PART 16

HAEMATOLOGICAL DISORDERS AND MALIGNANCIES
Anaemias of childhood

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Definition

Anaemia is a common medical condition throughout all ages of childhood. However, the common causes vary with age. Anaemia refers to a reduction in haemoglobin (and hence red cell mass) below that which is considered normal for the patient in question. Normative haemoglobin data differs with age and, in teenage years, gender. Clinicians need to ensure that, when considering a diagnosis of anaemia, correct age-specific and, where applicable, sex-specific reference ranges are used. These reference ranges may vary according to the laboratory analyser in use. Thus each laboratory should report their own specific age-related reference ranges. An example of the age-related variation is shown by the reference ranges in Table 16.1.1. The majority of reference ranges in clinical use reflect 95% confidence intervals, so that 2.5% of individuals who are in fact ‘normal’ would be expected to consistently have haemoglobin levels just below the lower limit of the reported reference range.

Physiology

The prime function of haemoglobin is tissue oxygen delivery. Hence anaemia threatens this critical bodily function. Acutely, severe anaemia can lead to hypoxic tissue injury, and chronic anaemia can lead to growth failure and organ dysfunction as a result of chronic hypoxia or failure of compensatory mechanisms. The physiology of tissue oxygen delivery is critical to understand, as it enables the clinician to understand the concepts of relative anaemia and to determine appropriate treatment of the anaemic patient.

Tissue oxygen delivery (ml/min) = cardiac output (l/min) \times \text{haemoglobin (gm/l)} \times \text{haemoglobin saturation (\%)} \times 1.34 (ml/g),

where 1.34 is a constant and represents the amount of oxygen carried by 1 g of normal haemoglobin.

The key issues in this basic physiological equation are that:

- the parameters are multiplied, such that small decreases in cardiac output and haemoglobin and haemoglobin saturation lead to an overall large decrease in tissue oxygen delivery. Thus patients with cardiac disease may tolerate less reduction in haemoglobin before developing tissue hypoxia, and hence often have considerable urgency in treating their anaemia. No single haemoglobin (Hb) level can be used as a indication for transfusion therapy as these other factors need to be considered
- in the presence of anaemia, cardiac output must be increased to maintain tissue oxygen delivery (Hb saturation cannot be increased above 100%). Failure of this compensatory mechanism or limitation of cardiac output by another disease will result in tissue hypoxia. Cardiac output is determined by cardiac stroke volume and heart rate. Therefore, heart rate is an important measure of the stress the anaemia is placing on the patient’s cardiac reserve. All anaemic patients should have their vital signs, especially heart rate and respiratory rate, assessed as part of their initial medical evaluation, and these parameters should be used to monitor progress and response to therapy
- Hb saturation is normally close to 100% in children without cyanotic congenital heart disease or significant lung pathology. Thus, in otherwise well children with severe anaemia, or children in whom the Hb saturation is measured as 99–100%, inspired oxygen therapy makes little if any contribution to improving tissue oxygenation. Recovery of red cell mass (and hence Hb) is the most effective therapy
- in children with cyanotic congenital heart disease or pulmonary pathology, the natural compensation for reduced Hb saturation is to increase Hb concentration. Hence, if a child with cyanotic congenital heart disease who usually has a relatively increased Hb was to develop a ‘relative anaemia’, they might develop symptoms of anaemia at Hb levels that would be considered normal in most children. Treatment of ‘relative anaemia’, if required, is based on the same principles as treatment of ‘true anaemia’.

Clinical presentations

Children with anaemia most often present with pallor (reflecting the reduced Hb) or signs of reduced exercise tolerance (reflecting inability to increase tissue oxygen delivery to meet the demands of exercise). Reduced exercise tolerance manifests differently according to age. In infants, poor feeding is
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Often described. In older children, shortness of breath on exertion or generalized lethargy are more common. Alternatively, incidental finding of anaemia when full blood examination has been performed for another indication is also very common.

Once the presence of anaemia is confirmed, thorough history taking and examination of the patient is required. Patient age and the duration of symptoms is important as a first step in determining the likely aetiology of the anaemia.

In addition, during the history and examination, other key considerations are:

- is there evidence of cardiac decompensation or other adverse events as a result of the anaemia? This clearly makes appropriate therapy a matter of urgency
- are there clues to the aetiology of the anaemia?
- is there evidence of multilineage cytopenias (neutropenia and thrombocytopenia)?
- is there evidence of an associated, perhaps causative, disease?

Information that assists in answering these questions is shown in Table 16.1.2.

<table>
<thead>
<tr>
<th>Table 16.1.1 Normal haemoglobin values for age</th>
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<td>Age</td>
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<tr>
<td>Birth</td>
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<td>&gt;12 years (male)</td>
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<th>Table 16.1.2 Relevant information required on history and examination for patients with anaemia</th>
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<td>Critical question</td>
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| Cardiac decompensation | Exercise tolerance  
Heart rate and respiratory rate  
Signs of congestive heart failure  
Altered conscious state, irritability, restlessness |
| Aetiology | Duration of symptoms (bone marrow failure and haematinic deficiency usually have a longer duration of symptoms)  
Family history (heritable spherocytosis, G6PD deficiency, haemoglobinopathies and others are inherited causes of anaemia. Maternal history, e.g. veganism, may be associated with B12 deficiency in infants)  
Birth and neonatal history (blood loss at birth, birth asphyxia and maternal blood group compatibility are all important in assessing neonatal anaemia)  
Jaundice at birth may give a clue to an episodic haemolytic disorder in older children  
Presence or absence of jaundice (haemolysis)  
Drug exposure: as a cause of haemolysis, or bone marrow suppression  
Blood loss: trauma, recent surgery, iatrogenic in neonates, epistaxis, menstrual loss  
Dietary history: iron deficiency can be predicted in infants less than 12 months of age fed cow’s milk, or in toddlers who have failed to transfer to solid foods adequately |
| Multilineage cytopenias | Bruising or bleeding, especially petechiae (thrombocytopenia)  
Infection, mouth ulceration (neutropenia) |
| Associated disease | Gastrointestinal symptoms (e.g. coeliac disease, inflammatory bowel disease)  
Joint or bone pain (e.g. leukaemia, sickle cell disease, arthritis)  
Renal disease  
Malignancy  
Infection: as a primary cause (e.g. malaria), a precipitant of acute deterioration in a more chronic anaemia, or a trigger to acute haemolysis  
Neurological disorders, developmental delay/regression, failure to thrive may reflect functional B12 deficiency in infants. Pica may be associated with iron deficiency  
Eating disorders in older children  
Bleeding disorders |
Initial investigations

Progressive selective investigation, guided by the history, the clinical findings and the result of the blood count, is recommended. The first investigation will be a blood count, which automatically includes red cell indices (full blood examination (FBE) or complete blood count (CBC)), reticulocyte count and examination of the blood film. These initial investigations will usually allow classification of the anaemia. The presence or absence of polychromasia on the blood film, and the reticulocyte count, enable the anaemia to be classified as regenerative or aregenerative. This is a most important initial decision to be made. The red cell indices, in particular the mean corpuscular volume (MCV), and the blood film, enable the anaemia to be classified by red cell size into microcytic, normocytic and macrocytic. Finally the blood film enables any specific red cell morphology to be determined and confirms the platelet and leukocyte parameters. At this stage a probable aetiology is likely and thus the direction of further investigations can be determined.

In the interpretation of these initial tests, there are a number of important considerations. First, sample integrity is vital, and preanalytical variables such as a clotted or inadequately mixed specimen can cause significant erroneous results. If the results do not match the clinical findings, repeat testing should always be considered. Second, MCV also varies with age. MCV is highest in the neonate (98–118 fl), falls to its lowest value between 6 and 24 months of age (79–86 fl), then increases progressively throughout childhood (75–92 fl). A low MCV indicates microcytosis and a high MCV indicates macrocytosis. Reticulocyte counts may be expressed as a percentage of the total red cell count (3–7% in the neonate, thereafter 0–1%), or more usually as an absolute count (normally 20–100 × 10⁹/l). If expressed as a percentage, the reticulocyte count can be misleading, so an absolute count is preferable. An increased reticulocyte count indicates active regeneration of red cells, seen after blood loss, haemolysis or in response to correct haematinic therapy. Blood loss and previous haematinic therapy can usually be excluded on history, so that an increased reticulocyte count is often suggestive of haemolysis. A low reticulocyte response in the presence of anaemia indicates a lack of marrow response, because of a deficiency of the necessary iron or vitamins or inappropriate therapy for the anaemia, or inability to respond, such as marrow aplasia or infiltration.

Examination of the blood film

This is as important as the evaluation of the red cell indices, leukocyte count and platelets. The presence of abnormal red cell size, shape, inclusions, Hb content, and evidence of regeneration will usually suggest the cause of the anaemia and direct the next stage of investigation. The presence of abnormal leukocytes or abnormal platelet numbers may suggest a specific diagnosis such as leukaemia. Examples of a normal blood film and blood films in some conditions associated with anaemia are shown in Figure 16.1.1. Further investigations are suggested by the algorithms in Figures 16.1.2 and 16.1.3.

Practical points

Determining the urgency of investigation of anaemia

- Mild anaemia (Hb > 8 g/l) may still require urgent investigation and management, depending on the cause. Hence, until the cause of anaemia has been determined in a broad sense, discharge from emergency department/hospital should not be considered
- Acute regenerative anaemia (blood loss or haemolysis) has the capacity to rapidly develop severe anaemia. Blood loss is usually obvious, so haemolysis must be excluded or the rate of haemolysis (multiple Hb levels over a number of hours) understood before a patient can safely leave hospital. Thus a FBE, reticulocyte count, blood film examination and serum bilirubin are almost always indicated in initial investigations
- Megaloblastic anaemia in infancy, irrespective of the level of anaemia, requires urgent investigation because of the potential for rapid neurological deterioration. Hence the MCV is a crucial piece of information in the initial FBE, as is the blood film examination. A history of failure to thrive and neurological impairment in infancy should lead to consideration of megaloblastosis, as anaemia is often not the presenting symptom. An FBE with careful consideration of the red cell parameters is always warranted in this circumstance
- Anaemia as part of a multilineage failure may have a degree of urgency because of the potential for febrile neutropenia or thrombocytopenic haemorrhage

Specific disease entities

Disorders of stem cell proliferation

Pluripotential stem cell failure (aplastic anaemia)

Normal marrow function is dependent on stem cell renewal and maturation of all cell lines. Failure of stem cell proliferation and differentiation results in aplastic anaemia. Both genetically determined and acquired forms occur (Table 16.1.3).

Fanconi anaemia

Fanconi anaemia, the commonest of the genetic forms of aplastic anaemia, is recessively inherited and is characterized by a variable phenotype,
progressive marrow failure and an increased risk of malignancy. There appear to be multiple gene defects in this condition which explains the diversity of clinical manifestations.

Approximately 75% of children have congenital abnormalities, with a wide range of defects. The commonest are café au lait spots, short stature, microcephaly and skeletal anomalies, with thumb and radial hypoplasia or aplasia being most characteristic. Renal anomalies, stenosis of auditory canals, micro-ophthalmia, hypogenitalism and a variety of anomalies of the gastrointestinal tract may also occur. The child shown in Figure 16.1.4 shows many features of this disorder.

The diagnosis may be suspected at birth if there are congenital abnormalities. Haematological
abnormalities are rare at birth. Pancytopenia develops gradually, usually by the age of 10 years. Onset is earlier in boys than girls. Macrocytosis is followed by thrombocytopenia, neutropenia, then anaemia. Bone marrow aspirate and trephine show hypoplasia or aplasia.

In contrast, infants with the thrombocytopenia–absent radii (TAR) syndrome are severely thrombocytopenic at birth and have radial anomalies without thumb abnormalities.

The diagnosis of Fanconi anaemia is established by special chromosome studies of lymphocytes. Chromosomes from patients with Fanconi anaemia show markedly increased spontaneous and alkylating agent (cells incubated with mitomycin C or diepoxybutane) induced chromosomal breaks, gaps, rearrangements, exchanges and endoreduplication. Antenatal diagnosis is possible.

Androgen therapy may produce long remissions of the anaemia but has little effect on thrombocytopenia and neutropenia. Its use is associated with masculinization and therefore is undesirable in young children, particularly girls. Granulocyte–macrophage colony-stimulating factor has been used with some success. Bone marrow transplantation offers the only possibility of cure of the aplasia. Supportive care with transfusions and antibiotics is required for patients without a marrow donor but death from infection, bleeding or the development of leukaemia usually occurs within a decade of diagnosis.

**Acquired aplastic anaemia**

A number of agents may cause marrow failure, either in a dose-dependent fashion (irradiation and cytotoxic drugs) or in an idiosyncratic fashion. Some viral infections are associated with marrow suppression. No cause is identified in about 50% of children.
Further Investigation of aregenerative anaemias

Polychromasia/increased reticulocytes: regenerative anaemia

- Biochemical markers of haemolysis*
  - No
  - Consider blood loss, recently treated haematitic deficiency, or recovering aplasia

- Yes
  - Consider Problems intrinsic or extrinsic to the red cells#

Intrinsic problems:
1. Membrane: hereditary spherocytosis or pyropoikilocytosis (in newborns)
2. Enzyme: G6PD deficiency, pyruvate kinase deficiency, rare defects
3. Haemoglobin: thalassemia, sickle cell, other haemoglobinopathies, unstable haemoglobin

Extrinsic problems:
1. Antibody mediated
2. Mechanical
3. TTP/HUS
4. Infection (severe sepsis, malaria)
5. Drugs

Relevant investigations:**
1. Direct Antiglobulin (Coombs) Test, viral serology, mycoplasma serology (if cold antibody)
2. Imaging of cardiac lesion or to search for vascular anomaly
3. Renal function
4. Blood cultures, thick and thin films if relevant

Reasonable first line investigation screen in haemolytic patients includes FBE, reticulocyte count, serum bilirubin, E5M, G6PD assay, Hb HPLC, DAT, renal function, and in neonates urine and blood culture.

BEWARE: Severe intravascular haemolysis (G6PD, some antibodies, microangiopathic (TTP/HUS, mechanical, sepsis) ) may release free Hb which falsly elevates the measured haemoglobin. Always check that the red cell count is proportional to the measured Hb. Methaemoglobinemia in severe G6PD haemolysis may increase tissue hypoxia for any given measured haemoglobin. All acute haemolytic anemias have the potential for life threatening haemolysis to develop within hours and as such should be treated with extreme caution. In general, admission to hospital, close monitoring of vital signs and FBE until the tempo of the haemolysis is established is recommended. Folate deficiency in haemolysis may reduce the ability of the bone marrow to respond and worsen the anemia as well as causing diagnostic confusion.

* Biochemical markers of haemolysis: in most cases the presence of an elevated unconjugated serum bilirubin is sufficient. Haptoglobins and LDH are frequently non contributory in small children.

# Blood film may be diagnostic. E.g. G6PD- blister and bite cells, spherocytosis (in neonates reflects either HS, ABO incompatibility or severe sepsis), sickle cells

** Osmotic fragility requires a large blood sample (up to 20 ml) and is not performed in many routine laboratories. The test is time-consuming and unsuitable for use in small children because of the volume of blood required. ESM requires less than 0.5 ml and is now offered by some laboratories instead of osmotic fragility. G6PD assay may be elevated in the presence of a reticulocytosis so borderline results should be repeated after the acute event and at least 3 months post transfusion if the clinical and blood film findings are suggestive. Most laboratories perform HPLC to detect abnormal haemoglobins and use electrophoresis to identify abnormal bands. DNA testing should not be ordered acutely, but as a confirmatory test electively. HPLC and sickle solubility are most useful initial tests.

+ Antibody mediated haemolysis may be warm (usually IgG, spherocytes on film) or cold (usually IgM, +/- complement fixation, agglutination on film). Haemolysis due to mechanical, TTP/HUS or severe sepsis (DIC) are usually characteristically microangiopathic in blood film morphology

## The Direct Antiglobulin (Coombs’) Test (DAT) is crucial to perform in all haemolysing children as IgG mediated haemolysis can be life threatening, and so the diagnosis should not be missed.
with marrow failure. Fanconi anaemia must be excluded by cytogentic studies, as not all affected individuals have congenital abnormalities.

Common causes are:

- drugs: chloramphenicol, anticonvulsants, non-steroidal anti-inflammatory agents and cytotoxic drugs
- chemicals: benzene, organic solvents, insecticides
- viral hepatitis: usually non-A, non-B, non-C hepatitis, less commonly Epstein–Barr virus, cytomegalovirus, parvovirus or human immunodeficiency virus (HIV)
- preleukaemic: acute lymphoblastic leukaemia occasionally has a transient period of aplasia before the onset of the disease
- paroxysmal nocturnal haemoglobinuria.

Presentation is with the gradual onset of pallor, lethargy and bruising. There may be a history of recent infection. Physical examination reveals little other than pallor, bruising, petechiae and oral mucosal bleeding. Importantly there is no enlargement of liver, spleen or lymph nodes but there may be fever and focal infection associated with the neutropenia.

The blood shows a pancytopenia with a normocytic anaemia without regeneration. Bone marrow aspirate and trephine biopsies reveal absent or decreased haemopoiesis.

Initial management depends on the severity and clinical manifestations of the aplasia. Potentially causative agents must be removed. Infections are treated vigorously. Supportive red cell and platelet transfusions are given as required. The general principles of transfusion therapy in aplastic anaemia are to avoid HLA sensitization by using leukocyte-depleted cellular products, and to minimize alloimmunization by minimizing donor exposure through the appropriate selection of blood products. Early referral to a tertiary centre is vital. Although a small number of children will recover within a few weeks, bone marrow transplantation from an HLA-compatible sibling is generally regarded as the treatment of choice for severe aplastic anaemia, particularly in the under-5-years age group. Only 30% of children will have a matched sibling donor. For the remainder, antithymocyte globulin, together with granulocyte colony-stimulating factor and ciclosporin, produces improvement or complete recovery in about two-thirds of children. Onset of response may not occur for 2–3 months after initiation of therapy and supportive care during this time is vital. For those failing to respond, unrelated donor transplantation is an option and a donor search should be initiated early.

Red cell aplasia (erythroid stem cell failure)
Isolated aplasia of red cells results in a normocytic normochromic anaemia without reticulocytosis. The platelets and white blood cells are normal. Congenital and acquired forms occur.

Congenital red cell aplasia (Diamond–Blackfan syndrome). This disorder is almost certainly heterogeneous, with sporadic, dominant and recessive forms occurring. The defect has not been determined but the disorder is possibly due to a defect in the erythroid progenitor cell.

Normocytic anaemia may be present at birth and usually is evident by 2–3 months of age. However, diagnosis beyond 1 year of age is reported. Early treatment with steroids results in a reticulocytosis and increase in Hb in about two-thirds of patients. In steroid responders, long-term low-dose steroids are recommended before total weaning is attempted. Some steroid-responsive patients are successfully weaned off steroids but many remain steroid-dependent. Those failing to respond to steroids or
Further Investigation of aregenerative anaemias

**Aregenerative anaemia**

- **Microcytic**
  - Likely causes:
    1. Iron deficiency
    2. Beta Thalassemia minor or alpha thalassemia
    3. Chronic disease/inflammation
  - Rare causes:
    4. Lead poisoning
    5. Sideroblastic anaemia/Pearson’s syndrome

- **Normocytic**
  - Likely causes:
    1. Acute blood loss
    2. Red Cell aplasia*
      a. DBS
      b. TEC
    3. Bone marrow failure
    4. Bone marrow replacement/infiltration
    5. Renal disease
    6. Anorexia / protein malnutrition

- **Macrocytic**
  - Likely causes:
    1. Megaloblastosis
      a. Vitamin B12
      b. Folate
    2. Fanconi’s anaemia
    3. Dyserythropoietic anaemias
    4. Hypothyroidism
    5. Liver disease

**Relevant Investigations:**
- 1. Ferritin#
- 2. HPLC, DNA analysis, family studies
  
  If rare causes suspected:
  - 1. Serum lead
  - 2. Bone marrow aspirate

**BEWARE:** Megaloblastic anaemia in infancy (<2 years) is often accompanied by severe failure to thrive and neurodevelopmental regression. Often these patients deteriorate very rapidly once they have finally reached medical attention, and investigation is a matter of urgency so that replacement therapy can be commenced ASAP and long term neurological sequelae minimized. The bone marrow aspirate confirms megaloblastic tissue quickly, such that treatment can be commenced pending further investigations of child and if a breast fed infant, investigation of the mother for Vitamin B12 or folate deficiency.

*Red cell aplasia may be isolated or part of broader marrow dysfunction. The differential between transient erythroleukopenia of childhood (TEC) and Diamond Blackfan Syndrome (DBS) is often difficult, even with thorough investigations.*

# Investigation of iron deficiency in children needs to be appropriate. In children with classic history of cow’s milk intake before 12 months, or inadequate transition to solids, no investigations may be required after the blood film diagnosis, and treatment should be commenced. In otherwise normal children, ferritin is the most useful investigation and other iron studies are rarely contributory. Ferritin is an acute phase protein, so testing may need to be delayed if an acute febrile illness is coexistent. Full iron studies may be of value in children with complex medical problems.

**In the absence of clear renal, liver or thyroid disease, bone marrow aspirate is indicated for most significant normocytic or macrocytic anaemias.**

Bone marrow aspirates must always be examined in conjunction with the peripheral blood smear, and ancillary investigations. Hence consultation with a haematologist early in the investigation of such patients is often worthwhile. With the exception of megaloblastic anaemia, where bone marrow examination is often an emergency procedure to allow commencement of replacement therapy immediately, BMA can often be performed electively, and should never delay transfusion of a borderline or decompensating patient. In cases of suspected aplasia, bone marrow trephine may assist in assessing marrow cellularity.
Fig. 16.1.3  Further investigation of a regenerative anaemia. *Red cell aplasia may be isolated or part of broader marrow dysfunction. The differential between transient erythroblastopenia of childhood (TEC) and Diamond–Blackfan syndrome (DBS) is often difficult, even with thorough investigation. † Investigation of iron deficiency in children needs to be appropriate. In children with a classic history of cow’s milk intake before 12 months, or inadequate transition to solids, no investigations may be required after the blood film diagnosis, and treatment should be commenced. In otherwise normal children, ferritin is the most useful investigation and other iron studies are rarely contributory. Ferritin is an acute-phase protein, so testing may need to be delayed if an acute febrile illness is coexistent. Full iron studies may be of value in children with complex medical problems. ‡ In the absence of clear renal, liver or thyroid disease, bone marrow aspirate is indicated for most significant normocytic or macrocytic anaemias. Bone marrow aspirates must always be examined in conjunction with the peripheral blood smear, and ancillary investigations. Hence consultation with a haematologist early in the investigation of such patients is often worthwhile. With the exception of megaloblastic anaemia, where bone marrow examination is often an emergency procedure to allow commencement of replacement therapy immediately, BMA can often be performed electively, and should never delay transfusion of a borderline or decompensating patient. In cases of suspected aplasia, bone marrow trephine may assist in assessing marrow cellularity. DEB, diepoxybutane; HPLC, MMA, methylmalonic acid; TCII, transcobalamin II.

Fig. 16.1.4  Child with Fanconi anaemia. Note short stature, absent right radius and thumb, micro-ophthalmia and the presence of a hearing aid.

requiring large doses will need regular blood transfusion and chelation therapy. Bone marrow transplantation has corrected the condition in steroid-resistant patients.

Acquired red cell aplasia. Pure red cell aplasia (PRCA) is primarily a disease of adults but cases have been documented in teenagers. A large number of disorders, including thymoma, malignancy, autoimmune disease, viral infection and drug administration, have been implicated. Therapy is directed primarily toward the cause but may include immunosuppression, plasmapheresis, thymectomy and splenectomy.

Transient erythroblastopenia of childhood (TEC). This self-limiting, regenerative anaemia occurs typically in children between 1 and 3 years of age. The aetiology remains unclear but antibodies directed against early red cell precursors have been documented in some children. Parvovirus B19 has not been consistently isolated.

The typical presentation is with pallor of gradual onset in an otherwise well child. The only abnormal clinical finding is pallor. The anaemia may be marked, without evidence of regeneration. A bone marrow aspirate will generally show absent or diminished erythropoiesis but if spontaneous recovery is already occurring at the time of presentation there may be many early erythroid progenitors present.

As the onset of the anaemia is gradual, most children will have compensated well and tolerate quite marked degrees of anaemia. If, however, there is no evidence of recovery occurring by the time the Hb falls to levels below 50 g/l, transfusion is likely to be required. Folic acid supplements should be given during the recovery phase. Spontaneous recovery usually occurs within 1–2 months and it is unusual for more than one transfusion to be required. Steroids have no role in the management of this disorder.
In some cases the distinction between DBS and TEC is extremely difficult. Neither the clinical scenario nor the bone marrow findings are absolutely diagnostic. In such cases, transfusion therapy without steroids may be useful initially to enable the patient every opportunity to recover. If steroids are introduced early, on the presumption of DBS, and recovery occurs, one is reluctant to cease steroid therapy quickly for fear of relapse and a spontaneously recovering TEC could potentially receive unnecessary steroids for a prolonged period.

Transient erythroid aplasia in chronic haemolytic anaemias. An aplastic crisis may occur in patients with one of the chronic haemolytic anaemias, such as sickle cell disease, hereditary spherocytosis and autoimmune haemolytic anaemia. Infection with human parvovirus B19 has been documented as the usual cause. Folic acid deficiency may be a further precipitating factor.

Because of the shortened red cell survival, there is a precipitous fall in Hb when erythroid proliferation ceases. Pallor and lethargy develop relatively quickly. The absence of jaundice, lack of increase in the degree of splenomegaly and absence of a reticulocyte response enables one to distinguish an aplastic crisis from increased haemolysis. Blood transfusion is likely to be required. Spontaneous recovery usually begins within 10–14 days.

Marrow replacement

Infiltration with neoplasia, particularly leukaemia, is the commonest cause of marrow failure in childhood. Several other childhood malignancies (neuroblastoma, non-Hodgkin lymphoma, Ewing sarcoma and rhabdomyosarcoma) metastasize to the bone marrow. Progressive pancytopenia with a normocytic anaemia and an associated shift to the left in the erythroid and myeloid series develops. Nucleated red cells and immature granulocytes (left shift) may be seen in the peripheral blood (leukoerythroblastic blood picture). Replacement of marrow with storage cells (e.g. Gaucher disease), fibrous tissue (myelofibrosis) or bone (osteopetrosis) will have a similar result. Careful examination of the blood film looking for leukaemic blasts, and a bone marrow examination that will identify abnormal cells, are required in any child with pancytopenia.

Dyserythropoietic/ineffective erythropoiesis

Congenital dyserythropoietic anaemias

This group of rare hereditary disorders of erythropoiesis is characterized by ineffective erythropoiesis resulting in shortened red cell survival with associated jaundice, a variable degree of anaemia, with normocytic to macrocytic red cell morphology, and anisopoikilocytosis and fragmentation in some types (Table 16.1.4). Bone marrow findings are characterized by erythroid hyperplasia, multinuclearity and internuclear bridging. The aetiology is unknown. Some patients in whom haemolysis is severe require regular transfusions.

Megaloblastic anaemia

Megaloblastic anaemias in childhood are rare but prompt diagnosis of the cause, especially in infants, is important to prevent potentially irreversible neurological damage, which may result from deficiencies of vitamin B₁₂ or its transport protein transcobalamin II.

Vitamin B₁₂ deficiency

Because the daily requirement for vitamin B₁₂ is low and body stores are generally high, dietary deficiency of vitamin B₁₂ is rare, occurring only after prolonged inadequate intake, as may occur in vegans. Breastfed infants of vitamin-B₁₂-deficient mothers are at risk and may present with anaemia in the first year of life. The commonest causes of maternal deficiency are undiagnosed pernicious anaemia and veganism. In infants with megaloblastosis it is important to determine whether maternal deficiency or transcobalamin II deficiency is the cause. Maternal deficiency requires short-term parenteral therapy of the infant; however, transcobalamin II deficiency requires long-term high-dose parenteral B₁₂ injections. The majority of older children with vitamin B₁₂ deficiency have a malabsorptive problem, either specific to vitamin B₁₂, as in pernicious anaemia, or secondary to inflammation or loss of the ileum, the portion of the small bowel in which vitamin B₁₂ absorption occurs.

Vitamin B₁₂ deficiency results in an anaemia with oval macrocytosis, hypersegmentation of neutrophils and thrombocytopenia. Bone marrow examination shows erythroid hyperplasia with megaloblastosis characterized by abnormally large erythroid and myeloid progenitors, in which nuclear maturation is delayed as compared to cytoplasmic maturation. Intramedullary destruction of erythroid precursors leads to a mild unconjugated hyperbilirubinaemia. Elevated serum homocysteine and urinary methylmalonic acid are useful to confirm the presence of intracellular vitamin B₁₂ deficiency.

Therapy depends on the cause of the vitamin B₁₂ deficiency. Dietary deficiency is treated by an initial dose of parenteral vitamin B₁₂, followed by dietary correction. Abnormalities of absorption, whether due to pernicious anaemia, ileal malabsorption or resection, require long-term intramuscular injection of the vitamin (hydroxycobalamin) at 1–3-month intervals according to the severity of the malabsorption.
Folate deficiency
Daily folate requirements are low but body stores are small. Folate is heat-labile and, although ubiquitous in food, is often destroyed by cooking.

Extra folate is required at times of rapid growth, during pregnancy and in patients with haemolytic anaemia. Deficiency is most likely to occur under these circumstances. Dietary deficiency most commonly occurs in infants fed exclusively on goat’s milk, which is deficient in the vitamin. Malabsorption occurs in generalized malabsorptive syndromes such as coeliac disease and Crohn disease.

Some anticonvulsant drugs, e.g. phenytoin, may interfere with folate absorption, and megaloblastic changes are common among patients taking these drugs.

Inherited disorders of folate metabolism are rare and may present diagnostic difficulty.

Folate deficiency presents with a macrocytic anaemia without neurological abnormality. Oral administration of folic acid is effective in reversing deficiencies. Doses required are small, as 0.1 mg daily produces an optimal haematological response. In patients with increased requirements or malabsorption, higher doses of 0.5–5 mg daily are given. It is essential to exclude coexistent vitamin $B_12$ deficiency before treatment as the haematological picture may improve initially with folate therapy but progression of the neurological effects of vitamin $B_12$ deficiency will still occur.

Defective haem synthesis
Iron deficiency
Iron deficiency is the commonest cause of anaemia in childhood, being particularly common in the first 2 years of life when iron requirements are increased because of rapid growth and dietary intake is often inadequate. Early adolescence is another risk period for development of iron deficiency because of rapid growth.

Low-birth-weight infants and infants having exchange transfusions or frequent blood sampling have low total body iron stores and are at high risk of early development of iron deficiency anaemia, as iron stores and dietary intake are inadequate to keep up with rapid postnatal growth. Breast milk and cow’s milk have a similar iron content but iron bioavailability from breast milk is approximately 50%, compared with 10% from cow’s milk. Breastfed term babies therefore are rarely iron-deficient in the first 6 months of life but iron concentrations in breast

<p>| Table 16.1.4 Anaemias that are due to ineffective erythropoiesis and dyserythropoiesis |</p>
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<td>Unknown</td>
<td>Congenital dyserythropoietic anaemia</td>
<td>Infancy to adulthood (megaloblastosis)</td>
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<tr>
<td></td>
<td>Vitamin $B_12$ deficiency</td>
<td>Transcobalamin II deficiency</td>
<td>Neonaotes–3 months</td>
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<tr>
<td></td>
<td>Congenital</td>
<td>Congenital pernicious anaemia</td>
<td>&lt;3 years</td>
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<tr>
<td></td>
<td>Acquired</td>
<td>Maternal $B_12$ deficiency</td>
<td>3–12 months</td>
</tr>
<tr>
<td></td>
<td>Acquired</td>
<td>Juvenile pernicious anaemia</td>
<td>&lt;10 years</td>
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<tr>
<td></td>
<td>Acquired</td>
<td>Ileal resection</td>
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<td>Folate deficiency</td>
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<td>Dietary deficiency</td>
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<td>Defective haem synthesis (microcytosis)</td>
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<tr>
<td>Reduced/absent globin chain synthesis</td>
<td>Gene deletion/mutation</td>
<td>Beta-thalassaemia major</td>
<td>6 months–5 years</td>
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<td>HBH disease (alpha-thalassaemia)</td>
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<td>Abnormal globin chain production</td>
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<td>Any age</td>
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<tr>
<td></td>
<td>Sickle cell disease</td>
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<td>1–4 years</td>
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milk decline postnatally and the iron content of breast milk is insufficient to meet the needs of the infant over the age of 6 months.

Oral iron supplementation (2 mg/kg/d) is given to low birth weight infants, generally from approximately 3 months of age. Iron-containing foods should be introduced by 6 months of age to all term babies. Most infant formulae are iron-fortified. Infants weaned early on to cow’s milk (before 12 months of age), particularly those in whom milk continues to be the major component of the diet without the appropriate introduction of mixed solid feeding, are the group presenting most commonly with gross iron deficiency. In some, iron deficiency is exacerbated by the development of cow’s milk protein enteropathy, leading to peripheral oedema secondary to hypalbuminaemia in addition to anaemia.

Older children with diets poor in iron-containing foods (red meat, white meats, legumes, green vegetables, egg yolks) are also at risk. Blood loss must always be considered in an iron-deficient child or adolescent without an appropriate dietary history. Menorrhagia is an important cause of iron deficiency in adolescent girls. Occult blood loss is usually gastrointestinal in origin, from such diverse causes as cow’s milk enteropathy, polyps, haemangiomas, Meckel’s diverticulum and hereditary telangiectasia, but repeated epistaxes and chronic blood loss from the renal tract must be excluded.

Iron malabsorption is uncommon and is usually associated with malabsorption syndromes such as coeliac disease or chronic inflammatory bowel disease.

Iron deficiency initially leads to depletion of marrow iron stores without any haematological abnormality. When iron stores are exhausted, serum iron concentration and transferrin binding falls and there is reduced intracellular iron availability for haem synthesis, with a consequent reduction in Hb production, leading to microcytosis and the development of anaemia.

Symptoms of early iron deficiency with no or minimal anaemia may include poor attention span and irritability. As anaemia develops, cognitive deficits may increase and lethargy and pallor become apparent. Some chronically iron-deficient children exhibit pica (the ingestion of non-food items such as dirt and clay, and chewing of ice).

Examination reveals pallor, most easily detected in the palmar creases and conjunctivae. Signs of cardiac decompensation will occasionally be present if the anaemia is severe. Mild splenomegaly is found occasionally but is more common in thalassaemia minor, from which iron deficiency must be distinguished.

Therapy of iron deficiency involves correction of the underlying cause and replenishment of iron stores. Improvement in the dietary intake of iron-containing foods is the most important strategy in the majority of iron-deficient children. Reduction in the total milk content of the diet may be necessary to allow the child to develop an appropriate appetite. If a source of blood loss is identified, appropriate therapy is undertaken and iron supplements are given until the deficiency is corrected.

Therapeutic iron is optimally given orally in two to three divided doses daily in a dose of 6 mg/kg per day of elemental iron. Absorption is enhanced when iron is taken with vitamin C and between meals but the side effects of abdominal discomfort are reduced when iron is taken with food. Ferrous sulphate is cheaper and better absorbed than ferrous gluconate but the gluconate is better tolerated. A reticulocyte response to iron should be seen within 7–10 days but iron therapy should continue for 3 months to replenish

Clinical example

Tan, a 15-month-old boy, had been breastfed for 10 months and then was given cow’s milk. He had occasional solid foods only, and rarely had any foods with a significant iron content. He had become irritable, seemed to be low in energy and slept more than his parents thought was usual. When he was seen by his doctor because of an upper respiratory tract infection, he was noted to have pale conjunctivae and pale palmar creases.

Tan’s Hb was 51 g/l, his MCV was 51 fl, and his mean corpuscular haemoglobin concentration (MCHC) was 15 pg. The total WBC was normal and his platelet count was 432 × 10^9/l. The blood film showed microcytic and hypochromic red cells; there was no reticulocytosis and no basophilic stippling. The serum ferritin was 4 µg/l (normal range 16–300).

Tan’s anaemia had all the features of an iron-deficiency anaemia due to a deficient iron intake in his diet. A dietician assisted in instructing his mother in ways to improve his diet by including foods such as red and white meats, green vegetables, legumes and egg yolks. Tan was given ferrous gluconate mixture at a dose of 6 mg/kg of expected weight per day, to be taken as two doses daily. His parents were asked to give this with orange juice to improve absorption. They were warned that the mixture could make Tan’s stools a grey-black colour but that this was not of concern. They were asked to brush his teeth after each dose to prevent any minor staining. They were warned of the toxic effects of iron if taken in overdose accidentally by an inquisitive toddler; the mixture was provided in limited amounts only in a bottle with a safety top, and they were asked to keep it in a secure place, preferably a locked cupboard.

The iron mixture was continued for 3 months. Tan’s reticulocyte count rose in a few days, and his Hb began to rise in 10 days. By 6 weeks of therapy his Hb was normal; the iron mixture was continued for another 6 weeks to ensure that his iron stores were replenished.
iron stores. The stools are grey-black in individuals on iron.

It is rarely necessary to use the parenteral route for iron administration but, in occasional children with poor absorption or poor compliance, intravenous infusions of iron may be required.

**Haemoglobinopathies**

Haemoglobin is a compound protein made up of two pairs of globin chains with a haem molecule inserted into each. One of these globin chains is designated as the alpha chain, the other variably being termed beta, delta, epsilon (ε), gamma and zeta (ζ). Zeta and epsilon chains are expressed only in early embryonic life, with zeta chain production switching to alpha chain production and gamma chain production replacing epsilon chain synthesis in the early weeks of gestation. In the perinatal period there is a further switch from gamma to beta chain production. The predominant fetal haemoglobin is HbF (αγβ). In children beyond 6 months of age and adults, the major haemoglobins are HbA (αβ) and HbA2 (αδ). A number of abnormalities of globin chain production or point mutations within globin genes may result in significant disease.

**Thalassaemias**

These are genetic disorders characterized by reduced or absent production of one or more of the globin chains of haemoglobin.

The thalassaemias are found commonly in people originating from the Mediterranean region, the Middle East, the Indian subcontinent, south Asia and Africa. The inheritance is in a mendelian recessive manner.

**Beta thalassaemia**

Beta thalassaemia occurs as a result of point mutations or deletions within one or both of the two beta globin genes, resulting in reduced or absent production of beta globin chains. The heterozygous state is termed thalassaemia minor and the homozygous state thalassaemia major.

**Beta thalassaemia minor.** Affected individuals are usually asymptomatic, with mild anaemia detected either during investigation of another illness or as a result of family screening. Mild pallor and splenomegaly may be noted but the examination is often unremarkable. There is a mild microcytic hypochromic anaemia with occasional target cells. The differential diagnosis is iron deficiency, although both may coexist. The HbA1 level is elevated. If present, iron deficiency may mask the thalassaemia minor, preventing diagnosis until the iron deficiency is corrected.

**Beta thalassaemia major (Cooley anaemia).** This is caused by the inheritance of two abnormal beta genes. At birth the haemoglobin is normal but, as the γ→β switch occurs, there are no (β0) or insufficient (β+) beta chains to balance alpha chains. Excess alpha chains precipitate, causing shortened red cell survival with destruction within the bone marrow (ineffective erythropoiesis) and spleen. HbA production is inadequate to compensate for the gradual fall in HbF as gamma chain production switches to inadequate beta chain production.

Children with thalassaemia major usually present between 3 months and 1 year of life with pallor and hepatosplenomegaly. There may be mild jaundice. Occasionally presentation is delayed to 4–5 years, with these children having increased skin pigmentation, frontal bossing and malar prominence due to chronic marrow expansion. The Hb may be very low, with blood examination revealing hypochromia, red cell stippling, microcytosis, macrocytes, target cells and nucleated red cells (Fig. 16.1.1F). An elevated HbF level (usually 50–100%) confirms the diagnosis. Globin chain synthesis studies can differentiate between β0 and β+ thalassaemia.

Without treatment, the severe chronic anaemia leads to growth retardation, poor musculoskeletal development and increased iron absorption, resulting in skin pigmentation. Extraduillary haemopoiesis in liver and spleen together with hypersplenism result in organ enlargement and abdominal distension. Marrow expansion produces the characteristic facial appearance with frontal bossing, maxillary hypertrophy with exposure of the upper teeth, prominence of the malar eminences and a flattened nasal bridge. Skull X-rays show expansion of the diploic space, and the subperiosteal bone has a typical ‘hair on end’ appearance. There is cortical thinning of long bones and fractures may occur. Death usually occurs within 10 years from cardiac failure, cardiac arrhythmias or infection.

Current treatment is with regular transfusion at 3–4-weekly intervals, aiming to suppress endogenous haemopoiesis (preventing marrow expansion) and to keep the Hb level above 100 g/l. Regular transfusion results in iron loading and chelation therapy must accompany transfusion support to prevent the toxic effects of iron on the myocardium, liver, pancreas and gonads (cardiac arrhythmias, cardiac failure, diabetes mellitus, hepatic fibrosis, infertility). The chelator desferrioxamine is currently given by subcutaneous infusion via a syringe pump over 10 hours nightly, usually after approximately 5 years of age. Compliance, particularly during adolescence, is often a problem. Many centres now transfuse by erythrocytaphaeresis to reduce iron loading. All patients receive folic acid supplements and hepatitis
B vaccination and are encouraged to participate in all normal activities. Splenectomy, preceded by appropriate vaccinations, is occasionally required. Bone marrow transplantation from matched siblings is producing high cure rates provided it is carried out before hepatic dysfunction develops, but long-term results are still to be evaluated.

With improvements in therapy some patients are now surviving into the fifth decade. A proportion of adults have preservation of gonadal function and have had children.

**Haemoglobin E/β thalassaemia**. Haemoglobin E (HbE) occurs extensively throughout south-east Asia. Neither the heterozygous nor the homozygous state produces clinical abnormalities. The doubly heterozygous state of HbE with beta thalassaemia results in a clinical condition similar to thalassaemia major. Diagnosis is confirmed by blood examination and haemoglobin electrophoresis. Clinical presentation and management are similar to a moderately severe beta thalassaemia.

### Alpha thalassaemia

There are four alpha globin genes and alpha thalassaemia results from the loss of one or more of these. The loss of one gene produces neither haematological nor clinical abnormality (silent carrier). Loss of two genes results in hypochromia and microcytosis, but no anaemia, and is known as alpha thalassaemia trait. Alpha thalassaemia occurs with a very high incidence in Asian populations and is assuming increasing importance in our community.

**Haemoglobin H disease**. The loss of three alpha genes results in the formation of excess beta chains, which form an unstable tetramer (HbH), accounting for 30–40% of the total haemoglobin. The clinical picture is similar to beta thalassaemia intermedia, with pallor, jaundice and moderate hepatosplenomegaly. There is a moderate anaemia (Hb 80–100 g/l) and persistent reticulocytosis. The anaemia is aggravated by infections, pregnancy and oxidant drugs (e.g. phenacetin or primaquine), which should be avoided. No specific treatment is necessary other than folic acid supplements.

**Haemoglobin Barts (hydrops fetalis syndrome)**. All four alpha genes are deleted and no alpha chains are produced. The haemoglobins present are HbBarts (HbH) 70%, HbH1 (HbH) 0–20% and HbPortland (Hbβ4). Severe fetal anaemia develops, resulting in cardiac failure, hepatosplenomegaly and generalized oedema. The infants are generally stillborn or die shortly after birth. In utero transfusions may result in a liveborn infant, and exchange transfusion followed by ongoing transfusion support has led to the survival of a few patients. Bone marrow transplantation should cure these patients.

### Sickle cell disease

Haemoglobin S (HbS) results from a single amino acid substitution in the beta globin chain (β7′/26Glu–Val). Under hypoxia conditions, deoxyhaemoglobin S polymerizes into fibre bundles, which distort the cell into a sickle shape. Sickling may be reversible on reoxygenation or may become irreversible. The sickle cell gene occurs in people from Africa, the Middle East and the Mediterranean region, as well as in the African-American population.

The heterozygous carrier (sickle trait) is asymptomatic, with normal Hb and red cell morphology. Haemoglobin electrophoresis reveals an HbA of approximately 60% and an HbS level of 30–40%.

In the homozygous state (sickle cell anaemia) there is a normochromic normocytic haemolytic anaemia with target cells, sickle cells, nucleated red cells, fragments and spherocytes (Fig. 16.1.1E). The diagnosis is confirmed by finding an elevated HbS (60–90%) on electrophoresis with approximately 2% HbA2, the remainder being HbF. The higher the level of HbF the less severe the symptoms of the disease.

The doubly heterozygous sickle trait–beta thalassaemia is expressed with clinical features very similar to those of homozygous sickle cell disease. In contrast to sickle cell anaemia, the red cells are microcytic and hypochromic and target cells are present. Sickling can be demonstrated and both HbS and HbA2 are elevated. Examination of the parents’ blood confirms sickle cell trait in one and thalassaemia minor in the other. The management of this condition is similar to that for sickle cell anaemia.

The clinical course of the patient with sickle cell disease, or doubly heterozygous sickle/thalassaemia, is characterized by ‘crises’ as a result of sickling of red cells that obstruct the lumen of capillaries and small venules, causing infarction of surrounding tissues. Haemolytic ‘crises’ may also occur during infective illness.

Presentation is usually between the ages of 6 months and 4 years with pallor, jaundice, abdominal or limb pain and/or swelling of the hands and feet. Haemolytic crises are characterized by increased pallor and jaundice, infarctive ‘crises’ with acute pain, generally of limbs or back, and aplastic crises with an aregenerative anaemia. Splenic sequestration crises occur in young children predominantly under the age of 5 years. In this potentially life-threatening complication, red cells are trapped in splenic sinusoids, resulting in hypovolaemia, a rapid increase in splenic size and profound anaemia. Patients with sickle cell disease have an increased risk of infection, particularly pneumococcal infection. Functional asplenia secondary to repeated splenic infarction occurs in most patients.
The emphasis in management is on avoidance of environmental factors known to precipitate a crisis. The following protective measures are recommended:

- good nutrition with regular folic acid supplements
- penicillin prophylaxis from infancy, with prompt treatment of infections
- appropriate immunization schedule
- maintenance of adequate hydration, particularly during hot weather
- prevention of vascular stasis. This may occur with tight clothing, the use of tourniquets applied during an operative procedure, and exposure to cold.

Vaso-occlusive crises require prompt control of pain, the maintenance of hydration and treatment of underlying infection. Severe crises (pulmonary syndrome or cerebral infarction) require blood transfusion to reduce the HbS concentration. Occasionally exchange transfusion may be required.

Patients with splenic sequestration require prompt restoration of intravascular volume and correction of acidosis.

Patients with frequent crises may be managed with hydroxycarbamide (hydroxyurea), which increases the proportion of HbF and reduces the number of sickle crisis. Hydroxycarbamide is not usually commenced until at least 3 years of age, but usually 5 years. In more severe cases, regular blood transfusions to suppress endogenous HbS production are required. These patients also require iron chelation. Successful bone marrow transplantation has been reported.

**Genetic counselling**

Current DNA techniques allow prenatal diagnosis of the thalassaemias and sickle cell disease. With increased community awareness and education, many couples who carry either a thalassaemia or sickle trait are now seeking antenatal counselling and prenatal diagnosis. This will have significant effects on the incidence of newly diagnosed homozygotes in the future.

**Anaemia due to increased red cell destruction (haemolysis)**

Anaemia secondary to haemolysis (Table 16.1.5) occurs when bone marrow replacement does not keep pace with the rate of destruction.

Haemolysis may be intravascular or may occur by phagocytosis within the spleen or liver. Intravascular haemolysis occurs in some autoimmune haemolytic anaemias, acute haemolysis in G6PD deficiency,

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<th>Usual age of presentation</th>
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<td>Membrane abnormality (decreased red cell deformability)</td>
<td>Congenital – splenic destruction</td>
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<td>Antibody-mediated membrane damage</td>
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<td>Haemolytic disease of newborn Autoimmune haemolytic anaemia</td>
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<td>Mechanical membrane damage</td>
<td>Membrane damage</td>
<td>Disseminated intravascular coagulopathy Haemolytic–uraemic syndrome Cardiovascular prosthesis</td>
<td>Any age Childhood</td>
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and acute transfusion reactions. Free haemoglobin is released and combines with haptoglobin. The complex is cleared by the reticuloendothelial system of the liver and spleen. If the free plasma haemoglobin concentration exceeds the haptoglobin binding capacity, haemoglobinuria occurs. The colour of the urine may vary from pink through brown to almost black, depending on the amount of free haemoglobin excreted.

If haemolysis occurs predominantly in the reticuloendothelial system (autoimmune haemolytic anaemia, membrane abnormalities), there is little free haemoglobin in plasma. Haemoglobin is converted to bilirubin within phagocytes, transported to the liver bound to albumin, then conjugated and excreted into the bile. Jaundice is variable, depending on the rate of haemolysis and hepatic conjugation. To compensate for the reduced red cell survival, the bone marrow increases its output of red cells, releasing immature reticulocytes and, in acute severe haemolysis, nucleated red cells into the peripheral blood.

**Intracellular enzyme defects**

Mature red cells lack a nucleus and intracellular organelles necessary for synthesis of proteins and generation of adenosine triphosphate (ATP) via oxidative pathways. Energy production for maintenance of the integrity of the red cell is via one of the two glycolytic metabolic pathways within it. About 95% of glucose metabolism is via the anaerobic Embden–Myerhof pathway and 5% through the hexose monophosphate shunt (pentose phosphate pathway). Enzyme defects in either pathway result in oxidative damage and haemolysis. Deficiencies or abnormalities of G6PD, the first enzyme in the hexose monophosphate shunt, are extremely common worldwide. All the documented enzyme deficiencies of the Embden–Myerhof pathway resulting in haemolytic anaemias are rare. Examples are pyruvate kinase deficiency and glucose phosphate isomerase deficiency.

**G6PD deficiency**

This X-linked enzyme deficiency is the commonest inherited disorder of the red cell. It is fully expressed in hemizygous males and in homozygous females. Heterozygous females show a variable level of enzyme activity due to variation in X chromosome inactivation. There are over 200 variant enzymes and the clinical expression of the disorder is variable, with four major clinical syndromes. Neonatal jaundice is common in the Chinese and Mediterranean variants; favism (acute haemolysis after ingestion of broad beans or inhalation of pollen) is a feature of the Mediterranean variant; while oxidative-stress-induced haemolysis (drugs, infection), although common to all variants, is the predominant feature in affected individuals of African descent. Individuals of northern European descent have chronic moderate haemolysis, while other variants only experience haemolysis with appropriate stress. Patients typically present severely anaemic with dark urine, having been well until 1–2 days prior to presentation. The precipitating factor is usually identifiable on history. Because of the rapidity of the fall in haemoglobin there often is profound lethargy and restlessness at presentation.

Examination of the blood film shows polychromasia and anisocytosis, and typically ‘blister’ cells. The diagnosis is established by enzyme assay in mature red cells. Enzyme levels are higher in reticulocytes in some variants and a normal enzyme level at the time of an acute haemolytic episode does not exclude the diagnosis. Management is to avoid precipitating factors. Patients having acute crises may require blood transfusion, although a brisk reticulocyte response may result in rapid spontaneous recovery.

**Clinical example**

Thomas was an 8-year-old boy from Hong Kong. He presented with the onset of pallor over 24 hours and was passing very dark urine. He had recently been treated for tonsillitis. He had no past history of serious illness. On examination, apart from marked pallor, splenomegaly was present. His urine contained haemoglobin. Blood tests revealed a haemoglobin of 40 g/l with an elevated reticulocyte response. Blister cells were evident on the blood film. The G6PD assay was borderline normal and assays on the parents showed that Thomas’s mother was heterozygous for G6PD deficiency. One month after this episode, Thomas was shown to have a severe deficiency of G6PD activity. The earlier borderline result was caused by the presence of many young red cells with high G6PD activity.

**Intrinsic membrane defects**

Abnormalities of the red cell membrane result in alterations of cell shape, usually due to changes in transmembrane electrolyte flux. Changes in cell shape cause decreased deformability, splenic trapping and destruction within the spleen, resulting in chronic haemolytic anaemia. The commonest membrane abnormality is hereditary spherocytosis, a dominantly inherited condition.

**Hereditary spherocytosis**

There is a marked variability in the severity of haemolysis in this condition. Neonatal jaundice is
common. Some children present with anaemia in infancy while others remain asymptomatic until a haemolytic or aplastic crisis occurs in association with a viral infection. Hypersplenism or gallstones may result in the presentation of a previously asymptomatic patient with well compensated haemolysis. A positive family history is often obtained. Examination reveals pallor, often mild jaundice and a variable degree of splenomegaly. The diagnosis is suggested by the presence of spherocytes in the peripheral blood (Fig. 16.1.1C). The best test currently to confirm the diagnosis is the E5M test. In this test, the dye eosin-5-maleimide reacts covalently with Lys-430 on the extracellular loop of band 3 protein. Reduced E5M staining is seen in patients with hereditary spherocytosis, Congenital dyserythropoietic anaemia type II and south-east Asian ovalocytosis and cryohydrocytosis.

Folic acid supplements should be given. Blood transfusion may be required for anaemia resulting from inadequately compensated haemolysis and for aplastic crises, during which the haemoglobin may fall precipitously. Aplastic crises usually are associated with parvovirus B19 infection. Haemolysis is abolished by splenectomy. Overwhelming postsplenectomy infection may occur, particularly in children less than 5 years of age. Pneumococcal, meningococcal and Haemophilus influenzae vaccination should be given pre-splenectomy, and penicillin prophylaxis should be continued indefinitely.

Decisions about splenectomy should be based on the following:
- degree of haemolysis and anaemia
- age
- size of spleen
- presence of gallstones.

Clinical example
Angela was 9 years of age. In the neonatal period she required exchange transfusion for severe jaundice. She had always been pale and had a small appetite. With upper respiratory tract infections, her pallor increased and jaundice had appeared. At 2 years of age hereditary spherocytosis was diagnosed and folic acid supplements were commenced. Angela’s father also had this condition. She presented with abdominal pain, pallor, icterus and splenomegaly of 6 cm. Ultrasound examination confirmed the presence of gallstones. Following pneumococcal and Haemophilus influenzae vaccination, splenectomy and cholecystectomy with removal of gallstones was undertaken. Prophylactic penicillin was commenced after the surgery and would continue indefinitely.

Extrinsic membrane damage
Acquired membrane damage leading to haemolysis can result from antibody–antigen reactions, mechanical insults (e.g. intravascular prosthetic patches), burns, toxins (e.g. copper) and infective agents (e.g. Clostridium perfringens).

Antibody-mediated haemolysis
The binding of immunoglobulin or complement, or a combination of the two, to the red cell membrane may result in premature cell destruction or immune haemolysis. The antibody involved may be IgG (warm antibody) or IgM (cold antibody). Immune haemolytic anaemias may be classified as follows:

Isoimmune haemolysis in the newborn
- Rhesus incompatibility (mother Rh-ve; baby Rh+ve)
- ABO incompatibility (mother group O; baby group A or B).

Autoimmune haemolysis in children
- Idiopathic. In many instances of IgG warm-antibody-mediated haemolysis, no definite aetiological agent is identified
- Postinfectious. Many common infectious diseases, such as measles (IgG), infectious mononucleosis (IgM) and mycoplasma infection (IgM) may be associated with acute haemolysis
- Drug related. This is very uncommon in children. Some drugs, e.g. α-methyl dopa, stimulate the production of antibodies that are directed against red cell antigens but not against the drug. A second mechanism involves a drug, such as penicillin, binding to the red cell membrane, with antibody to the drug being formed and attaching to the drug. The antibody-coated red cells then undergo destruction in the spleen. The third mechanism of drug-related haemolysis involves the deposition of antibody–antigen complexes on the red cell surface with activation of complement and brisk intravascular haemolysis
- Associated with connective tissue disease or malignancy. This is rare in childhood but may be associated with systemic lupus erythematosus in adolescence.

Presentation of a child with immune-mediated haemolysis is usually acute with rapid onset of pallor, severe anaemia and dark urine. Jaundice may be present. Life-threatening anaemia may develop rapidly, with vasoconstriction, cardiac failure and hypoxia. Modest splenomegaly is often present.

The peripheral blood shows a predominantly normocytic anaemia with spherocytes, fragmented red cells and rouleaux formation (Fig. 16.1.1D). In cold
agglutinin disease, agglutination is seen on the blood film. As a compensating reticulocytosis develops, polychromasia and macrocytosis are seen. A positive direct antiglobulin test (DAT) confirms the diagnosis. The specificity of the positive DAT classifies the type of antibody involved. The commonest are warm IgG antibodies, but cold IgM antibodies are found in association with mycoplasmal infection and infectious mononucleosis.

Urgent blood transfusion may be required. In some cases the presence of strong autoantibody in recipient plasma makes the provision of compatible blood and the exclusion of underlying alloantibodies difficult. Transfused cells may be haemolysed rapidly and careful observation is required. Repeated transfusions may be necessary. Adequate hydration must be maintained to avoid renal tubular damage from haemoglobinuria. Where a warm antibody is identified, steroid therapy is instituted and maintained until the Hb stabilizes, then tapered gradually. Haemolysis is usually self-limiting over the course of days to weeks. Occasional patients may have severe ongoing haemolysis, or frequent relapses. Plasma exchange, exchange transfusion or high-dose immunoglobulin may be useful but, if these measures fail, splenectomy may be life-saving.

**Blood loss**

Blood loss, if acute, results in vasoconstriction, then tachycardia and finally hypotension. The haemoglobin, if measured very early in the course of a bleeding episode, will be normal or only slightly reduced. When there has been time for haemodilution to occur, the haemoglobin falls. A compensatory reticulocytosis occurs after approximately 48 hours. Chronic blood loss results in iron-deficiency anaemia.

**Blood transfusion therapy**

The majority of children with anaemia do not require transfusion therapy. The critical questions that must be addressed in deciding whether to transfuse are:

- Has the patient evidence of cardiovascular decompensation?
- Is the anaemia likely to be progressive and at what rate?
- What is the likely timing of spontaneous recovery?
- Are there alternative therapies that are likely to succeed?

Major acute blood loss due to trauma, acute haemolytic anaemias and chemotherapy-induced anaemia are the most likely causes of acute anaemia to require transfusion. The exact transfusion trigger will be a function of the physiological considerations discussed previously in this chapter. Major haemoglobinopathy and bone marrow failure syndromes may require chronic transfusion programmes. Nutritional anaemia rarely requires transfusion therapy in the absence of cardiovascular instability.

There are specific indications for exchange transfusion in neonates and, for example, older children with sickle cell disease.

**Risks of blood transfusion therapy**

Parents worry about viral infections from blood transfusion, although this remains an extremely low risk. If the clinician has used the principles above to determine the need for transfusion, then the risks of not transfusing usually far outweigh the risks of transfusion. In terms of viral safety Australia has one of the safest blood supplies in the world. Factors contributing to this are that every blood donor is a volunteer (unpaid) and must meet strict selection criteria, including answering a comprehensive questionnaire about their health and lifestyle and undergoing a personal interview by trained staff at which they sign a declaration. Every blood donation is screened for syphilis, hepatitis B and C, HIV and human T-cell leukaemia/lymphoma virus (HTLV). Two types of test for hepatitis C and HIV are now performed – antibody testing and nucleic acid testing (detects viral materials directly and therefore infection at an earlier stage). Only blood that is negative for all these tests is released for use.

**Current risks of transfusion transmitted infection**

Australian Red Cross Blood Service (ARCBS) uses sophisticated mathematical models to calculate the current infection risks for blood transfusions in Australia, which are shown in Table 16.1.6. These risks are very small compared to the risks of everyday living. The chance of being killed in a road accident in Australia is about 1 in 10,000.

**Non-viral risks associated with blood and blood products**

ABO incompatibility remains one of the most common fatal complications of blood transfusion and most cases are due to avoidable errors (most commonly associated with patient/sample identification). Table 16.1.7 gives estimates of risk based on
reports from a number of countries, which are subject to the problem of underestimation due to lack of reporting and recognition of transfusion reactions (hence the broad ranges). The transfusion of autologous blood is not without risk and the same indications apply as for the use of homologous blood.

### Table 16.1.6 Risks based on ARCBS data 1 July 2000 to 30 June 2003

<table>
<thead>
<tr>
<th>Infection</th>
<th>Residual risk with tested blood per unit transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 7,299,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1 in 3,636,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 in 1,339,000</td>
</tr>
<tr>
<td>HTLV</td>
<td>Considerably less than 1 in 1,000,000</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Considerably less than 1 in 1,000,000</td>
</tr>
<tr>
<td>Variant CJD</td>
<td>Unknown: possible and cannot be excluded</td>
</tr>
</tbody>
</table>

CJD, Creutzfeldt–Jakob disease; HIV, human immunodeficiency virus; HTLV, human T-cell leukaemia/lymphoma virus.

### Practical points

**Deciding if a patient needs a red cell transfusion**
- The actual haemoglobin level, while important, does not alone determine the need for a transfusion.
- Consider the cause and time-course of the anaemia. Haematinic deficiencies rarely need transfusion. Acute blood loss (especially if ongoing) and acute haemolysis frequently need transfusion.
- Coexistent disease is important in determining the likely ability of the patient to cope with a degree of anaemia. Cardiac and lung function, as well as haemoglobin level, are important determinants of oxygen delivery. The ability to maintain oxygen delivery is the key question when considering most acute red cell transfusion questions.
- Reduced oxygen saturation measured by pulse oximetry may reflect lung disease, cyanotic heart disease or abnormal Hb with reduced oxygen affinity (e.g. methaemoglobin) and may reduce the transfusion threshold. In the absence of adequate cardiac output or Hb, normal pulse oximetry does not equate to adequate tissue oxygen delivery.
- Clinical signs of cardiac stress (increased heart rate) or hypoxia (restlessness, altered conscious state/behaviour) are critical indicators of the need for urgent transfusion. In children, hypotension is a late sign in acute blood loss. These factors should be monitored closely in anaemic patients. In a child with cardiovascular decompensation from anaemia, do not delay urgent transfusion therapy in favour of thorough investigation. A live child who remains a diagnostic dilemma is better than a dead child in whom you know the diagnosis.

### Table 16.1.7 Non-viral serious risks of blood transfusion (per unit transfused unless specified)

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial sepsis</td>
<td>1 in 40,000 to 500,000</td>
</tr>
<tr>
<td>Platelets</td>
<td>1 in 10,000 to 100,000</td>
</tr>
<tr>
<td>Haemolytic reactions</td>
<td>1 in 12,000 to 38,000</td>
</tr>
<tr>
<td>Acute</td>
<td>1 in 1,000 to 12,000</td>
</tr>
<tr>
<td>Delayed</td>
<td>1 in 20,000 to 50,000</td>
</tr>
<tr>
<td>Anaphylaxis – IgA deficiency</td>
<td>1 in 100–700 per patient</td>
</tr>
<tr>
<td>Fluid overload/cardiac failure</td>
<td>1 in 5,000–100,000</td>
</tr>
<tr>
<td>TRALI*</td>
<td>1 in 5,000–100,000</td>
</tr>
<tr>
<td>TA-GVHD†</td>
<td>Rare</td>
</tr>
</tbody>
</table>

* Transfusion-related acute lung injury (TRALI) is characterized by acute respiratory distress (within hours of transfusion) with non-cardiogenic pulmonary oedema. Full recovery in 48 hours is usual if the patient is well resuscitated/supported. TRALI is likely to be significantly under-reported.
† Transfusion-associated graft versus host disease (TA-GVHD) is due to viable engraftment of T lymphocytes and usually affects severely immunocompromised patients or recipients who share an HLA haplotype with a specific donor. Gamma-irradiation of blood products for specific at-risk groups of patients (refer to hospital guidelines) prevents this rare but usually fatal event.
Bleeding disorders range from those that are severe and potentially life-threatening through to mild disorders that may be difficult to distinguish from normal.

Abnormal bleeding is the result of a disorder of one of the following:
- the blood vessel or its supporting tissue
- the platelets
- the coagulation mechanism.

**Clinical approach to diagnosis**

As a general rule, history taking, physical examination and a small number of relatively simple laboratory tests will find most causes of abnormal bleeding. The history, with particular reference to the past and family history, will usually provide the most valuable information.

### Practical points

**Bleeding disorder assessment**
- History to determine normal from abnormal is the most valuable tool
- Simple coagulation tests such as platelet count, activated partial thromboplastin time (aPTT), prothrombin time (PT/INR) and fibrinogen will confirm the majority of diagnoses
- Mucosal bleeding needs assessment for von Willebrand disorder
- Assessment of other family members is often required

### History

**What is abnormal?**

The main question to answer in the history is whether the bleeding symptoms are within or outside normal limits. Isolated bruises over the shins are common, while spontaneous petechiae are abnormal. Finger-induced epistaxis is common and not indicative of a bleeding disorder; however, recurrent nose bleeds lasting more than 10 minutes or leading to anaemia are often related to a bleeding disorder. Table 16.2.1 gives some clinical guidance.

**When did the bleeding start?**

**Prenatal and neonatal**
- congenital infection may result in a bleeding disorder
- mucosal bleeding occurs with haemorrhagic disease of the newborn
- umbilical stump bleeding is associated with factor XIII deficiency and dysfibrinogenemias
- intracranial haemorrhage may occur with factor deficiencies and with neonatal alloimmune thrombocytopenia
- prolonged bleeding following circumcision is suggestive of haemophilia and may be the presenting feature of haemorrhagic disease of the newborn

**Early childhood**
- often implies a congenital defect
- bruising, muscle and joint bleeding is strongly suggestive of haemophilia
- petechiae and mucosal bleeding suggests a platelet problem or von Willebrand disorder

**Sudden onset**
- usually an acute problem such as immune thrombocytopenic purpura
- non-accidental injury may have a haemorrhagic presentation with inadequate explanations for each specific bruise, which may have an unusual distribution (Ch. 3.9). Skeletal trauma and other stigmata of non-accidental injury may be present

### Where is the bleeding?

Specific bleeding sites have characteristic associations:
- **Joint bleeding**: haemophilia A and B
- **Nasal mucosa**: local irritation; von Willebrand disorder and platelet dysfunction
- **Gums, periosteum, skin**: scurvy
- **Gastrointestinal**: haemorrhagic disease of the newborn in babies; liver disease in older children
• Retro-orbital: haematological malignancy or disseminated solid tumour.

Other aspects of history

Family history
Haemophilia A and B are X-linked; most von Willebrand disorder subtypes and haemorrhagic hereditary telangiectasia are recessive and several platelet function disorders are dominantly inherited. Clinical penetrance in haemophilia carriers and von Willebrand disorder may be variable.

Past history
Easy bruising, bruising at abnormal sites, prolonged bleeding following trivial trauma or bleeding following surgery and dental extractions are all indications for investigation.

Associated diseases
In the presence of disorders such as systemic lupus erythematosus, liver disease, extrapanetic portal hypertension, gross splenomegaly, giant haemangiomas, reticuloendothelial malignancies and leukaemia, bleeding is anticipated and is readily explicable.

Drug ingestion
Drugs may produce abnormal bleeding through:
• depression of clotting factors: anticoagulants, liver toxins
• bone marrow depression: chloramphenicol, cytotoxic agents, radiation
• antigen–antibody reactions with platelet membranes: quinine group of drugs
• direct inhibition of enzymes in platelets: aspirin effects on platelet cyclooxygenase.

Table 16.2.1 What symptoms and signs may be related to a bleeding disorder?

<table>
<thead>
<tr>
<th>Site</th>
<th>Within normal limits</th>
<th>May be abnormal and due to a number of causes</th>
<th>Usually due to a bleeding disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose</td>
<td>Finger-induced</td>
<td>Unilateral</td>
<td>Recurrent, requiring medical intervention or causing anaemia</td>
</tr>
<tr>
<td>Oral</td>
<td>Blood on brush</td>
<td>Gum ooze &lt; 30 min</td>
<td>Gum ooze &gt; 30 min</td>
</tr>
<tr>
<td>Gut</td>
<td>Rectal fissure, blood in nappy</td>
<td>Haematemesis, melena</td>
<td></td>
</tr>
<tr>
<td>Menstrual loss</td>
<td>4–7 days</td>
<td>‘Same as Mum’</td>
<td>Loss leading to anaemia or transfusion</td>
</tr>
<tr>
<td>Skin</td>
<td>Shins don’t count</td>
<td>Bony prominences</td>
<td>Spontaneous bruising over soft areas, laceration bleeding &gt;30 min</td>
</tr>
<tr>
<td>Joints and muscles</td>
<td>Trauma induced</td>
<td>Spontaneous</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>Neonatal, trauma-induced</td>
<td>Spontaneous</td>
<td></td>
</tr>
</tbody>
</table>

Physical examination
The following should be noted on physical examination.

The type of skin bleeding
Petechiae alone strongly suggest a platelet or vessel problem, while ecchymoses alone suggest a factor deficiency. Combined petechiae and ecchymoses suggest a severe disorder, often of platelet origin.

The site of the bleeding
Confirmation of history, defining the number of all different bleeding sites and assessment of severity of bleed and functional implications are all important aspects for both diagnosis and management.

Splenomegaly
Hypersplenism occurs when a large spleen removes platelets from the circulation, which leads to bleeding. The problem is the underlying cause of the splenomegaly. Hepatomegaly, splenomegaly, lymphadenopathy and/or anaemia, in association with bleeding, strongly suggest leukaemia.

Miscellaneous
Bleeding in association with eczema is a feature of Wiskott–Aldrich syndrome; telangiectasia and mucosal bleeding are typical of hereditary haemorrhagic telangiectasia. Hyperelastic skin, hyperextensible joints and bruising are associated with Ehlers–Danlos syndrome.
Investigation of bleeding in childhood

The tests in Table 16.2.2 are the most important.

Other tests
Measurement of von Willebrand factor level (antigen), activity (ristocetin cofactor and/or collagen binding assay) and factor VIII level are required to diagnose von Willebrand disorder. The bleeding time has lost favour because of its scarifying potential but is characteristically prolonged in thrombocytopenia (normal 2–7 min), von Willebrand disorder and platelet function disorders and will be normal in other coagulation disorders.

Disorders of bleeding due to vascular defects
The commonest vascular defects seen in childhood are:

- anaphylactoid purpura
- infective states
- nutritional deficiency.

Table 16.2.2 Interpretation of initial blood tests in children with abnormal bleeding

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>More common causes</th>
<th>Less common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood count</td>
<td>Isolated thrombocytopenia</td>
<td>ITP, NAIT, Leukaemia</td>
<td>Congenital anomaly, Early SAA, Myelodysplasia, Osteoporosis, Myeloproliferative disorders</td>
</tr>
<tr>
<td></td>
<td>Pancytopenia</td>
<td>SA, Leukaemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High white cell count and</td>
<td>Thrombocytopenia, red cell fragmentation</td>
<td>Microangiopathic anaemia, e.g. HUS</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
<td>Small platelets, Giant platelets</td>
<td>Wiscott–Albright syndrome, Bernard–Soulier syndrome</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Isolated prolongation</td>
<td>Vitamin K deficiency, Warfarin therapy, DIC, Septicaemia, Liver disease</td>
<td>Congenital factor VII deficiency, Factor X, Factor V, prothrombin or fibrinogen deficiency</td>
</tr>
<tr>
<td>time (PT/INR)</td>
<td>Prolonged PT and aPTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td>Isolated prolongation</td>
<td>Unfractionated heparin therapy, Haemophilia A or B, ‘Lupus anticoagulant’</td>
<td>Factor XI deficiency, Contact system* deficiency</td>
</tr>
<tr>
<td>All tests</td>
<td>Normal</td>
<td>Non-accidental injury</td>
<td></td>
</tr>
</tbody>
</table>

* Contact system refers to factor XII, prekallikrein and high-molecular-weight kininogen.

aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; HUS, haemolytic–uraemic syndrome; INR, international normalized ratio; ITP, immune thrombocytopenic purpura; NAIT, neonatal alloimmune thrombocytopenia; SAA, severe aplastic anaemia.

Anaphylactoid purpura (Henoch–Schönlein purpura)
The aetiology of this disorder is still not clear. It is readily recognized by the characteristic distribution of the rash over the buttocks, legs and backs of the elbows (Fig. 16.2.1). Frequently, it is accompanied by abdominal pain, melaena, joint swellings and occasionally a glomerulonephritis. In anaphylactoid purpura the bleeding time, international normalized ratio (INR), activated partial thromboplastin time (aPTT) and platelet counts are normal; the Hess test is positive in only 25% of cases. Thus, diagnosis must be made on the clinical picture alone. The outlook is excellent, except for an occasional child who develops a progressive renal lesion (Ch. 18.1). No specific therapy exists, although in children with severe abdominal pain corticosteroids may be helpful.

Infective states
The purpura associated with such disorders as meningococcaemia, other septicemias and dengue haemorrhagic fever are the result of a severe angitis.
caused by antigen–antibody complexes. Severe bleeding, which may accompany these states, is the result of activation of the coagulation mechanism producing disseminated intravascular coagulation. Management involves that of the infection and of the associated vascular collapse.

**Nutritional deficiency**

Scurvy is uncommon and occurs in the artificially fed infant with inadequate vitamin C supplementation. The child is often pale, with skin bruises; is immobile in the frog position because of painful subperiosteal haemorrhages; and has gingival bleeding. A wrist X-ray will demonstrate the characteristic dense lines in the metaphyses of the radius and ulna and the ‘eggshell’-like epiphyses. Treatment with vitamin C (100–200 mg/d) reverses the clinical features within a week.

**Purpura fulminans**

This is a life-threatening and rare form of non-thrombocytopenic purpura that may follow such infections as scarlet fever, varicella, measles and some other viral infections. Typically there are rapidly spreading skin haemorrhages involving the buttocks and lower extremities. Congenital deficiencies of either protein C or protein S are the cause of neonatal purpura fulminans.

**Miscellaneous**

Bleeding from vascular wall defects is a feature of a group of rare disorders. These include hereditary haemorrhagic telangiectasia, polyarteritis nodosa, other vasculitides and uraemia. Anoxia, and thus damage to the capillary wall, may cause purpura in the asphyxiated newborn. The bleeding that accompanies Cushing syndrome, Ehlers–Danlos syndrome and cutis laxa is the result of defects in vascular supporting issue.

**Bleeding due to platelet disorders**

Bleeding disorders resulting from platelet abnormalities are usually due to thrombocytopenia but may be due to qualitative platelet defects. The various types of inherited and acquired thrombocytopenia are listed in Table 16.2.3.

**Immune thromboycytopenic purpura**

Immune thrombocytopenic purpura is the most common acquired bleeding disorder in children. It may be acute or chronic (defined as lasting longer than 6 months), episodic or continuous. Common to all clinical variations is the marked reduction in platelet life span due to immune-mediated splenic sequestration.

Features of typical acute immune thromboycytopenic purpura:

- 80–90% of paediatric immune thromboycytopenic purpura cases
- preceding viral illness is common
- peak age 2–5 years
- abrupt onset of bleeding
- mucosal and skin bleeding
- petechiae common
- otherwise normal examination, i.e. no lymphadenopathy or hepatosplenomegaly
- platelet count usually <20 × 10^9/l
- normal red cell and white cell parameters.

There is no need for other investigations if these ‘typical’ features are present.

Differential diagnosis is predominantly that of evolving aplastic anaemia.

*Chronic immune thromboycytopenic purpura* occurs in 10–20% of cases and often has an insidious onset in children aged over 7 years; it affects girls.
more commonly than boys. Recurrent immune thrombocytopenic purpura is rare and is characterized by thrombocytopenia at more than 3-month intervals.

Treatment approaches to immune thrombocytopenic purpura are shown in Table 16.2.4.

### Bleeding due to qualitative platelet defects

The child with a functional platelet defect will have a normal platelet count but abnormal platelet function tests. These tests analyse aggregation of platelets in response to several stimuli. The more common disorders in this group are the ‘aspirin-like’ syndrome and platelet storage pool disorders. The most severe disorder is Glanzmann disease. Before undertaking

### Clinical example

Chloe presented at the age of 4 years, 2 weeks after a viral upper respiratory infection, with a 3-day history of a petechial rash on her face and gum bleeding with toothbrushing. Examination revealed several fresh skin bruises along with the petechiae. There was no hepatosplenomegaly and the only palpable lymph nodes were slightly tender, 2 cm diameter tonsillar nodes. The only abnormality on full blood examination was a platelet count of 9 × 10^9/l. Chloe was treated with prednisolone 4 mg/kg daily in three divided doses for 4 days as an outpatient, with alternate daily platelet counts. On the second day of treatment her platelet count was 65 × 10^9/l and the count became normal within 5 days. She had no further episodes of thrombocytopenia.

### Table 16.2.3 Inherited and acquired thrombocytopenias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Key information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inherited</strong></td>
<td></td>
</tr>
<tr>
<td>With platelet dysfunction</td>
<td>Bernard–Soulier syndrome</td>
</tr>
<tr>
<td></td>
<td>Wiscott–Aldrich syndrome</td>
</tr>
<tr>
<td></td>
<td>X linked thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Grey platelet syndrome</td>
</tr>
<tr>
<td></td>
<td>Gplb–V–IX adhesion re ceptor defect – inability to bind with vWF</td>
</tr>
<tr>
<td></td>
<td>Small platelets, eczema, infections, X-linked, WASP mutations</td>
</tr>
<tr>
<td></td>
<td>Small platelets, X-linked, WASP mutations</td>
</tr>
<tr>
<td></td>
<td>Granule defect, bone marrow fibrosis</td>
</tr>
<tr>
<td>Without platelet dysfunction</td>
<td>May–Heglin anomaly</td>
</tr>
<tr>
<td></td>
<td>Alport syndrome</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia with absent radii (TAR)</td>
</tr>
<tr>
<td></td>
<td>Decreased megakaryocytes, typical bone anomalies</td>
</tr>
<tr>
<td></td>
<td>Large platelets, autosomal dominant</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia often precedes other cytopenias</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
<td></td>
</tr>
<tr>
<td>Neonatal</td>
<td>Immune thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Intrauterine infection</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td></td>
<td>Birth asphyxia</td>
</tr>
<tr>
<td></td>
<td>Giant haemangioma</td>
</tr>
<tr>
<td></td>
<td>‘Kasabach–Merritt syndrome’ features platelet consumption</td>
</tr>
<tr>
<td>Any age</td>
<td>Immune thrombocytopenia (ITP)</td>
</tr>
<tr>
<td></td>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td>Haemolytic–uraemic syndrome</td>
</tr>
<tr>
<td></td>
<td>Bone marrow infiltration</td>
</tr>
<tr>
<td></td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td></td>
<td>Drug induced</td>
</tr>
<tr>
<td></td>
<td>Hypersplenism</td>
</tr>
<tr>
<td></td>
<td>Neonatal alloimmune or maternal autoimmune TORCH</td>
</tr>
<tr>
<td></td>
<td>The most common acquired thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid antibodies may be present</td>
</tr>
<tr>
<td></td>
<td>Sepsis or other cause evident. Low coagulation factors</td>
</tr>
<tr>
<td></td>
<td>Microangiopathic haemolysis, usually normal INR and aPTT</td>
</tr>
<tr>
<td></td>
<td>Leukaemia, lymphoma, disseminated solid tumours, HLH</td>
</tr>
<tr>
<td></td>
<td>Severe aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic therapy, chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Platelets trapped in spleen, as in portal hypertension</td>
</tr>
</tbody>
</table>

HLH, haemophagocytic lymphohistiocytosis; TORCH, toxoplasmosis, other (e.g. HIV and parvovirus B19), rubella, cytomegalovirus, herpes simplex; vWF, von Willebrand factor.
Table 16.2.4  Treatment options for acute immune thrombocytopenic purpura with either bleeding problems or if the platelet count is less than 10 x 10^9/l

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Time course to resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>No drug side effects</td>
<td>Longest time to platelet &gt;20 x 10^9/l &lt;1% risk of ICH while awaiting platelet recovery</td>
<td>75% remission in 4–6 weeks 15% take 4–6 months</td>
</tr>
<tr>
<td>Corticosteroids (standard dose*)</td>
<td>No blood product exposure</td>
<td>Steroid side effects† common</td>
<td>1 week</td>
</tr>
<tr>
<td>Corticosteroids (high dose†)</td>
<td>No blood product exposure</td>
<td>Steroid side effects‡ less common</td>
<td>Platelets &gt;20 x 10^9/l: 2 days Platelets &gt;50 x 10^9/l: 3–4 days Platelets &gt;20 x 10^9/l: 1–2 days Platelets &gt;50 x 10^9/l: 3 days</td>
</tr>
<tr>
<td>Intravenous gammaglobulin (IVIG)§</td>
<td>Rapid rise in platelets</td>
<td>Pooled blood product with two viral inactivation steps</td>
<td></td>
</tr>
</tbody>
</table>

| **Second-line therapy** | | | |
| Anti-Rh(D) antibody | Most useful in children >5 years old with chronic ITP | Only useful in Rhesus-positive children Similar efficacy to IVIG and steroids | Rapid in the majority |
| Splenectomy | | Immunizations for meningococcus, Haemophilus influenzae and pneumococcus are mandatory Lifelong antibiotic prophylaxis | |

* Standard dose: prednisolone 2 mg/kg body weight daily for 21 days. † High dose: prednisolone 4 mg/kg body weight daily for 4 days. ‡ Steroid side effects include gastric irritation, transient diabetes and other metabolic derangements, immune suppression, cushingoid body fat distribution, growth delay, osteopenia and rarely avascular necrosis of the femoral head. § IVIG (e.g. Intragam P, Sandoglobulin) 0.8 g/kg body weight, repeat within 1–7 days if platelets remain <10 x 10^9/l or any platelet count with problematic bleeding. IVIG side effects include flu-like symptoms and rarely transient aseptic meningitis. Blood products may theoretically transmit viral and prion particles.

ICH, intracranial haemorrhage; ITP, immune thrombocytopenic purpura.

### Practical points

**Acute bleeding history**
- Differentiate ‘wet’ purpura (mucosal bleeding) from ‘dry’ purpura (skin bleeding) as some authorities claim increased likelihood of intracranial bleeding in the presence of wet purpura
- Always examine the fundi for bleeding changes
- Splenomegaly, lymphadenopathy or hepatomegaly indicate a systemic illness, e.g. Epstein–Barr virus infection, leukaemia
- Anaemia and reticulocyte response aid determination of severity and duration of bleeding

**Bleeding due to coagulation disorders**

**Physiology of coagulation**

Following the formation of a platelet plug at the site of vessel injury, fibrin is laid down and is cross-linked to form a protein mesh. This process (coagulation) is usually initiated by factor VIIa binding to exposed tissue factor (Fig. 16.2.2) This complex activates factors IX and X. Activated factor X recruits a cofactor, factor Va, to activate prothrombin (factor II). This process takes place on a phospholipid surface such as a platelet. Thrombin is a
powerful procoagulant, activating factors V, VIII and XI and cleaving fibrinogen to form fibrin. The activation of ‘upstream’ coagulation factor causes more thrombin generation (Fig. 16.2.3). Fortunately, thrombin also activates key inhibitors of coagulation to prevent excessive clot formation. Clearly a defect in any major protein could lead to significant bleeding problems.

**Clinical example**

Albert was born at term, received intramuscular vitamin K and developed a large bruise in his thigh. No circumcision was performed. He always seemed to have fingerprint bruises under his arms from being picked up. When he began sitting unaided he developed buttock bruising and when he began walking he presented to the accident and emergency department with a swollen, hot right ankle. The joint had virtually no movement and an ultrasound confirmed a fluid-filled joint. The history was highly suggestive of haemophilia. The INR was normal, the aPTT was 90 seconds and the factor VIII level was less than 1%. Haemophilia A was diagnosed and prophylaxis with 25 U/kg recombinant factor VIII three times per week was commenced. At the age of 4 years Albert fell from a chair on to his occiput after missing a dose of prophylaxis. Within 2 hours he had a falling level of consciousness and respiratory depression. A computed tomography scan diagnosed a subdural haematoma. Treatment with high-dose factor VIII and neurosurgical intervention led to an uneventful recovery.

**Haemophilia**

**Prevalence**

- Haemophilia A (factor VIII deficiency): 5–10 males per 100 000
- Haemophilia B (Christmas disease, factor IX deficiency): 0.5–1 per 100 000.
• Factor XI deficiency (haemophilia C): rare
• other factor deficiencies: exceedingly rare

Genetics
Haemophilia A and B are both X-linked. Up to one-third of all new cases of haemophilia are due to new mutations. Female carriers sometimes have low levels of factor VIII or IX and may have a bleeding disorder.

Severity
Defined by plasma factor level and correlates with clinical severity:
• severe: <2%, frequent spontaneous deep tissue bleeding
• moderate: 2–5%, infrequent spontaneous bleeding
• mild: 6–30%, bleeding with trauma and surgery, not spontaneously.

Clinical manifestations

Neonatal
A positive family history or known carrier status allows for definitive diagnosis in the newborn period. Cord blood genetics are most reliable. Some laboratories will perform factor VIII or factor IX assays on cord blood but technical difficulties may arise and results should be interpreted with caution. There is prolonged bleeding following circumcision. Intracranial haemorrhage is suspicious of a bleeding disorder in the term neonate.

Early childhood
Skin and soft tissue bleeds are common in the first year and beyond. Haemarthroses usually only occur once the child is walking. The ankles are common bleeding sites in young children; elbow and knee bleeding (Fig. 16.2.4) occur more commonly in older children.

Specific bleeds
Bleeding into the forearm may occlude the neurovascular bundle and cause a Volkmann ischaemic contracture. Bleeding into the posterior pharyngeal wall may interfere with respiration and cause dysphagia. Iliopsoas bleeding may be complicated by femoral nerve compression. Intracranial vascular accident is the cause of death in 7% of patients with haemophilia. Haematuria is common in adolescents and is seldom serious.

Chronic illness
There is synovial hypertrophy and arthritis. HIV/AIDS occurred in more than 50% of patients receiving blood products in the years 1980–1985. Hepatitis C infection is also common prior to viral identification, screening and viral inactivation of plasma products. Variant Creutzfeldt–Jakob disease (vCJD) is a prion disease. It has been shown to be transmissible in blood products and is not removed by current viral inactivation processes. Fortunately there have been no cases of vCJD described in patients with haemophilia. Psychosocial problems arise as a result of chronic illness, lifestyle restrictions and the need for injections.

Complications
Inhibitors are anti-factor-VIII or anti-factor-IX antibodies, which prevent regular doses of factor concentrate from working. Central lines may be required to ensure venous access in young children. These may be complicated by infection or large vein thrombosis.

Management
Correct or prevent the bleeding tendency
• mild and moderate haemophilia A often responds to desmopressin acetate infusions to elevate plasma factor VIII
• 1 unit of factor VIII/kg body weight given intravenously increases the factor VIII by approximately 2%
• life-threatening bleeds require plasma factor levels of more than 80%
• most other bleeds require plasma factor levels of 30–60%.
• prophylactic infusions of 25–40 U/kg three times a week ‘converts’ severe disease into moderate disease, thereby decreasing the risk of spontaneous bleeding.

Choice of product
• most developed countries, including Australia, now offer recombinant product to all haemophilia patients
• plasma-derived factor products are still available. These are screened for HIV and hepatitis B and C and then undergo two viral inactivation steps in the processing.

Orthopaedic
• rest, immobilization, ice, compression and elevation (RICE) are usually sufficient to control pain
• splinting followed by exercises when pain has settled preserves function.

Haemophilia centres
• focus of education and training for patient and family
• multidisciplinary group with expertise in haemophilia management.

Inhibitors
• occur in up to 30% of patients
• at least half of these are low-titre inhibitors, which can be treated by high-dose factor VIII
• high titre inhibitors require ‘immune tolerance’ therapy for eradication of inhibitor, and infusions of the factor VIII and IX bypass agent, recombinant factor VIIa, to treat bleeds.

Clinical example
Vanessa was a 13-year-old girl with menorrhagia since menarche. She had always had ‘easy bruising’ and required a transfusion after tonsillectomy due to excessive bleeding. She often bled from her gums after brushing her teeth. Her older sister and her mother both had heavy periods but neither had had severe postsurgical bleeding. Platelet count, INR and aPTT were all normal. von Willebrand antigen was 30%, activity (ristocetin cofactor) 25% and factor VIII 35%. She was diagnosed with mild von Willebrand disorder.

Von Willebrand disorder
This disorder has the following features:
• quantitative (types 1 and 3) or qualitative (type 2) defect in von Willebrand factor (vWF), a molecule which assists platelet adhesion to the subendothelium

• Common: 125 per million population
• Type 1 is inherited as autosomal dominant, is mild and is the most common
• Types 2 and 3 are rare
• Mucosal bleeding, excessive bruising and postoperative or post-traumatic bleeding
• Prolonged bleeding time but normal INR and aPTT, unless severe disease is present
• Abnormal vWF antigen and activity (ristocetin cofactor)
• Treatment for type 1 vWF is DDAVP which releases stored vWF/factor VIII
• DDAVP may be repeated once stores have reaccumulated, usually after 12–24 hours
• Plasma derived factor VIII products often contain vWF and may be used in those unresponsive to DDAVP
• Cryoprecipitate should be avoided due to lack of viral inactivation.

Haemorrhagic disease of the newborn
Haemorrhagic disease of the newborn fortunately is now rare, since the introduction of routine vitamin K administration for all babies at the time of delivery. Features of haemorrhagic disease of the newborn:
• Coagulation factors requiring vitamin K for post-transcriptional modification:
  • factor II (prothrombin)
  • factor VII
  • factor IX
  • factor X
  • protein C and S
These fall in neonates as a result of nutritional deficiency
• Bleeding is usually from the gastrointestinal tract or following circumcision
• Occurs early, often day 2–3
• Prophylactic vitamin K eliminates this disease
• Vitamin K 1 mg given by the intramuscular route stops bleeding rapidly.

Clotting due to coagulation disorders

Physiology of anticoagulation
The formation of a fibrin clot is tightly regulated in its local environment by anticoagulants. Local thrombin binds thrombomodulin located on normal endothelium which activates protein C. Activated protein C (APC) with the cofactor, protein S, inhibits
factors Va and VIIIa by cleaving the molecules. A mutation of factor V at one cleavage point prevents the APC inhibitory effect and is termed APC resistance. The mutation is called factor V Leiden. The other key coagulation inhibitor is antithrombin, a direct inhibitor of thrombin and also factors Xa, IXa, XIa and XIIa. Heparins potentiate the effect of antithrombin greatly. The largest risk factor for paediatric thrombosis is not a protein deficiency but the presence of a central venous catheter.

Table 16.2.5 lists the causes and features of thrombosis in childhood.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical features</th>
<th>Diagnostic tests</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous access device</td>
<td>Blocked access/emboli, limb swelling</td>
<td>Echocardiography and contrast radiography</td>
<td>Heparin. Removal of device</td>
</tr>
<tr>
<td>Phospholipid antibodies</td>
<td>Superficial/deep vein thrombosis</td>
<td>Prolonged INR/aPTT, not corrected by normal plasma</td>
<td>Often no therapy, may require corticosteroids or heparin</td>
</tr>
<tr>
<td>Protein C and S homozygous</td>
<td>Purpura fulminans</td>
<td>Very low protein C or S</td>
<td>Protein C replacement + heparin</td>
</tr>
<tr>
<td>Protein C and S heterozygous</td>
<td>Superficial/deep vein thrombosis; rare cerebral, mesenteric and renal vein thrombosis</td>
<td>Low protein C or S</td>
<td>Heparin followed by long term warfarin</td>
</tr>
<tr>
<td>Factor V mutation, (Arg506 to Gln), ‘FV Leiden’</td>
<td>Early onset vascular disease in family</td>
<td>Activated protein C resistance test</td>
<td>Heparin and long term warfarin</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Venous thrombosis in adolescence</td>
<td>Decreased level of antithrombin</td>
<td>Antithrombin replacement, heparin and warfarin</td>
</tr>
<tr>
<td>Dysfibrinogenaemia</td>
<td>Rare thrombosis in childhood</td>
<td>Prolonged thrombin time and snake venom times</td>
<td>Replacement therapy</td>
</tr>
<tr>
<td>Homocysteinaemia</td>
<td>Arterial and venous thrombosis</td>
<td>Biochemical tests</td>
<td>Diet and short-term anticoagulants</td>
</tr>
</tbody>
</table>
The last 30 years have seen dramatic improvements in the treatment of childhood cancer. Survival rates have climbed from below 30% to more than 80%. This improvement is largely due to the use of clinical cancer trials conducted through collaborative national and international childhood cancer study groups and underpins the need for a cohesive approach to the treatment of rare diseases. Prompt referral to a paediatric oncology centre for diagnostic workup and management is critical for all children with a suspected malignancy. A multidisciplinary team approach utilizing skills of specialist medical, nursing and allied health practitioners is the gold standard in delivery of excellence in care to children with cancer.

Reflecting improved cure rates, it is projected that by 2010, one in every 250 adults will be a survivor of childhood cancer. This has lead to widespread study of potential late effects of cancer treatments in childhood. Despite these remarkable improvements, it is sobering to acknowledge that 20–25% of children diagnosed with cancer are not cured with current therapies. Childhood cancer remains the leading cause of disease-related mortality among children. This clearly dictates the need for ongoing research to improve survival outcomes.

There are four principal therapeutic modalities used in the treatment of childhood cancers; surgery, radiotherapy, chemotherapy and biological therapies. These are used as single agents or in combination depending on tumour type and stage.

Incidence and distribution of childhood cancers

Approximately 1 in 600 children will be diagnosed with cancer before the age of 15 years. The distribution of cancer types in children aged 0–14 years is shown in Table 16.3.1. Acute leukaemia (acute lymphoblastic (ALL) or acute myeloblastic leukaemia (AML)) accounts for close to one-third of all childhood cancer. Primary brain or central nervous system (CNS) tumours are the most common solid cancer, followed by lymphoma, neuroblastoma, Wilms tumour, bone tumours and soft tissue sarcomas.

Aetiology of childhood cancer

When confronted with a diagnosis of childhood cancer, parents often ask ‘Why did this happen to my child?’ or ‘Did this happen because of something I have done or passed on to my child?’. With the exception of several known predisposing genetic syndromes (Table 16.3.2) the proportion of paediatric cancers that have a clearly hereditary component is small. Similarly, despite extensive epidemiological studies, few environmental agents have been consistently linked with childhood malignancy. Broadly speaking, it is hypothesized that cancer initiation results from a series of genetic mutations resulting in the inability of a cell to respond normally to intracellular and/or extracellular signals that control cell proliferation, differentiation or death (apoptosis). Examples include mutations involving tumour suppressor genes (e.g. RB1, p53 or WT1) or activation of cellular proto-oncogenes (e.g. myc or abl). The number of required genetic alterations may differ depending on the type of malignancy from as few as one to a complex cascade arising directly or indirectly from inherited gene mutations, environmental, chemical or radiation-induced DNA damage or random errors in DNA synthesis.

Acute leukaemia

While the cause of leukaemia remains unknown, the prevailing theory for leukemic development is that a mutant stem cell, capable of indefinite renewal, gives rise to abnormal proliferation of lymphoblasts (ALL) or myeloblasts (AML) in the bone marrow. These cells occupy the marrow space, leading to reduced numbers of normal haematopoietic cells, resulting ultimately in pancytopenia. Secondary involvement of the reticuloendothelial system (leading to lymphadenopathy and hepatosplenomegaly), bone, joints and rarely CNS, testes and skin can occur. A two-step pathogenesis for ALL (Greaves’ hypothesis) has been suggested, with the initial event, occurring during fetal life, driving clonal expansion and a second trigger occurring during childhood, possibly resulting from viral stimuli of cellular proliferation.
This theory stems from evidence that a significant proportion of children presenting with ALL have molecular evidence of leukaemic clones identified retrospectively at birth on newborn screening cards.

**Table 16.3.1 Frequency of malignancy in childhood**

<table>
<thead>
<tr>
<th>Malignant disease</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>35</td>
</tr>
<tr>
<td>Primary central nervous system tumours</td>
<td>20</td>
</tr>
<tr>
<td>Lymphoma: non-Hodgkin and Hodgkin</td>
<td>10</td>
</tr>
<tr>
<td>Wilms tumour</td>
<td>6–8</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>6–8</td>
</tr>
<tr>
<td>Rhabdomyosarcoma, soft tissue sarcoma</td>
<td>5</td>
</tr>
<tr>
<td>Sarcoma of bone: Ewing and osteosarcoma</td>
<td>4</td>
</tr>
<tr>
<td>Histiocytosis</td>
<td>5</td>
</tr>
<tr>
<td>Teratoma</td>
<td>2</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 16.3.2 Inherited/genetic syndromes associated with increased risk of childhood malignancy**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Associated syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Trisomy 21, Bloom syndrome, Fanconi anaemia, ataxia telangiectasia, neurofibromatosis, Kostmann syndrome, Klinefelter syndrome, Li-Fraumeni syndrome, Diamond–Blackfan anaemia, Noonan syndrome</td>
</tr>
<tr>
<td>CNS Tumours</td>
<td>Neurofibromatosis, tuberous sclerosis, Li-Fraumeni syndrome, von Hippel–Lindau syndrome</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Immunodeficiency disorders</td>
</tr>
<tr>
<td>Wilms tumour</td>
<td>Denys–Drash syndrome, Beckwith–Weidemann syndrome, WAGR syndrome</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Li-Fraumeni syndrome</td>
</tr>
</tbody>
</table>

ALL accounts for 80% of all childhood leukaemia, with AML accounting for the majority of the remainder. In ALL, presentation peaks at age 2–5 years, whereas there is no peak in AML. Chronic leukaemia, including chronic myeloid leukaemia (CML) and juvenile myelomonocytic leukaemia (JMML), is rare, accounting for fewer than 5% of cases.

Leukaemia can be further classified on the basis of morphological characteristics, immunobiology and cytogenetic or molecular markers. Immunophenotype as determined by flow cytometric detection of cell surface antigens is commonly used to differentiate distinct ALL categories into:

- precursor B-cell ALL (early pre-B, pre-B, transitional pre-B) – 80–85%
- mature B-cell ALL – 2–3%
- T-cell ALL – 10–15%.

In AML, characteristic morphological and cytochemical features include the presence of Auer rods as well as positive staining for myeloperoxidase and monocyte-associated esterases. Classification into one of eight morphological subclasses using the French/American/British (FAB) system is possible. In addition to morphology and immunophenotype, genetic features of leukaemic cells can provide diagnostic and prognostic information. In ALL, for example, the number of chromosomes per leukaemic cell influences prognosis, with more favourable survival in patients with hyperdiploid leukaemic cells (>50 chromosomes per cell). Specific chromosomal translocations can also be identified, e.g. t(8;14) in B-cell ALL and the unfavourable t(9;22) or the BCR-abl gene (Philadelphia chromosome) identified in CML and 5% of paediatric patients with ALL. In AML, characteristic translocations are seen within FAB morphological subgroups: for example, M3 or acute promyelocytic leukaemia (APML) is identified by the translocation t(15;17), and t(8;21) is a favourable cytogenetic abnormality seen in FAB M1 and M2.

**Acute lymphoblastic leukaemia**

The clinical presentation of ALL can be quite variable; however, most children will present with a 3–4-week prodrome that may include pallor, increased bruising or bleeding, lethargy, anorexia, recurrent infection or fevers, anorexia, bone pain or reluctance to walk. Physical examination may show:

- pallor (80%)
- petechiae (50%)
- lymphadenopathy (35%)
- hepatomegaly or splenomegaly (50–60%)
- rarely, skin infiltration (chloroma) and testicular infiltration (usually presents as a painless swelling).
The peripheral blood film can be normal but will usually demonstrate the presence of leukaemic blasts with or without anaemia and thrombocytopenia. The white blood cell count (WCC) is frequently elevated at diagnosis (leucocytosis), with a presenting WCC below $10 \times 10^9/l$ in 25%, $10-50 \times 10^9/l$ in 50% and above $50 \times 10^9/l$ in 25% of patients. A bone marrow aspirate and biopsy (trephine) are the gold standard diagnostic tests and will show replacement of normal haematopoiesis by leukaemic cells. A lumbar puncture is also done during the staging work-up with approximately 5–10% of patients showing leukaemic spread to the cerebrospinal fluid (CSF). T-cell leukaemia, more common in older boys, presents with a mediastinal mass in 50% that can result in life-threatening airway compression and obstruction of the superior vena cava. 30% of patients with T-cell ALL present with a leucocyte count greater than $100 \times 10^9/l$ and there is a higher incidence of CNS disease.

Table 16.3.3 shows prognostic risk factors for ALL. Clinical features such as age and WCC at diagnosis are becoming less significant with the advent of newer molecular methodologies. Furthermore, the response to treatment is becoming a critical determinant in prognosis. For example, reduction of initial blast count following steroid therapy is an important prognostic factor, as is detection of minimal residual disease (MRD) by molecular methods after exposure to chemotherapy.

Current combination chemotherapy protocols for ALL result in cure of 80% of patients. Much of the required therapy can be given on an outpatient or day-stay basis. Treatment consists of phases of therapy including induction, consolidation, CNS directed therapy, re-induction and continuation or maintenance therapy. By the end of the first month of therapy (induction) with 3–4-drug combination chemotherapy (vincristine, asparaginase, prednisone, daunorubicin), remission will be achieved in more than 95% of patients. Further combination therapy is required to prevent relapse. The optimal total duration of therapy is not known – most centres elect to treat for 2–3 years. CNS-targeted therapy using high-dose intravenous and intrathecal methotrexate has allowed for cranial irradiation to be generally avoided except in patients with overt CNS disease at diagnosis, sparing potential deleterious effects on cognition and growth.

| Table 16.3.3 Risk group classification for acute lymphoblastic leukaemia |
|-----------------------------|-----------------------------|-----------------------------|
| Risk group                  | Clinical features           | Molecular/genetic features  |
| Low risk                    | Age 2–10 years, WCC <50 × 10⁹/l | DNA index >1.6              |
|                            | Not T-cell phenotype        | Absence of: t(9;22) BCR–abl |
|                            | No central nervous system or testicular disease | t(1;11) MLL/AF⁶ |
|                            | Rapid response to induction therapy | t(1;19) TXL/AML |
|                            |                             | MLL rearrangement           |
| High risk and very high risk| Induction failure            | t(9;22), t(4;11)            |
|                            | Age < 12 months             | MLL rearrangements          |
|                            | Poor prednison response     |                             |
|                            | High MRD levels             |                             |
Acute myeloid leukaemia

AML accounts for 20% of acute leukaemia. Presenting symptoms and signs are similar to ALL and can include pallor, bleeding, fever, anorexia, malaise and bone pain. Certain subtypes of AML have more distinctive presenting clinical features. Acute promyelo- cytic leukaemia (APML) can present with serious haemorrhage or disseminated intravascular coagulation, whereas acute monoblastic or myelomonoblastic leukaemia may present with skin infiltration (chloroma) or gum hypertrophy. CNS leukaemia is diagnosed in 5–15% of patients. Like ALL, the differential diagnosis can include infection, juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, aplastic anaemia and osteomyelitis.

In contrast to ALL, therapy for AML is of shorter duration and more intensive, often requiring frequent hospital admissions with aggressive supportive care, including blood products and antimicrobials during lengthy periods of marrow suppression. Overall, the outlook for patients with AML is less optimistic, with survival rates reported of 50–70%.

Clinical example

Angela was a 10-year-old girl who presented with a 1-week history of lethargy, poor appetite, recurrent epistaxis and gum bleeding on brushing her teeth. Examination revealed anaemia, gum hypertrophy, bruising on the lower limbs and trunk, hepatosplenomegaly and inguinal lymphadenopathy. A full blood count confirmed anaemia and thrombocytopenia with a haemoglobin of 8.2 g/l and platelets $12 \times 10^9/l$. Leukocytosis was noted, with a white cell count of $120 \times 10^9/l$ with circulating blast cells. Coagulation profile was prolonged, consistent with mild disseminated intravascular coagulation. Bone marrow aspirate confirmed the diagnosis of acute monocytic leukaemia. Lumbar puncture was performed to exclude CNS spread. A double-lumen central line was inserted following attention to thrombocytopenia and coagulation abnormalities, and combination chemotherapy was commenced as soon as practical. Tumour lysis syndrome or uric-acid-induced nephropathy can be an early complication of leukaemia therapy as tumour cells die, releasing uric acid, potassium and phosphate with consequent life-threatening electrolyte abnormalities and renal impairment. Vigorous hydration with intravenous fluid, forced diuresis and allopurinol are standard. Dialysis is occasionally required.

Haematopoietic stem cell transplant

For most patients with high-risk, relapsed or refractory leukaemia, haematopoietic stem cell transplantation is the treatment of choice. Stem cells can be sourced from the bone marrow, from peripheral blood or from the umbilical cord of a newborn infant. Siblings have a 25% chance of being an identical match. Those lacking a sibling donor are reliant on volunteer bone marrow and cord blood donors sourced through international donor registries. Umbilical cord blood transplants are used with increased frequency because of the advantages of speed of availability and greater likelihood of matching.

Brain and central nervous system tumours

Brain tumours or tumours of the CNS are the most common solid cancer, representing approximately 20% of all childhood malignancies. Brain tumours as a group are heterogeneous with regard to clinical presentation, location, histological type and natural history. 95% of CNS tumours occur within the brain, often in specific sites for different age groups. Posterior fossa tumours are more common in childhood, except during the first year of life, and in adolescence, where supratentorial sites predominate. The most common histological subtypes are:

- astrocytomas (50%)
- primitive neuroectodermal tumours (21%)
- gliomas (15–20%)
- ependymomas (9%).

Table 16.3.4 shows a working classification of CNS tumours. Early symptoms and signs of CNS tumours may be few and difficult to elicit (Table 16.3.5). Evidence of raised intracranial pressure is the most common because posterior fossa and deep midline tumours usually obstruct CSF pathways. Treatment of brain tumours depends on tumour type and location and can include surgery, chemotherapy and radiation therapy. A number of factors impact on outcome and survival, including age, tumour location and operability, histological subtype and

<table>
<thead>
<tr>
<th>Table 16.3.4 Central nervous system tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Supratentorial</td>
</tr>
<tr>
<td>a. Hemisphere: astrocytoma; glioblastoma; primitive neuroectodermal tumour</td>
</tr>
<tr>
<td>b. Midline: craniopharyngioma; optic nerve glioma; pineal</td>
</tr>
<tr>
<td>2. Infratentorial</td>
</tr>
<tr>
<td>a. Cerebellar and fourth ventricle: astrocytoma; medulloblastoma; ependymoma</td>
</tr>
<tr>
<td>b. Brain stem: brain-stem glioma</td>
</tr>
<tr>
<td>3. Spinal cord</td>
</tr>
<tr>
<td>Astrocytoma; ependymoma</td>
</tr>
</tbody>
</table>
presence or absence of neuraxis dissemination. Survival has improved considerably over time for some types of tumour, notably medulloblastoma. For other tumour subtypes, however, such as brain-stem gliomas, outcome remains poor. Additionally, increasing attention is being paid to the longer-term toxicity of treatment. This is particularly true of radiation therapy, which, where possible, is spared in younger children because of the potential impact on cognition and growth.

### Lymphoma

Lymphomas, accounting for approximately 10% of childhood cancers, are the third most common form of malignancy in childhood. There are two basic types: non-Hodgkin lymphoma (NHL) and Hodgkin disease. Both are more common in boys than in girls. Although lymphadenopathy attributable to an infectious aetiology is more common in childhood, any child with persistent adenopathy (>2–3 weeks) should be considered for a biopsy. Site of adenopathy (e.g. supraclavicular) or character (firm, >1–2 cm) may indicate the need for earlier biopsy.

#### Non-Hodgkin lymphoma

Childhood NHL has quite different features from its adult counterpart. Childhood NHL is more often disseminated, diffuse not nodular, high-grade immature T- or B-cell lineage with frequent spread to extranodal sites, marrow and CNS. In contrast, NHL occurring in adulthood is usually a low-grade malignancy with predominantly nodal involvement. Clinical and pathological staging is achieved with organ imaging (computed tomography (CT) of chest/abdomen/pelvis, positron emission tomography (PET) scan or gallium scan), lymph node biopsy/resection, bone marrow aspirate and biopsy (trephine) and CSF examination. When more than 25% of bone marrow is involved, disease is classified as T- or B-cell ALL. NHL in childhood can be classified as:

- lymphoblastic NHL – diffuse, poorly differentiated, primarily T-cell lineage
- small non-cleaved (undifferentiated) Burkitt or non-Burkitt subtypes, primarily of B-cell origin. A t(8;14) translocation is characteristic of Burkitt lymphoma
- large cell lymphoma – can be cleaved or non-cleaved and of B-cell or T-cell origin.

A mediastinal primary of T-cell immunophenotype accounts for 25% of NHL and often presents with acute superior vena caval and/or airway obstruction (a medical emergency) producing stridor and cough, usually with an associated pleural effusion and characteristically occurring in preteen or early teenage males. Diagnosis, immunophenotyping and cytogenetics may be made on pleural aspirate, suprasternal or supraclavicular node biopsy, or rarely on direct biopsy of the mediastinal mass. Abdominal lymphoma accounts for 35–40%, is of B-cell immunophenotype and characteristically presents as either local tumour causing intussusception and readily removable, or massive diffuse abdominal disease, often with ascites. The later is often associated with uric-acid-induced nephropathy or tumour lysis syndrome. Release of uric acid, potassium and phosphate from rapidly growing tumours, particularly following commencement of chemotherapy.

<table>
<thead>
<tr>
<th>Table 16.3.5</th>
<th>Signs and symptoms of brain and central; nervous system tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raised intracranial pressure</strong></td>
<td>Headache, often on waking</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Papilloedema</td>
</tr>
<tr>
<td></td>
<td>Tense fontanelle and increased head circumference in infants indicating hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Drowsiness, bradycardia and hypertension (late signs)</td>
</tr>
<tr>
<td><strong>Posterior fossa signs</strong></td>
<td>Truncal ataxia due to central cerebellar tumours</td>
</tr>
<tr>
<td></td>
<td>Coordination difficulties and tremor due to lateral lesions</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve palsies, suggesting a brain-stem lesion</td>
</tr>
<tr>
<td></td>
<td>Defective upward gaze with tumours of the pineal region</td>
</tr>
<tr>
<td></td>
<td>Deep midline tumours around the third ventricle</td>
</tr>
<tr>
<td></td>
<td>Impaired visual acuity and visual field defects due to craniopharyngioma or optic nerve glioma</td>
</tr>
<tr>
<td></td>
<td>Diabetes insipidus and growth failure</td>
</tr>
<tr>
<td></td>
<td>Severe wasting and anorexia due to the diencephalic syndrome of a hypothalamic tumour</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>Uncommon as sole presenting symptom</td>
</tr>
<tr>
<td></td>
<td>Consider tumour with focal seizures or progressively more difficult to control seizures</td>
</tr>
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</table>
can result in significant renal impairment and life-threatening electrolyte disturbances (hyperkalaemia, hyperphosphataemia, hypocalcaemia).

Following pathological diagnosis and staging, multiagent chemotherapy is initiated; the intensity and duration depends upon stage and immunophenotype. Stages I and II have a more than 90% cure rate and stages III and IV a 70–80% cure rate.

**Clinical example**

Luke was a 12-year-old boy with a short history of cough, wheeze and sudden onset of faint stridor. Examination revealed supraclavicular adenopathy, a mass palpable in the suprasternal notch, decreased air entry and dullness to percussion note at the right base. Luke's face was suffused with venous distension. Symptoms and signs suggested superior vena cava syndrome with airway obstruction. This constituted an oncological emergency. Chest X-ray confirmed a large mediastinal mass and a right pleural effusion. Urgent diagnosis and commencement of therapy (steroids) was required to prevent complete airway obstruction. Thoracentesis and cytological analysis confirmed that the diagnosis was T-cell lymphoblastic lymphoma. Precautionary admission to the intensive care unit was recommended. Full staging workup required chest/abdo/pelvis CT, nuclear medicine PET or gallium scan, bone marrow biopsies and lumbar puncture. Although uncommon, the diagnosis of an obstructive mediastinal mass should be entertained in children/adolescents with onset of wheezing, particularly when there is no prior history of asthma.

**Hodgkin disease**

Hodgkin disease, more common in boys than girls, is rare before the age of 5 years, with a progressively increasing incidence in adolescents. A viral aetiology is suspected, with the genome of Epstein–Barr virus identified in some Hodgkin cells; however, the significance of this is not clear. A painless progressive swelling of lymph nodes (above the diaphragm in two-thirds of patients) is the most common clinical presentation. Dissemination to spleen, liver, lungs, bones and bone marrow can occur. Constitutional symptoms, including weight loss, night sweats, rash and fever, occur in one-third of patients. Open biopsy confirms the diagnosis and pathological staging with CT chest/abdo/pelvis, gallium or PET scan and marrow aspirate and trephine completes the workup. Chemotherapy is the mainstay of treatment, with radiotherapy having a supplemental role in patients with massive mediastinal involvement. Cure rates are excellent, with survival greater than 90%. Emphasis on cure without cost has become paramount in this disease, with a shift to therapy combinations that allow for preservation of fertility, reduction in rates of secondary cancers (associated with the use of radiation and etoposide) and reduced longer-term organ morbidity (e.g. lung toxicity with bleomycin, cardiomyopathy with anthracyclines) without compromising cure rates.

**Neuroblastoma**

Accounting for about 8–10% of childhood cancers, neuroblastoma is the most common extracranial solid tumour in childhood. Most cases occur in children under the age of 5 years, with a median age at presentation of 23 months. Neuroblastoma along with ganglioneuroblastoma and ganglioneuroma derive from primitive neural crest cells. Variations in the location, degree of differentiation, clinical and biological behaviour of these tumours are diverse. Spontaneous regression and differentiation into benign neoplasms is seen at one end the spectrum and highly aggressive tumours resistant to intensive chemotherapy at the other. Metastatic neuroblastoma in children older than 1 year has a poor prognosis. Unfortunately, over 75% of patients present with metastatic disease at the time of diagnosis.

The clinical manifestations of neuroblastoma are variable and depend on primary site and the extent of disease. The classic presentation is of a 3–4-year-old, pale, irritable child reluctant to walk, with peri-orbital ecchymoses. Primary tumours can commonly arise in the abdomen (70%), in the adrenal gland or abdominal paravertebral sympathetic chain. Disease arising in the thorax (25%) or pelvis (5%) occurs less commonly. Various paraneoplastic syndromes, including hypertension, secretory diarrhoea and opsomyoclonus, have been reported at presentation. The latter, occurring in 5% of patients with neuroblastoma, is a syndrome of myoclonic, irregular, jerking random eye move-ments that can be associated with cerebellar ataxia. Common sites for metastatic disease are bone, lymph nodes and bone marrow. Neuroblastoma can present in the newborn or early neonatal period. Infants <12 months with Stage IVs disease (localized primary tumour with metastatic disease to skin, liver or bone marrow, but not bone cortex) generally have excellent survival, with tumours spontaneously regressing without the need for treatment.

Biopsy is required for histological diagnosis. Staging investigations include CT/magnetic resonance imaging (MRI) scan of the primary tumour, bilateral bone marrow aspirate and trephine (core) biopsies, bone scan and meta-iodobenzylguanidine (MIBG) scan. MIBG is a radiolabelled compound taken up by cells of the sympathetic nervous system that demonstrates catecholamine synthesis.
Approximately 90–95% of neuroblastomas show uptake of MIBG. Measurement of urinary catecholamines is also a valuable test both at diagnosis and to assess disease responsiveness, with 90–95% of patients with neuroblastoma excreting elevated levels of vanillylmandelic acid, homovanillic acid and other catecholamines. Serum levels of lactate dehydrogenase, ferritin and neuron-specific enolase are also elevated in neuroblastoma.

Diagnosis is confirmed by histology following biopsy of tumour. Neuroblastoma is one of the ‘small, round, blue cell’ cancers of childhood that also include Ewing sarcoma, NHL, rhabdomyosarcomas and primitive neuroectodermal tumours. Pathological grading systems, including the Shimada criteria and the International Neuroblastoma Pathology Classification, help in defining the patient with a poor prognosis. The N-myc oncogene is present in increased numbers of copies in about 30% of neuroblastomas and correlates with poor survival.

Treatment depends on staging and includes surgical resection only in stage I and II disease, chemotherapy and surgery in stage III disease and intensive chemotherapy, surgical resection, tumour bed irradiation and autologous bone marrow transplantation in stage IV patients, as well as a subset of patients with high-risk stage III disease. Long-term survival in stage IV patients remains poor at 30–50%. Novel cytotoxic agents, targeted radionucleotide therapy and immune-mediated therapy are all currently being investigated in clinical trials.

**Wilms tumour (nephroblastoma)**

Wilms tumours account for 6% of childhood malignancies and represent the vast majority of primary renal cancers in childhood. Over 90% of children diagnosed with Wilms tumour are under 5 years of age.

**Clinical presentation, differential diagnosis, staging and treatment of Wilms tumour**

- Clinical presentation is most commonly with abdominal swelling or an asymptomatic abdominal mass
- Malaise, abdominal pain, gross or microscopic haematuria, fever, anorexia or hypertension occur in approximately 25% of patients
- 8–10% of patients with Wilms tumour will have an acquired von Willebrand factor abnormality with prolonged coagulation studies at diagnosis
- Differential diagnosis includes polycystic kidney disease, hydronephrosis, hepatoblastoma and neuroblastoma
- Common sites of blood-borne metastases are liver and lung. Extension to regional lymph nodes, hepatic adhesion and tumour invasion of the renal vein and inferior vena cava which can extend up to the right atrium can occur rarely
- Investigations usually include a contrast-enhanced CT scan of abdomen ± lungs, chest X-ray and abdominal ultrasound, with Doppler if tumour extension or involvement of the inferior vena cava is suspected
- Through collaborative multimodal clinical trials, survival of Wilms tumour patients exceeds 90% overall. Surgery can be performed up front or delayed until after response to chemotherapy. The frequency and intensity of chemotherapy depends on stage and histological subtype (favourable versus unfavourable or anaplastic). Radiotherapy is used in patients with stage III and IV disease. Cure rates exceed 90% for stage I–III and 85–90% for stage IV disease.

**Clinical example**

Brigitte, aged 4 years, was brought into the Emergency Department with a short history of abdominal pain, fever, general malaise and weight loss. On examination, she appeared to be an irritable child with tachycardia and mild hypertension. She had a distended abdomen with a large, poorly defined, palpable, hard mass in the periumbilical area. A plain X-ray showed calcification within the mass. A large primary adrenal mass was confirmed on CT imaging. Open biopsy confirms neuroblastoma and the remaining staging examination (bone marrow biopsy, nuclear medicine bone scan and MIBG scan) demonstrated metastatic disease to the bone marrow and bone cortex of three vertebrae. Differential diagnosis of an abdominal mass in childhood includes neuroblastoma, Wilms tumour, lymphoma, rhabdomyosarcoma and germ cell tumours.

**Rhabdomyosarcoma and soft tissue sarcoma**

Soft tissue sarcomas make up 5% of paediatric cancer; about 50% of these are rhabdomyosarcomas. Rhabdomyosarcomas occur in early childhood with a median age at diagnosis of 5 years. There is a recognized association between rhabdomyosarcoma and familial syndromes, including neurofibromatosis and Li–Fraumeni syndrome. Li–Fraumeni syndrome includes clusters of soft tissue sarcomas, adenocortical carcinoma and early-onset breast cancer and results from germline mutations in the p53 tumour suppressor gene. Rhabdomyosarcomas are included in the small, round, blue cell tumours of childhood and are thought to arise from mesenchymal cells committed to muscle differentiation. There are two major histological subtypes of rhabdomyosarcoma: embryonal (80%) and the more aggressive alveolar (20%).
Clinical presentation varies widely depending on the site of the primary disease, which can include:

- orbit, head and neck including parameningeal (40%)
- extremities (20%)
- genitourinary (20–25%)
- trunk (10–15%).

Approximately half of all patients will have unresectable tumours at diagnosis. Less than 25% of patients will have metastatic disease at diagnosis involving lung, bone marrow, bone or lymph nodes. MRI of primary tumour is the investigation of choice for children with rhabdomyosarcomas. Technetium-99m bone scan, CT of the lung and bone marrow biopsy are required to assess for metastatic disease. Therapy for rhabdomyosarcomas depends on the location and stage of disease and is often multimodal, involving surgery, adjuvant chemotherapy and radiotherapy. Prognostic variables include metastatic disease at diagnosis, site of disease, surgical resectability, histological subtype and age. Early-stage disease is curable in more than 85% of patients. Patients with more aggressive disease have a poorer prognosis, ranging from 30–50% depending on risk factors.

**Osteosarcoma and Ewing sarcoma**

Primary bone tumours in childhood occur less frequently than bony metastases to the skeleton. Bone tumours are the sixth most common tumour type in childhood, increasing to the third most frequent tumour type in adolescence and young adults. Osteosarcoma is more common than Ewing sarcoma.

**Osteosarcoma**

The peak incidence of osteosarcoma occurs in the second decade of life during the adolescent growth spurt, and the condition occurs more commonly in males. For the most part, the aetiology of osteosarcoma is not clear. There is a known association with exposure to ionizing radiation, although this accounts for only a small proportion of patients diagnosed with osteosarcoma. Mutations in two recessive oncogenes, RB (the retinoblastoma susceptibility locus) and p53, have been postulated to play a role in tumorigenesis in osteosarcoma. The commonest mode of presentation is with bone pain, with associated swelling and decrease in activity.

The following are important to note:

- approximately 60% of osteosarcoma arise around the knee, in the metaphysis of the femur or tibia
- metastatic disease can occur to lungs and less commonly to bones
- diagnostic workup should include a plain X-ray and MRI ± CT of primary lesion, CT of the lung and bone scan to identify potential disease spread
- surgical biopsy is needed for definitive histological diagnosis. Treatment consists of chemotherapy followed by surgical resection of tumour. The traditional surgical approach to achieve local control of osteosarcoma of the extremity is amputation; however, modern techniques allow for limb-salvage surgery in the majority of patients
- cure rates for patients with non-metastatic disease at diagnosis are over 70%. Histological response of tumour following chemotherapy is a predictor of outcome, with patients with a good response (defined as >90% necrosis) having a long-term survival rate in excess of 80%, compared with poor or standard responders with a survival rate of 40–60%. The survival outcome for patients with metastatic disease at diagnosis remains poor, at less than 50%.

**Clinical example**

Peter, aged 13, had a 4-month history of pain around the knee. In the last 2 weeks this had become severe and he was able to walk short distances only. Peter recalled a minor injury playing sport at the onset of his symptoms 4 months ago. Examination demonstrated swelling on the medial aspect of the proximal tibia with a diffuse, firm, non-tender mass present. The most likely diagnosis was a bone or soft tissue sarcoma. Plain X-ray of the tibia confirmed a soft tissue mass and destructive bony lesion with “sunburst” appearance reflecting periosteal elevation in the metaphyseal region. CT and MRI scan were required to delineate anatomy, followed by biopsy, which confirmed osteosarcoma. Staging with CT lung and bone scan to determine extent of the disease were required. Prognosis and the therapy required depend on staging. A history of trivial injury is often associated with bone tumours but there is sparse evidence to suggest a causal relationship and more probably the injury serves as a trigger to seek medical attention.

**Ewing sarcoma**

Ewing sarcoma accounts for 10–15% of primary malignant bone tumours in childhood and adolescence. Most originate in the bone, although they can occasionally arise in soft tissue (extraosseous Ewing). The primary site of disease in Ewing sarcoma is either in the extremities (53%) or the axial skeleton (47%). The most common sites are:

- pelvis (25%)
- chest wall (20%)
- femur (15%)
- tibia (9%)
- vertebra (8%)
- fibula (7%)
- humerus (5%).
Unlike osteosarcomas, which typically arise from the metaphysis, Ewing tumours of the long bone more commonly originate from the diaphysis. Pain (96%) and a palpable mass (61%) are the most common presenting features. About 15% of patients have a pathological fracture at time of diagnosis. Approximately 25% of patients have a evidence of metastatic disease at diagnosis. Common sites of spread are lung, bone and bone marrow.

Diagnostic tests include plain X-ray of the lesion in two planes, with MRI as the gold standard for local staging. A CT scan of the primary lesion may also be required, particularly to demonstrate cortical fractures. A bone scan, bilateral bone marrow aspirates and biopsies and CT of the chest are performed at diagnosis to define the metastatic spread of disease. The typical X-ray appearance of Ewing sarcoma shows a poorly defined, destructive or ‘moth-eaten’ pattern, often accompanied by a multilaminated ‘onion skin’ periosteal reaction with elevation (Codman’s triangle). A tumour biopsy is required in all patients to confirm the histological diagnosis. The differential diagnosis includes non-malignant pathology (osteomyelitis, eosinophilic granuloma) and malignant pathology (osteosarcoma, lymphoma, neuroblastoma, spindle cell sarcoma). Molecular testing will identify a translocation involving t(11;22) or EWS (Ewing sarcoma gene) in over 90% of Ewing tumours.

Treatment consists of a combination of surgery, radiation and combination multiagent chemotherapy. Several prognostic factors have been identified, including tumour site, tumour size, histological grade, response to therapy and the presence or absence of overt metastatic disease at diagnosis. With current therapies, 60–70% of patients with localized disease will be cured. Survival for patients with metastatic disease remains poor, at less than 50%, underpinning the need for ongoing investigation into novel agents.

### Palliative care

Cancer is the most common cause of non-accidental death in childhood, with approximately 20–25% of children diagnosed with a malignancy dying of their disease. Optimal palliation requires open and ongoing communication between all members of the healthcare team, the child and family. Management of symptoms, including pain, dyspnoea, nausea/vomiting and bowel abnormalities, is important, as is optimization of psychological, social and spiritual needs. Open discussion regarding the desired place of death (e.g. home, hospital or hospice) should take place in advance. A child’s understanding of death will vary depending on age and the individual but many studies suggest that children as young as 6 have an understanding of death and should be given the opportunity to talk openly about their illness. Following the death of a child, one of the essential roles of the treating team is to provide bereavement support for parents and siblings.

### Rare tumours

A detailed review of all childhood malignancy is beyond the scope of this chapter. The reader is referred to more extensive paediatric oncology material for a review on retinoblastoma, hepatoblastoma, germ cell tumours, histiocytic disorders, nasopharyngeal carcinomas and other malignant diseases occurring in childhood.

### Late effects of cancer therapy

It is projected that by 2010 1 in 250 persons aged 15–45 years will be a survivor of childhood cancer. Although there has been considerable effort to reduce the toxicity of treatment protocols without compromising cure, based on current data, approximately 50% of long-term survivors of childhood cancer will have or develop disabilities that impact on quality of life. Clearly, the potential for the long-term toxicity of treatments should be discussed up front at the time of initial diagnosis, prior to treatment. Late effects depend on prior treatment exposure and can include growth failure, skeletal abnormalities, endocrinopathies, dental anomalies, learning disabilities, cardiopulmonary disease, hearing loss, infertility and second malignancy. Systematic surveillance and management of late effects of therapy is now the focus of many childhood cancer units and cooperative study groups.