for exo-erythrocytic stages (radical cure)	Primaquine (can cause haemolysis in G6PD deficiency)

G6PD, glucose-6-phosphate dehydrogenase.

Blood transfusion

The decision to transfuse blood is based on the degree and rapidity of anaemia development, the physiological state of compensation and availability of safe blood. As a general guideline, transfusion should be considered if the haemoglobin level falls to below 7 g/dl in adults and to below 5 g/dl in children based on their symptoms and signs.

5.5 HIV/AIDS

HIV infection and AIDS is caused by viruses belonging to the family of human retroviruses and the subfamily of lentiviruses, mainly HIV-1 and occasionally HIV-2.

Transmission

The highest risk of acquiring HIV per exposure is after transfusion of blood contaminated with the virus. Other modes of transmission are sexual, needle-stick and transplacental. However, blood transfusion is a rare cause of HIV transmission in many countries as the risk of transmission has been greatly reduced by the implementation of appropriate procedure for donor selection and the blood screening.

Stages and clinical course of HIV infection.

After viral transmission to an individual, there are classically three clinical stages.

1. Acute HIV infection: the patient may be entirely asymptomatic, or develop a viral "infectious mononucleosis" type of illness with fever, myalgias, sore throat, adenopathy and skin rash. The HIV viral load is high.

2. Chronic HIV infection without AIDS.

3. AIDS: characterized by a CD4 count <200 cells/mm^3 or any AIDS-defining condition.

AIDS-defining illnesses can be classified according to infecting organism, pathology or organ involvement with different clinical manifestations. A high index of suspicion is required to diagnose underlying HIV/AIDS. A simplified categorization is given in Table 5.4.

Table 5.4. AIDS-defining conditions

AIDS-defining illnesses, classified in broad groups	
Bacterial infections (multiple, recurrent)	• Salmonella septicaemia • Pneumonia
Fungal infections	• Candidiasis • Coccidiodomycosis • Cryptococcosis • Histoplasmosis • *Pneumocystis jirovecii* pneumonia
Viral	• Cytomegalovirus (CMV) disease (other than liver, spleen, lymph nodes), retinitis • Herpes simplex: chronic ulcers or bronchitis, oesophagitis, pneumonitis
Mycobacterium	• *Mycobacterium tuberculosis* • *Mycobacterium avium* complex or *kansasii* or other species: disseminated or extrapulmonary
Parasitic	• Toxoplasmosis of the brain • Cryptosporidiosis, chronic intestinal
Central nervous system	• Progressive multifocal leukoencephalopathy (PML) • Encephalopathy attributed to HIV
AIDS-defining illnesses, classified in broad groups	
Malignancy	• Cervical cancer, invasive • Kaposi's sarcoma • Lymphoma: Burkitt's • Lymphoma: immunoblastic • Lymphoma: primary brain
Wasting syndrome of brain	

Source: Adapted from Centers for Disease Control and Prevention *(6)*.

Management

Individuals infected with HIV are treated with combination antiretroviral therapy (ART). This treatment has led to a major reduction in morbidity, mortality and spread of disease by reducing viral loads. An ART regime generally consists of three agents, a dual nucleoside combination plus a third agent from another class to prevent and treat any resistant strains (Table 5.5).

Due to provision of low-cost generic drugs, funding and political support, the availability of ART in low- and middle-income countries has increased tremendously. Different strategies and drug combinations are being used in various countries and the regional recommendations should be followed.

Table 5.5. Drugs used in the treatment of HIV/AIDS

Class of drugs	Specific medications
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Lamivudine, zidovudine, tenofovir, abacavir, emtricitabine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine, efavirenz, etravirine, rilpivirine
Protease inhibitors	Ritonavir, darunavir, atazanavir
Entry inhibitors	Maraviroc, enfuvirtide
Integrase inhibitors	Raltegravir, elvitegravir, dolutegravir

Anaemia and blood transfusion in HIV/AIDS patients

There are multiple causes of anaemia in people living with HIV/AIDS, including chronic inflammation, infections, medications and deficiencies *(7)*. Management is symptomatic with treatment of the cause. Transfusions are indicated as per the recommendations given in earlier sections.

5.6 Bone marrow failure

Bone marrow (BM) failure results in an inability to produce adequate blood cells, which manifests as anaemia, leukopenia and thrombocytopenia – alone or in combination as pancytopenia. Examples of the various causes are shown in Table 5.6.

Table 5.6. Examples of causes of bone marrow (BM) failure

Mechanism	Main causes
Hypocellular BM	
Aplastic anaemia	• Idiopathic in 70–80% of cases • Post-hepatitis (likely autoimmune): 10–15% of cases • Some medications for example, chloramphenicol • Inherited: Fanconi's anaemia and many other causes now increasingly recognized using molecular diagnostics
Hypoplastic with abnormal cells	• Hypoplastic myelodysplastic syndrome (MDS) • Hypoplastic acute leukaemia
Cellular BM	
Infiltration	Acute leukaemia, lymphoma, myeloma, metastasis
Megaloblastic	Vitamin B12 or folate deficiency
Normal hypercellular	Hypersplenism
Systemic disease	Kala-azar, tuberculosis

Clinical manifestations

The clinical manifestations are caused by the cytopenias as well as the underlying disorders.

- *Anaemia*: in BM failure, the fall in the haemoglobin level is generally slow (at 1 g/dl per week) unless there is bleeding or haemolysis.

- *Thrombocytopenia*: bleeding is mainly in the skin (petechiae, ecchymosis) and mucosa (gums, epistaxis, GI bleeding, menorrhagia). Spontaneous serious bleeding occurs if platelets levels are <10 000/µl (intracranial, retinal, GI), while bleeding after trauma or surgery may occur with milder thrombocytopenia.

- *Neutropenia*: sudden onset of severe infections (bacterial or fungal) can occur when absolute neutrophil count is <500/µl.

Underlying disease-related features vary according to the underlying cause, which includes a wide range of inherited and acquired disorders.

Investigations

The most important investigations are complete blood counts (CBC), peripheral blood film and BM examination. Further investigations depend on the likely cause, and may include flow cytometry, cytogenetics and microbiological testing.

Management

The management of BM failure syndromes is complex and based on the underlying cause. An outline is given in Table 5.7. Aplastic anaemia is relatively more common in low- and middle-income countries and treatment requires sophisticated resources *(8)*.

The indications for transfusion of blood components are covered in other sections. Due care should be taken to minimize risks of alloimmunization and transfusion-related infections. Use of granulocyte colony-stimulating factor (G-CSF) and tranexamic acid are covered in other chapter.

Table 5.7. Principles of management of BM failure syndromes

Cause	Treatment
Supportive care	
Anaemia	Transfuse red cells if anaemia is symptomatic and severe
Thrombocytopenia	• Platelet transfusions if bleeding, or prophylactically • Tranexamic acid
Neutropenia	Use G-CSF selectively in life-threatening infection. Granulocyte transfusion can be considered in very severely infected patients if resources are available
Infection and fever	Use antibiotics and antifungal agents early, empirically. See guidelines on "febrile neutropenia"
Exposure to toxins	Stop exposure to potentially myelotoxic drugs or chemicals

Cause	Treatment
Specific treatment	
Aplastic anaemia	Based on resources and etiology: • Allogeneic bone marrow transplantation (BMT) if a donor is available and age of patient is <40–50 years • Anti-thymocyte globulin and cyclosporin if no donor is available or age of patient is >40–50 years • Anabolic steroids, eltrombopag
Megaloblastic anaemia	Vitamin B12, folic acid
Infective causes	Treat the infection
Malignancy-related	Specialized oncology therapy

G-CSF, granulocyte-colony stimulating factor.

5.7 Genetic disorders of haemoglobin

Genetic disorders of haemoglobin are the most important inherited monogenic disorders and beta- thalassaemia and sickle cell disease are the most frequent of these. These haemoglobinopathies are seen predominantly in malaria-endemic areas, as the carrier state provided a survival advantage against the severe types of malaria.

Sickle cell disease (SCD) is a qualitative globin defect. This is due to an abnormal beta-globin allele carrying the sickle mutation, which leads to sickle cell trait or SCD. There are three states:

- Homozygous state (HbSS): this is the most severe.
- Compound heterozygous states (HbSC, HbS/beta thal): these tend to be less severe than HbSS.
- Carrier state: HbAS: this is not usually clinically significant.

In sub-Saharan Africa, more than 300 000 newborns have HbSS, while the trait is present in 10–20% of the population in central Africa.

Thalassaemias are quantitative globin defects. Mutations in the alpha- or beta-globin genes lead to reduced or absent alpha or beta chain production, termed as thalassaemia. The most severe form is beta- thalassaemia in which the beta-globin chain is reduced or absent.

Sickle cell disease

Sickle haemoglobin is less soluble than adult or fetal haemoglobin and deoxygenated sickle haemoglobin (HbS) undergoes polymerization, binding to the RBC membrane, which increases its rigidity. The affected RBC morphologically resembles a sickle. Intravascular sickling causes vaso-occlusion of microcirculation, release of cytokines, leukocyte interactions with tissue ischaemia and damage.

The diagnosis of SCD is made after birth as the fetal haemoglobin declines. Investigations include microscopy (sickle cells), haemoglobin electrophoresis, high performance liquid chromatography (HPLC) and/or DNA testing. For low-resource countries, point-of-care (POC) testing can be used for screening. In a recent trial a POC test kit, using test

strips embedded with monoclonal antibodies against haemoglobin A, S and C, could detect them by visual inspection in about 10 minutes at a low cost (<US$ 2 per test) *(9)*. Other technologies that simplify detection of SCD are being developed and tested.

The main complications seen in sickle cell anaemia can be acute or chronic. They include:

- Vaso-occlusive crises: pain crisis, acute chest syndrome, stroke, priapism, renal infarction and splenic infarction.
- Infections (due to splenic dysfunction) and sepsis: pneumococcal, haemophilus influenza and meningococcal infection.
- Acute crises characterized by a sudden fall in the haemoglobin level, which can be life- threatening:
  - aplastic crisis: mainly due to parvovirus B19 infection, with a sudden drop in reticulocytes, resolving in 2–4 weeks;
  - splenic sequestration: sudden pooling of blood in the spleen;
  - haemolytic crisis: exacerbation of haemolysis.
- Chronic organ damage: neurological decline, pulmonary arterial hypertension, renal impairment, sickle nephropathy, pigment gall stones, jaundice, folic acid deficiency and iron overload.

Management

The principles of management are outlined below:

- Infection prevention: immunization (pneumococcal haemophilus and meningococcal), penicillin prophylaxis
- Pain control: analgesia, hydration, oxygen, hydroxyurea
- Acute crisis: exchange RBC transfusion whenever possible, otherwise RBC transfusions
- Acute organ dysfunction: hydration, consider exchange transfusion
- Chronic organ damage: hydroxyurea, regular transfusions
- Folic acid deficiency: regular folic acid
- Iron overload: iron chelators.

Hydroxyurea is a useful drug which induces production of fetal haemoglobin (HbF) and has shown clinical efficacy in reducing acute vaso-occlusive events, chronic organ damage, infection, malaria, transfusion and death *(10)*. Treatment with hydroxyurea should be initiated in childhood, with a recommended starting dose of 15–20 mg/kg per day and subsequently increased to the maximum tolerated dose.

Transfusions in sickle cell disease

Blood transfusions are indicated in specific situations for sickle cell anaemia for the following reasons:

1. To increase tissue oxygenation by increasing HbA in acute anaemic crises.

2. To decrease the percentage of sickle haemoglobin to <30% to reduce viscosity, sickling and subsequent vaso-occlusion.

3. To suppress endogenous erythropoiesis.

When there is an urgent need to reduce the percentage of HbS, exchange RBC transfusion can be done by trained personnel, if facilities exist.

Beta-thalassaemia

Homozygous beta-thalassaemia results in reduced production of beta chains, leading to accumulation of unpaired alpha-chains, which precipitate and cause ineffective erythropoiesis and haemolysis of red cells. Combinations of the beta-thalassaemia allele with haemoglobin variants (HbS or HbE) result in varying clinical phenotypes.

Beta-thalassaemia is diagnosed by microscopy (microcytic hypochromic RBCs), haemoglobin electrophoresis, HPLC and/or genetic testing. It is important to take a sample before any blood transfusion.

Although beta-thalassaemia is traditionally classified as thalassaemia major, intermedia and minor, a more practical classification is:

- transfusion-dependent thalassaemia (TDT): requiring regular blood transfusion, before the age of 2 years; or
- non-transfusion-dependent thalassaemia: requiring occasional transfusions at times of growth, surgery, pregnancy and stress.

Heterozygous beta-thalassaemia (minor or carrier state) is typically asymptomatic, with only mild hypochromic microcytic anaemia.

Clinical features of beta-thalassaemia (TDT)

- Anaemia: presents by 6–12 months of age, severe haemoglobin deficiency (3–4g/dl).
- Jaundice: haemolysis, gallstones, viral hepatitis (transfusion-related).
- Hepatosplenomegaly: extramedullary haemopoiesis, haemolysis.
- Skeletal deformities: facial changes, deformities in bones.
- Iron overload: skin pigmentation, cardiac, liver and endocrine damage.
- Endocrinopathies: hypogonadism, hypothyroidism, diabetes mellitus (due to iron overload).

The principles of management are given in Table 5.8. With regular blood transfusion and iron chelation, patients who adhere to their treatment have a near normal lifespan *(11)*.

Table 5.8. Management of transfusion-dependent thalassaemia

Measure	Rationale and precautions
Blood transfusion	Keep pretransfusion haemoglobin levels between 9 and 10 g/dl
Iron chelation	Start soon after regular transfusions begin. Available agents: • Deferoxamine: parenteral, subcutaneous, requires pump • Deferiprone: oral, three times a day • Deferasirox: oral once a day
Splenectomy	Beneficial in reducing transfusion requirements in selected cases
Allogeneic bone marrow transplant	Potentially curative; best results if performed in the first decade of life

5.8 Congenital bleeding and clotting disorders

Features suggestive of bleeding disorders (hereditary or acquired) are:

- spontaneous bleeding
- excessive bleeding after trauma, dental extraction, or during menstruation or childbirth
- delayed bleeding after surgery or trauma
- bleeding from multiple sites.

Disorders of bleeding are classified into three main types:

1. Platelet disorders: these include skin bleeding (petechiae, bruising) or from the mucosa (epistaxis, menorrhagia).
2. Coagulation disorders: these include joint bleeding, muscle bleeding, and bleeding during or after trauma or surgery.
3. Vascular disorders: these resemble platelet bleeding disorders.

Investigations

Specific tests for bleeding disorders are platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and, rarely, skin bleeding time. Specific coagulation factor assays are required to diagnose factor deficiencies and platelet aggregation testing is needed to diagnose platelet disorders. Genetic tests for detecting mutations related to congenital coagulopathies can be done in reference laboratories.

Features suggestive of congenital bleeding disorders are:

- family history
- early age of onset

- typical presentation (joint bleeds in patients with haemophilia).

The most severe congenital bleeding disorders are haemophilia A and B, which are due to deficiency of Factor VIII and Factor IX, respectively *(12)*.

- Haemophilias are X-linked recessive disorders (affecting male children of maternal carriers); one third are due to spontaneous mutation.
- Haemophilia A is more common and accounts for 80–85% of all haemophilias.
- Severity depends on level of factor and can be classified as mild, moderate or severe.
- Diagnosis: prolonged aPTT, low Factor VIII or Factor IX level, genetic diagnosis.
- Treatment: factor concentrate replacement can be:
  - episodic (on demand); or
  - prophylactic home-/outpatient-based (to prevent damage).
- Musculoskeletal management is comprehensive and team-based.
- For appropriate care those affected should carry identification with their diagnosis and information on its severity.
- Establish a network of haemophilia treatment centres, based on local resources and in partnership with international centres of excellence.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by a decrease in the level or activity of Von Willebrand factor (VWF). It has the following characteristics:

- mostly autosomal dominant
- clinically presents as platelet disorder (platelet plug formation is impaired)
- diagnosis is by low VWF antigen and activity and low Factor VIII.

Treatment is as described below.

Management principles for common congenital bleeding disorders

1. Avoid antiplatelet drugs: for example, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs).
2. Avoid intramuscular injections.
3. Antifibrinolytic drugs are useful in mild, mainly mucosal bleeding.
4. Desmopressin (DDAVP) releases Factor VIII and VWF from storage pools, raising levels 3- to 5-fold in patients with mild haemophilia A and most types of VWD. It is also useful in the treatment of platelet dysfunction.

5. Factor VIII concentrates, either fractionated plasma-derived (containing other clotting factors) or recombinant can be given.

6. Factor IX concentrates, either fractionated plasma-derived or recombinant can be given.

7. VWF, either fractionated plasma-derived (in factor VIII concentrates) or recombinant can be given.

8. Cryoprecipitate contains fibrinogen, Factor VIII, Factor XIII and VWF but should only be used when fractionated or recombinant specific factor replacement therapy is not available.

9. Fresh frozen plasma (FFP) should only be used when fractionated or recombinant specific factor replacement therapy is not available.

10. Blood transfusion should be used only for replacement of red cells.

The optimum management of haemophilia and VWD requires raising deficient factors to appropriate levels, which is not effectively achievable with FFP, cryoprecipitate or fresh blood. In resource-poor regions, where these are the only products available, they may be used in emergency life- and limb-saving situations. However, they are associated with poorer outcomes and a risk of transfusion-transmitted infections.

5.9 Acquired bleeding and clotting disorders

Features suggestive of bleeding disorders have been described in section 5.7. In contrast to haemophilia where joint bleeding is common, acquired coagulation disorders are characterized by large ecchymoses, deep tissue haematomas and internal bleeding. The major causes of acquired coagulation disorders and their management are outlined below. Important investigations are: platelet counts, PT, aPTT, TT and fibrinogen. Coagulation factor assays, fibrin degradation products (FDP) and platelet function tests may be required in special cases.

Blood components may be required for treatment of severe anaemia (red cell transfusions) or to prevent bleeding (platelet concentrates or clotting factors).

Coagulation disorders

1. *Disseminated intravascular coagulopathy* is characterized by:

   - bleeding from multiple sites and venepuncture sites;

   - usually being caused by an underlying etiology, such as:
     - trauma, burns
     - sepsis
     - obstetric complications
     - snake-bite
     - cancer.

- prolonged PT, aPTT, TT, low platelets, low fibrinogen, increased FDPs, thrombotic microangiopathy and intravascular haemolysis;

- Treatment *(13)*:
  - Treat underlying cause, which determines outcome.
  - Replace deficient clotting factors (plasma transfusion) and platelets when indicted.
  - Avoid heparin.

2. *Vitamin K deficiency* (malabsorption, malnutrition), or vitamin K antagonist anticoagulants (warfarin):

   - PT and international normalized ratio (INR) prolonged (low levels of factors II, VII, IX and X).

   - Treatment:
     - In the case of vitamin K deficiency or if anticoagulation is not required, administer vitamin K, 10 mg orally or intravenously, for 3 days.
     - If anticoagulation is essential, administer:
       - prothrombin complex concentrate (PCC) or FFP
       - low-dose vitamin K <1 mg
       - optimize dose of anticoagulant.

3. *Coagulopathy of liver disease*:

   - Initially PT is prolonged, later aPTT and TT are prolonged and there is a deficiency of most clotting factors.

   - If bleeding is significant, replace clotting factors with FFP or cryoprecipitate.

4. *Heparin overdose*:

   - aPTT and TT are typically prolonged.

   - Stop heparin and use antidote.

5. *Overdose of low-molecular-weight heparin or non-vitamin K antagonist oral anticoagulants (NOAC)*:

   - Routine coagulation tests may be normal.

   - Access to reversal agents varies per country or region.

   - These agents generally have a short half-life: withhold medication; if needed use PCC if available, and supportive care.

   - Other conditions are beyond the scope of this chapter. Seek specialist advice on their diagnosis and management.

Platelet disorders

1. *Immune thrombocytopenia (ITP)*

   - ITP reduces platelet counts (due to increased destruction). Coagulation test (for example, PT, aPTT) results should be normal. BM examination may be normal or it can show an increased number of megakaryocytes (performing a BM biopsy is not routinely required in typical ITP).

   - Treatment:
     - Avoid platelet transfusions unless bleeding is life-threatening (as platelets will be destroyed).
     - Administer steroids or intravenous immunoglobulin (IVIG) as initial therapy if treatment is required. Subsequent therapeutic options include, splenectomy, rituximab, immunosuppressive agents.
     - Administer antifibrinolytics such as TXA.
     - Avoid antiplatelet drugs: for example, aspirin, NSAIDs.

2. *Congenital causes of thrombocytopenia*, due to reduced production:

   - low platelet count, may have other features associated with underlying cause;

   - BM: depends on underlying cause (for example, amegakaryocytic thrombocytopenia);

   - management: refer to section 5.5 (Bone marrow failure).

3. *Platelet dysfunction*

   - mostly due to medications like aspirin;

   - normal platelet counts, abnormal platelet function tests (not required if cause is obvious);

   - stop the drug if possible – bleeding is self-limiting;

   - give platelet transfusion for significant bleeding.

5.10 Management of burn patients

Burns cause injury to the skin and other tissues due to heat. They are classified according to the depth of injury:

1. superficial: epidermal;

2. partial-thickness: includes portions of dermis;

3. full thickness: all layers of dermis and often subcutaneous tissue injured;

4. extension to deep tissues (fourth-degree): underlying soft tissue.

Various methods are available to assess total body surface area (TBSA).

- Rule of nines (valid for adults): head is 9% TBSA, each arm 9%, each leg 18%, anterior and posterior trunk are each 18%, and perineum is 1%.
- Palm method: the palm of the patient's hand including fingers is 1% TBSA.

The extent (surface area) of burns determines whether a patient should be transferred to a specialized unit. The patient should be transferred to a burns unit if burns affect >10% of body surface area in children or elderly people, or >20% in adults. Transfer to a burns unit is also necessary if >5% of the body surface area is affected by full thickness burns and also if burns involve the face, eyes or genitalia, as well as for patients with inhalation burns.

Patients need urgent resuscitation with maintenance of airways, breathing and circulation. Fluid replacement is required in adults if burns affect >15% of the body surface area (10% in children), to ensure organ perfusion with the aim of urine output between >0.5 and 1.0 ml/kg per hour or 30–50 ml per hour in adults. The following are also required:

- disability control
- pain control
- management of hyper-catabolism
- infection prevention
- wound care.

In regions where there are no dedicated burns centres, the survival chances of patients with >50% burns are very low. If there are multiple patients with burns injuries, triage may be required to save the greatest number.

Blood transfusion in burns patients

In patients with severe burns, or when more than 10% of the body surface area is involved, it is common for anaemia to develop due to acute thermal injury, as well as blood loss following skin grafting and surgery.

Formerly, it was common practice to transfuse blood to keep haemoglobin levels >10 g/dl. More recent studies suggest that the transfusion trigger should be reduced and liberal blood transfusion (i.e., transfusion of RBCs at higher haemoglobin thresholds) may be detrimental *(14)*.

- Anaemia is well tolerated so long as intravascular volume is maintained.
- There is no universal haemoglobin threshold value for blood transfusion in burns patients. It should be based on the patient's clinical condition, physiological state, blood volume and need for surgical intervention.
- Supplementation with folic acid and vitamin B12 should be considered.
- Iron supplementation should be avoided, as iron therapy can increase the risk of infections and production of free radicals.

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