5.13 Rheumatology

**BOX 5.13.1 Minimum standards**
- Penicillin.
- Aspirin.
- Prednisolone.
- Haloperidol, diazepam and lorazepam.
- Anti-endocarditis measures.
- IV gamma globulin if at all possible.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Sulphasalazine.
- Ocular steroids and mydriatics.
- Intra-articular steroids.
- Physiotherapy and family support.

Introduction
Making a diagnosis of a rheumatic disease in a child relies primarily on clinical skill and experience, as there are few diagnostic laboratory tests. Although these diseases are rare in children, symptoms that raise the possibility of rheumatic disease are common. Rheumatic symptoms may be relatively specific, such as joint swelling, or relatively non-specific, such as fever, lethargy, pallor, anorexia, failure to thrive, muscle weakness, musculoskeletal pain, rash, headache and abdominal pain. The interpretation of these clinical features requires a meticulous approach to characterising the nature of each feature and considering the overall pattern of all the clinical features in the individual patient. The aims of this section are to assist in the recognition of common patterns of clinical features, and to provide guidance for appropriate treatment and monitoring of rheumatic disease in children.

pGALS ( paediatric Gait, Arms, Legs and Spine) is a simple quick approach to joint examination and helps to discern abnormal from normal joints; this is especially useful in the context of non-specific features such as limp or fever. pGALS includes incorporates a series of simple manoeuvres to assess all joints quickly (takes approximately 2–3 minutes). It has been validated in school-aged children (although can be performed in younger children) and has been shown to be effective when performed by non-specialists in detecting significant joint abnormalities in acute paediatric practice (including in Africa). The interpretation of pGALS requires knowledge of normal musculoskeletal development and the clinical context to facilitate a differential diagnosis (www.arthritisresearchuk.org/health-professionals-and-students/video-resources/pgals.aspx).

Rheumatic fever
Rheumatic fever is an abnormal immune response to group A streptococcal infection in genetically susceptible individuals. It is most common between the ages of 6 and 16 years. Symptoms of acute rheumatic fever follow streptococcal pharyngitis after a latent period of approximately 3 weeks. The disease usually presents with joint pain, but may have an insidious onset, especially if carditis is the predominant feature. There is no definitive test, and diagnosis depends on recognition of clinical signs known as the Jones criteria.
Diagnosis: Jones criteria

The diagnosis in an individual is made by the Jones criteria (revised by the WHO in 2003) on the basis of the presence of either two major criteria (which include polyarthritis, erythema marginatum rash, subcutaneous nodules, carditis and chorea) or one major criterion and two minor criteria (minor criteria include persistent fever, arthralgia, raised ESR or CRP, persistent leukocytosis, abnormal ECG except if carditis is the major feature, and previous episode of rheumatic fever). Each combination must also include evidence of streptococcal infection, usually a rising titre of antistreptolysin O.

- Evidence of streptococcal infection (usually a pharyngitis secondary to group A beta-haemolytic streptococcus) with positive throat swab culture or, preferably, a positive serology for recent streptococcal infection. This is usually accompanied by a prolonged fever and followed by other clinical features after a 2- to 3-week period.
- Arthritis of the large joints. This is a reactive arthritis (rather than a septic arthritis), often affecting many joints, and it is migratory in nature. It usually responds dramatically to aspirin, up to 120 mg/kg/day in four to six divided doses by mouth after food, but do not exceed 75–80 mg/kg/day if facilities for assay of salicylate levels are not available. Alternatively, use non-steroidal anti-inflammatory drugs (NSAIDs; see below). The presence of joint pain without swelling (i.e. arthralgia alone) may still indicate rheumatic fever in the presence of the other clinical features compatible with a diagnosis of acute rheumatic fever.
- Rash and subcutaneous nodules: erythema marginatum is an uncommon feature. It has a “snake-like” appearance, usually over the trunk, and occurs early in the disease, is usually transient, and disappears within a few hours. Subcutaneous nodules are not uncommon, occurring over bony prominences such as the elbows and knees.
- Carditis: this may range from a tachycardia with a prolonged PR interval seen on the ECG through to myocarditis with a systolic apical mitral murmur, pericarditis or cardiac failure. Cardiac inflammation may involve the endocardium (valvulitis mostly affecting the mitral and aortic valve), the myocardium (impaired cardiac function) or the pericardium in severe cases (pericarditis). Examination may reveal a pericardial friction rub, an apical pansystolic murmur from mitral regurgitation, or an early diastolic decrescendo murmur from aortic regurgitation. As the valves heal they may scar and fibrose. Mitral regurgitation, mitral stenosis and aortic regurgitation are the commonest long-term consequences of acute rheumatic fever.
- Chorea is an involuntary movement disorder, often of the face, tongue and upper limbs. It may appear as dysarthria or clumsiness, and is associated with emotional lability. It is a late manifestation of acute rheumatic fever, and is more common in girls.

The disease may be prevented by detecting group A streptococcus in cases of pharyngitis (throat swab or rapid antigen test) and treating with penicillin (see below).

Treatment

Management of acute rheumatic fever

- Eradicate streptococcal infection (give oral penicillin V 10–12.5 mg/kg/dose (maximum dose 500 mg) three times a day for 10 days).
- Commence aspirin 90–120 mg/kg a day in four divided doses after food. Monitor serum salicylate levels (the optimal level is 15–25 mg/dL). Reduce the dose to two-thirds of the original dose when there is a clinical response.
- When the CRP and ESR decrease to normal levels, taper the aspirin dose over 2 weeks.
- Give prednisolone 2 mg/kg/day (maximum 60 mg/day) in place of aspirin if there is moderate to severe carditis or pericarditis.
- If prednisolone is given, continue treatment for 3 weeks, and then taper the dose over a further 2–3 weeks. As the prednisolone dose starts to taper, commence aspirin 50 mg/kg/day in four divided doses and stop aspirin 1 week after prednisolone is stopped.
- Treat heart failure as described in Section 5.4.B.
- Urgent valve replacement is sometimes required.

The requirement for bed rest during the acute attack is controversial; it is also very difficult to enforce on young children. For arthralgia, give aspirin as described above or an NSAID (e.g. ibuprofen 30–60 mg/kg daily up to a maximum of 2.4 G in three to four divided doses after food). Naproxen at 20 mg/kg/day in two divided doses appears to be a better alternative.

Treatment of streptococcal infection with IM benzylpenicillin (1.2 million units as a single injection, often given as 0.6 million units in each thigh) or a 10-day course of oral penicillin at high dose (12.5 mg/kg four times a day). Once there has been one episode of rheumatic fever a recurrence is likely. The recurrence risk is minimised by giving long-term penicillin prophylaxis, preferably for life. This is usually given as intramuscular injections of 1.2 million units of benzathine penicillin every 3 weeks (this drug must not be given IV). If oral penicillin is required, the highest dose generally recommended is 250 mg twice daily for all ages, as doses of oral penicillin in children below the age of 5 years need not be given because rheumatic fever does not occur in this age group. For patients who are allergic to penicillin, erythromycin in the same doses can be used.

For acute carditis, prednisolone given orally (2 mg/kg/ day) for 2–3 weeks or by intravenous infusion is effective.

Chorea may respond to haloperidol, 12.5–25 micrograms/kg twice daily (maximum 10 mg a day). Extrapyramidal side effects may occur. Chorea usually becomes less of a problem within a few weeks.

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**TABLE 5.13.A.1 Jones criteria for diagnosis of rheumatic fever**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Previous history of rheumatic fever</td>
</tr>
<tr>
<td>Migratory large-joint polyarthritis</td>
<td>Fever</td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>First-degree heart block</td>
</tr>
<tr>
<td>Chorea (onset 2–6 months after pharyngitis)</td>
<td>Elevated acute-phase reactants (ESR and CRP)</td>
</tr>
</tbody>
</table>
Vasculitis in children
Vasculitis in childhood may be primary, including Henoch–Schönlein purpura, Kawasaki disease and the rare vasculitides, or secondary to multisystem connective tissue diseases, including juvenile dermatomyositis and systemic lupus erythematosus (SLE). In all of these diseases, skin manifestations are usually prominent, but the combination with other clinical features helps to ascertain the diagnosis.

Henoch–Schönlein purpura (HSP)

Presentation
- Purpuric rash: a palpable purpuric rash is most commonly seen over the buttocks and around the ankles and legs. The purpura occurs in crops and may range from small petechiae-like lesions to large ulcerating ecchymoses. Oedema and urticaria may precede the purpura, particularly at the ankles, scrotum and face.
- Gastrointestinal pain: abdominal pain is a prominent feature early in the disease, and is often accompanied by vomiting. Occasionally, frank gastrointestinal haemorrhage may occur.
- Arthritis: this typically affects the large joints of the lower limb, especially the ankles. Ankle swelling may be difficult to interpret in the presence of tissue oedema. The joint pain is usually transient. Arthritis in HSP is never erosive.
- Renal disease: haematuria and proteinuria are common manifestations of the disease, but are usually only detected on dipstick urine analysis. A small proportion of children (1–3%) may develop renal failure secondary to severe glomerulonephritis. Clinically significant renal disease is uncommon below 5 years of age.

Treatment
Henoch–Schönlein purpura is usually a self-limiting disease, requiring supportive care and symptomatic treatment with simple analgesia only. If the abdominal pain is severe, prednisolone (1–2 mg/kg/day) for 1 week may be helpful.

Kawasaki disease
Kawasaki disease is characterised by a combination of most of the following features in a young child (usually less than 5 years old) who is extremely irritable.

- Fever: an irregular spiking fever that persists for 1–3 weeks despite antibiotics is characteristic during onset.
- Skin involvement: rash is variable and polymorphic, ranging from diffuse erythema of the trunk and face to minimal macular lesions on the limbs. The rash in Kawasaki disease is never vesicular. Tissue oedema of the dorsal surfaces of the hands, feet and perineum is characteristic. These changes are followed within days to weeks by desquamation, usually of the finger and toe tips (periungual desquamation), but occasionally more widespread.
- Mucositis and conjunctivitis: inflammation of the mucous membranes of the mouth and eyes results in a characteristic appearance of red eyes (conjunctival ‘injection’ rather than conjunctivitis) and red swollen cracked lips.
- Lymphadenopathy: this usually affects the cervical lymph nodes, often unilaterally.
- Cardiac disease: myocarditis with heart failure or pericarditis is a rare but serious complication of Kawasaki disease. Coronary artery aneurysms may be present from early in the disease process. Clinical manifestations are relatively non-specific, but the two-dimensional echocardiography appearances are diagnostic of the condition. However, echocardiography may be completely normal in Kawasaki disease.
- It is important to exclude infections (e.g. measles, adenovirus or streptococci), as they may present in a similar manner, despite having distinct clinical characteristics.

Kawasaki disease is a rheumatological emergency. Delays in recognition and treatment of this condition can result in the development of coronary artery abnormalities with disastrous long-term consequences, including fatalities.

Treatment
- Hospitalisation and monitoring of cardiac status.
- Aspirin, 50–75 mg/kg/day in 4 divided doses after food until the acute inflammatory phase of the disease settles, then 1–10 mg/kg/day (usually 3–5 mg/kg/day) (antiplatelet doses).
- Intravenous gamma globulin 2 grams/kg immediately on diagnosis, if available. Every effort must be made to procure intravenous gamma globulin for the treatment of these children, as this is the only effective therapy for Kawasaki disease. This treatment reduces the likelihood of coronary artery aneurysms if given as early as possible during the illness (several inexpensive brands of intravenous gamma globulin are now available in resource-limited countries).
- Corticosteroids (e.g. prednisolone 1–2 mg/kg/day) may have a role in controlling the acute inflammation of Kawasaki disease, but are generally not recommended.
- Follow-up clinical examination and echocardiography (if available) is recommended at 6–8 weeks, as coronary artery aneurysms may appear after the initial presentation.

Juvenile idiopathic arthritis
Juvenile idiopathic arthritis is one of the more common physically disabling chronic diseases of children. The most prominent clinical features include joint swelling, restriction of joint movement, joint pain and tenderness at the joint margins, muscle wasting and any of the features mentioned below. The most common mistake is to diagnose arthritis in the absence of objective evidence of persistent joint swelling.

Diagnosis of juvenile idiopathic arthritis
All of the following four criteria are required:
1. The presence of arthritis, defined by swelling of a peripheral joint. Loss of joint range of movement and pain on movement are sufficient for the definition of arthritis involving the hip or spine (in the absence of other causes for the pain).
2. Persistence of arthritis for more than 6 weeks.
3. Onset of arthritis before the child’s 16th birthday.
4. The absence of any known cause for the arthritis.

Classification and differential diagnosis
There are a variety of different forms of juvenile idiopathic arthritis that are important to consider when advising on the prognosis and most appropriate treatment of the illness.
- Arthritis affecting only a few joints: oligo-arthritis
carries the best prognosis; 30% of these children may have arthritis in adulthood.

- **Arthritis affecting many joints:** polyarthritis is likely to persist into adulthood in 40% of cases.

- **Arthritis affecting few or many joints with prominent extra-articular features:**
  - **Systemic arthritis:** with fever, rash, and enlargement of the liver, spleen and lymph nodes, Pericarditis and macrophage activation syndrome are life-threatening complications. Macrophage activation syndrome presents with persistent fever, encephalopathy, liver failure and clotting abnormalities and low platelet counts. The persistence of arthritis with this illness carries the worst prognosis: over 50% of these children have arthritis as adults.
  - **Psoriatic arthritis:** often associated with a psoriatic rash, nail pitting and a family history of psoriasis. This has a similar outcome to polyarthritis.
  - **Enthesitis-related arthritis:** the clinical manifestations of enthesitis include pain, tenderness and occasionally swelling localised to the exact site of tendon insertion. Other features include back pain, red painful eyes and urethritis. There is a 60% risk of development of ankylosing spondylitis in adulthood.

**Monitoring for complications and disease progress in juvenile idiopathic arthritis**

There are several important complications of juvenile idiopathic arthritis, including joint failure, chronic anterior uveitis and local growth disorders, as well as the general complications of chronic inflammatory disease in children, such as anaemia, fatigue, delayed puberty and growth failure. Three of these complications, namely joint failure, chronic anterior uveitis and growth disorders, will be discussed in more detail.

**Joint failure**

- Inability to walk without pain and stiffness.
- Inability to write or perform activities of self-care without pain and stiffness.
- The integrity of joint cartilage and bone density is affected from the onset of the disease.
- If the inflammation remains poorly controlled, destruction of cartilage, joint space narrowing and erosion of bone will result in permanent loss of joint function.

**Differential diagnosis of juvenile idiopathic arthritis**

- **Transient arthritides:** irritable hip, reactive arthritis.
- **Septic arthritis** and osteomyelitis, including immunodeficiency.
- **Acute lymphoblastic leukaemia, neuroblastoma, lymphoma and local neoplasia.**
- **Bleeding diatheses:** haemophilia.
- **Haemoglobinopathies:** thalassaemia, sickle-cell crisis.
- **Epiphysial disorders:** dysplasia, avascular necrosis, osteonecrosis, slipped upper femoral epiphysis.
- **Metabolic and endocrine disorders.**
- **Traumatic joint disease, including non-accidental injury.**
- Hypermobility and inherited connective tissue diseases.
- Systemic connective tissue diseases, including systemic lupus erythematosus, dermatomyositis and vasculitis.
- Idiopathic musculoskeletal pain syndromes.

**TABLE 5.13.A.2 Important sites of joint contracture**

<table>
<thead>
<tr>
<th>Joint affected</th>
<th>Type of contracture</th>
<th>Consequence of contracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibio-talar gait</td>
<td>Plantar flexion</td>
<td>Circumduction or high-deformity stopping</td>
</tr>
<tr>
<td>Knee</td>
<td>Flexion</td>
<td>Quadriceps wasting, limping gait</td>
</tr>
<tr>
<td>Hip</td>
<td>Flexion</td>
<td>Limited ‘swing-phase’ gait</td>
</tr>
<tr>
<td>Wrist</td>
<td>Flexion</td>
<td>Poor writing</td>
</tr>
<tr>
<td>Neck</td>
<td>Flexion</td>
<td>Poor neck rotation</td>
</tr>
</tbody>
</table>

- Arthritis of inflammatory bowel disease.

**Eye disease**

- Chronic anterior uveitis is typically insidious and asymptomatic: all children with juvenile idiopathic arthritis (but especially those with oligo-arthritis) should undergo slit-lamp eye examination to detect cells in the anterior chamber and protein “flare”. Delay in the diagnosis can lead to blindness.

  - Inflammation is treated with ocular topical corticosteroids (hydrocortisone 1% eye drops or ointment 0.5%) three times daily and mydriatics (3 minutes after hydrocortisone) (atropine 0.5% eye drops or 1% ointment).
  - Severe chronic anterior uveitis may require systemic treatment with corticosteroids or methotrexate.

**Growth disorders**

- Generalised growth failure may be due to inadequate energy intake (chronic inflammatory disease increases energy demands) or the adverse effects of medication. It is usually treated with dietary energy supplements.
- Local growth disturbance: bony overgrowth of the knee with an increase in leg length, sometimes with a valgus knee deformity. Arthritis of the small joints of the hands is likely to cause premature fusion of the epiphyses and reduced growth of the affected fingers.

**Treatment of juvenile idiopathic arthritis**

- The first priority is to exclude the differential diagnoses, especially the emergencies of septic arthritis, acute lymphoblastic leukaemia or other malignancies, and non-accidental injury. Septic arthritis will require large doses of intravenous antibiotics (see Section 5.17).
- The effective treatment of juvenile idiopathic arthritis usually requires a team of trained healthcare professionals, including therapists and medical staff.
- Education of the patient and family is important, especially concerning the risks and benefits of all treatment and the natural history of the disease.
- Physiotherapy, hydrotherapy and occupational therapy...
work together to maintain joint function and muscle bulk, correct joint deformities and rehabilitate affected joints.

- Drug treatment should begin as soon as the diagnosis is made, with the following:
  - Non-steroidal anti-inflammatory drugs (NSAIDs): Give ibuprofen up to 60 mg/kg/day up to a maximum of 2.4 g in three or four divided doses after food. Naproxen at 20 mg/kg/day in two divided doses is possibly a better alternative. Avoid using more than one NSAID at a time.
  - Intra-articular corticosteroids: Strict aseptic conditions, no-touch technique, appropriate sedation, and local or general anaesthetic must be given. Triamcinolone hexacetonide is the most effective steroid, at a dose of 1 mg/kg/large joint (e.g. knee, hip or shoulder) or 0.5 mg/kg/small joint (e.g. ankle, wrist or elbow). This technique requires an experienced operator.

For children with polyarthritis or systemic arthritis, in addition to the above, the following should be considered:

- Methotrexate: Begin with 500 micrograms/kg/week (up to 15 mg/week) starting dose, given orally 1 hour before food, and increased if necessary by 2.5 mg every month until 1.0 mg/kg/week (maximum 30 mg/week). Alternative dosage is 10–15 mg/m² once weekly starting dose and increased if necessary to a maximum dose of 25 mg/m² once weekly (see Section 9 for chart showing how to calculate m² from weight). The drug may be given by subcutaneous injection in severe cases. The patient should be monitored monthly for cytopenia (with full blood counts) and liver function abnormalities. Administration is sometimes accompanied by nausea, a side effect that can be improved with folic acid 1 mg once daily (not on the day of methotrexate treatment, but beginning the day after the methotrexate dose).

- Intravenous methylprednisolone: This may be needed for severe disease flares or for complications such as pericarditis. Give 30 mg/kg/dose (maximum dose of 1 gram) once a day for 3 days by slow intravenous infusion over a 2- to 3-hour period. Blood pressure monitoring for acute hypertension during the administration of this medication should take place every 30 minutes.

- Sulphasalazine: Begin with 12.5 mg/kg/day for the first week, increasing by 12.5 mg/kg/day each week until the maximum dose of 50 mg/kg/day in two divided doses is reached, or until adverse drug reactions occur. These may include a rash, nausea, abdominal pain and pancytopenia. Monitoring with 2- to 3-monthly full blood counts is a sensible precaution.

- More recently, a new group of drugs have been developed which appear to slow the progress of disease in some patients. They work by opposing tumour necrosis factor alpha, which contributes to cell damage, and are immunosuppressants. They include etanercept and infliximab. These drugs are currently very expensive.

Paediatric systemic lupus erythematosus (SLE)

**Pattern of clinical features in SLE**

There is a malar rash and erythema of the hard palate with hair loss in a child with multiple constitutional symptoms.

Juvenile dermatomyositis (JDM)

**Pattern of clinical features in JDM**

There is erythema over the face, shawl area, knuckles, and local or general anaesthetic must be given. Triamcinolone hexacetonide is the most effective steroid, at a dose of 1 mg/kg/large joint (e.g. knee, hip or shoulder) or 0.5 mg/kg/small joint (e.g. ankle, wrist or elbow). This technique requires an experienced operator.

Paediatric systemic lupus erythematosus (SLE)

**Pattern of clinical features in SLE**

There is a malar rash and erythema of the hard palate with hair loss in a child with multiple constitutional symptoms.

Children with polyarthritis or systemic arthritis, in addition to the above, the following should be considered:

- **Methotrexate**: Begin with 500 micrograms/kg/week (up to 15 mg/week) starting dose, given orally 1 hour before food, and increased if necessary by 2.5 mg every month until 1.0 mg/kg/week (maximum 30 mg/week). Alternative dosage is 10–15 mg/m² once weekly starting dose and increased if necessary to a maximum dose of 25 mg/m² once weekly (see Section 9 for chart showing how to calculate m² from weight). The drug may be given by subcutaneous injection in severe cases. The patient should be monitored monthly for cytopenia (with full blood counts) and liver function abnormalities. Administration is sometimes accompanied by nausea, a side effect that can be improved with folic acid 1 mg once daily (not on the day of methotrexate treatment, but beginning the day after the methotrexate dose).

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- More recently, a new group of drugs have been developed which appear to slow the progress of disease in some patients. They work by opposing tumour necrosis factor alpha, which contributes to cell damage, and are immunosuppressants. They include etanercept and infliximab. These drugs are currently very expensive.

**Treatments**

- **The first step is to rule out other conditions which can mimic SLE, such as infection, malignancy, post-streptococcal nephritis, other rheumatic diseases and drug-induced lupus-like syndromes.**

- **For mild musculoskeletal disease, NSAIDs (e.g. ibuprofen 20–40 mg/kg/day in three daily doses) are effective.**

- **For rapid control of acute moderate-to-severe disease, glucocorticoids (e.g. prednisone up to 2 mg/kg per day) are useful, tapering rapidly to the lowest tolerated dose.**

- **Hydroxychloroquine (5–7 mg/kg/day) is now a standard adjunctive therapy for limiting joint, skin and constitutional symptoms.**

- **Immunosuppressive agents (e.g. azathioprine, cyclophosphamide, mycophenolate mofetil) are useful additions in moderate to severe disease.**

- **Other general health measures that need to be considered include the following:**
  - Bone health: weight-bearing exercises with calcium and vitamin D supplementation.
  - Cardiovascular health: education on modifiable risk factors for atherosclerosis, together with advice on reducing weight, smoking and cholesterol.
  - Health education (regarding vaccination, sun protection, dietary advice, exercise and reproductive health) and psychological support.
  - Routine 2- to 3-month follow-up is necessary to monitor for complications. This should involve full blood count, renal and liver profiles, ESR, urinalysis, and urine protein:creatinine ratio, together with complement and anti-dsDNA antibody levels.
and knees, associated with proximal muscle weakness (which may be subtle).

Juvenile dermatomyositis is the most common inflammatory myopathy of childhood, and the diagnosis is based on the following criteria:

- **Muscle weakness:** a symmetrical, usually progressive weakness affecting proximal muscles.
- **Skin rash:** erythematous rashes occurring over the face or extremities, heliotrope rash over the eyelids, and Gottron’s papules over extensor joint surfaces. More severe complications include skin ulceration and calcinosis at pressure points, causing functional disabilities. Capillary loop abnormalities seen proximal to the cuticles with an auroscope are a very characteristic sign if present.
- **Laboratory evidence of muscle disease:** this can include increased activity of muscle enzymes in the blood (creatine kinase, lactate dehydrogenase, transaminases), or results from more invasive tests, such as muscle biopsy or electromyography (if available).

**Treatment**

- High-dose corticosteroids are the standard treatment, namely early IV methylprednisolone 30mg/kg per day (maximum 1 gram daily) with or without low-dose daily oral corticosteroid (500 micrograms/kg per day).
- It can be useful to add methotrexate (15mg/m²/week orally or subcutaneously) as a steroid-sparing agent and intravenous immunoglobulin in resistant cases (where available).
- Skin disease may also be helped by routine photoprotective agents and topical corticosteroids or tacrolimus.
- Physiotherapy and aerobic exercise are helpful for improving function and strength.

### TABLE 5.13.A.3 Differential diagnosis of childhood idiopathic inflammatory myopathies

<table>
<thead>
<tr>
<th>Weakness alone</th>
<th>Weakness with or without rash</th>
<th>Rash alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscular dystrophies (e.g. Duchenne’s, limb-girdle)</td>
<td>Viruses (enterovirus, influenza, coxsackie, echovirus, polio)</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Metabolic myopathies (e.g. glycogen- or lipid-storage disorders)</td>
<td>Bacterial (Staphylococcus, Streptococcus, Lyme disease)</td>
<td>Eczema</td>
</tr>
<tr>
<td>Endocrine myopathies (hypothyroidism, hyperthyroidism, Cushing’s syndrome, diabetes mellitus)</td>
<td>Parasitic (toxoplasmosis, trichinosis)</td>
<td>Allergy</td>
</tr>
<tr>
<td>Drug-induced myopathies (e.g. glucocorticoids, hydroxychloroquine, growth hormone)</td>
<td>Other rheumatic conditions (SLE, mixed connective tissue disease, scleroderma, juvenile idiopathic arthritis, vasculitis)</td>
<td></td>
</tr>
<tr>
<td>Neurological (myasthenia gravis, spinal muscular atrophy)</td>
<td>Other inflammatory conditions (coeliac disease, inflammatory bowel disease)</td>
<td></td>
</tr>
</tbody>
</table>

### 5.14 Cancer in children

#### BOX 5.14.1 Minimum standards

- Local enthusiastic clinical lead.
- Supporting team of doctors and nurses.
- Basic diagnostic pathology and imaging (X-ray and ultrasound).
- Centre with provision for some chemotherapy and surgery.
- Access to antibiotics.
- Access to blood products.
- Access to palliative care drugs (see Section 1.16).

#### Ideal extra requirements

- Imaging with computed tomography (CT) scan.
- Access to radiotherapy.
- Indwelling long-term vascular access.

**Introduction**

- More than 85% of all newly diagnosed children with cancer and 95% of deaths in children with cancer occur in low- and middle-income countries.
- With an increasing global population, principally in resource-limited countries, the number of children will continue to increase both in terms of absolute numbers and proportionally in these countries.
- As malnutrition and infection decline, particularly in young children, the worldwide contribution to mortality from cancer will increase.
- Only a limited proportion of all children with cancer in resource-limited countries receive curative therapy, and most do not even receive any form of palliative care.
- A child diagnosed with cancer who lives in one of the poorest countries has an 80% probability of dying, compared with less than 30% in the most well-resourced countries (see Figure 5.14.1).
Epidemiology

Globally, the reported incidence rate of cancer in children (aged < 15 years) ranges from 80 to 150 per million per year. Boys are around 20% more likely to develop cancer overall than girls. However, there are some differences between resource-limited and resource-rich countries. The incidence rates in children from low- and middle-income countries are towards the lower end of the range, which may partly be due to both under-diagnosis and under-reporting. The ratio of boys to girls registered with childhood cancer increases with decreasing gross domestic product and with increasing infant mortality, suggesting a gender bias in diagnosing and registering cases in some resource-limited countries.

There are clear variations in the incidence of different childhood cancers around the world – for example, a reported excess of retinoblastoma in India, Pakistan and sub-Saharan Africa. It is likely that some of this ‘excess’ is due to better diagnosis and recognition of retinoblastoma, which once at an advanced stage is easy to identify. On the other hand, the incidence of brain tumours and neuroblastoma is generally lower in resource-limited settings, and this may be due to varying levels of case ascertainment. In many countries, most noticeably those in sub-Saharan Africa, the HIV pandemic has been associated with a significant increase in cancers such as Kaposi’s sarcoma and other tumours.

The cause of the majority of childhood cancers is unknown. Most cancers probably result from the interaction of environmental factors with a genetic predisposition. For example, African Burkitt lymphoma is related to infection with the Epstein–Barr virus (EBV) very early in life, with persistence of induced genetic rearrangements within B lymphocytes. However, the widespread use of medicinal plants which may increase the likelihood of cell transformation by EBV, chronic malnutrition that induces immunosuppression, and frequent infections that cause B-cell proliferation are all likely aetiological factors.

Problems of treating children with cancer in resource-limited countries

The problems listed below are not exclusive to resource-limited countries, and not mutually exclusive (i.e. many factors interact, compounding the difficulties in treating cancer).

- Poverty: national, regional, local and personal. This is often associated with low government expenditure on healthcare, absence of social care, and lack of insurance for medical illnesses.
- Lack of suitable treatment centres and training programmes. Existing centres lack trained staff and resources.
- Lack of trained staff, especially nurses, but also lack of surgeons, pathologists and paediatricians (especially paediatric oncologists).
- Healthcare professional resources
  Staff morale problems (see Section 1.1)

Low morale may be due to low wages, overwork and dirty crowded conditions, compounded by too many patients and by becoming accustomed to low patient survival rates. Solutions may include better training and remuneration, better working and living conditions, and making staff feel valued.

It is important that all healthcare professionals recognise that nursing care is fundamental. Nurse bonus schemes for work effectively performed can be helpful (e.g. IV antibiotics and chemotherapy correctly administered for all patients).

Nurses often rotate every few months between departments. Try to ensure that, for paediatric oncology, a cohort of nurses remains permanently on the ward, as much of the work is very specialised (e.g. chemotherapy administration).

Paediatric oncologists

An effective service needs good leadership in a major centre. This can develop through training and the development of fellowship programmes. There can be support from overseas experts, perhaps with
“twinning” of hospitals from a well-resourced country to share decision making on complex cases and to supply visiting experts. Much useful work can be done in oncology with email and web conferencing to facilitate knowledge sharing in both directions. As there is an increase in the number of trained and training staff, round-the-clock expertise in paediatric oncology can be achieved with the development of on-call rotas.

- Late presentation
  - Patients’ families are often very poor.
  - They may present to traditional healers first, leading to a delay in diagnosis and referral.
  - They often cannot afford transport.

- High cost of treatment
  - Expensive cytotoxic agents, counterfeit medications, quality control problems, cold chain difficulties (e.g. asparaginase is an enzyme and must be kept cool), restrictions (e.g. on oral morphine).
  - Cost of diagnostic imaging and pathology.
  - Cost of supportive care: antibiotics and other antimicrobials, blood products.
  - Cost of caring for critically ill children: high-dependency/intensive care, postoperative care.

- There is a need for multiple support networks and institutions to develop the paediatric oncology service in the face of the poverty that causes the above problems. These will include individuals and their families, non-governmental organisations (NGOs), corporate business, public social responsibilities, twinning, and public private-partnership. Government involvement is vital.

- Inadequate provision of analgesics and other drugs
  - For all patients, and especially where cure is not possible, palliative care is a vital part of oncology treatment. Analgesics play a large part in supportive care and procedural sedation and analgesia, as well as in palliative care. The lack of these drugs is often coupled with a poor understanding and awareness of pain management in healthcare professionals.

- There is often an interrupted supply and insufficient quality control of all drugs.

- Comorbidities
  - There is often a high prevalence of co-infections, malaria, anaemia, helminths and malnutrition which can confound the diagnosis and cause decreasing tolerance of cytotoxic therapy.

- Untimely and inappropriate cessation of treatment (i.e. abandonment of treatment)
  - A lack of education and knowledge about uncommon diseases among families, communities and healthcare workers leads to a lack of understanding of the need for treatment.
  - There is then a lack of financial and social support as treatment is lengthy and the parent has to stay with the child in hospital. This makes it difficult to look after other children at home, and to work, leading to loss of employment.
  - Traditional beliefs include unrealistic preconceptions about cancer and reliance on traditional medicines. In Swahili, ‘the never healing sore’ refers to the fact that there is no expectation of cure, and therefore no point in treatment.
  - Adolescents frequently treated on adult wards.
  - Patients may be left on wards for months because of a lack of diagnostic facilities (e.g. children with brain tumours or osteosarcomas). It is important to search the wards for such patients and to alert colleagues to refer children to an oncologist where the diagnosis is unknown.

- Impact on family structure
  - The loss of parental income may result in disruption and potential disintegration of the family, and at the very least to a change in family roles, especially where both parents need to work to maintain the family income.

Management of children with cancer in resource-limited countries

The following principles and practices should guide the management of children with cancer in resource-limited settings.

- Engage in twinning – that is, developing a link between a treatment centre in a resource-limited country and one in a resource-rich country, with the objective of sharing professional and technological expertise along with other resources.

- Initially, target curative treatment for cancers that are common and have a relatively good prognosis. When curative treatment is not an option or is not offered, it is essential to provide palliative care to reduce suffering. Both curative and palliative care must be seen as active forms of therapy.

- If curative treatments are to be undertaken, then whenever possible they should be given in a specialist children’s cancer centre (see below). There is potential for greatly increasing suffering by only offering ‘half treatment’ of cancer for children. It has to be done fully and professionally, or alternatively the child must be given palliative care (see Section 1.16).

- Adapt treatment protocols in accordance with local infrastructure and facilities, maintaining a balance between treatment response and cure on the one hand and treatment toxicity and mortality on the other.

- Take steps to ensure compliance with and completion of treatment. Anticipate abandonment of treatment, and address the causes, which vary from country to country.

- Maintain a database of patients using free resources such as POND4kids (www.pond4kids.org).

- Engage in the education and training of healthcare professionals, including nurses and doctors, by using free resources such as cure4kids (www.cure4kids.org) as well as conducting in-house workshops.

- Aim to be part of regional, national and international collaborative groups to derive benefit from shared expertise and uniformity of treatment and supportive care.

- Develop parent support groups and provide resources for food, lodging and transport.

In countries where there is an improving infrastructure, the following cancers may have a good or reasonable chance of cure:

- **Standard-risk acute lymphoblastic leukaemia:** children aged 2–10 years, with a white blood cell count of <5 × 10⁹/litre, have a reasonable chance of cure with induction chemotherapy (vincristine, prednisolone, asparaginase) followed by maintenance chemotherapy as described below without the use of intensification.
modules. However, CNS-directed therapy with cranial radiotherapy plus limited intrathecal methotrexate or intrathecal methotrexate throughout therapy is required in all cases.

- **Hodgkin’s disease**: chlorambucil, vinblastine, procarbazine, prednisolone (ChVP) or mustine, vinblastine, procarbazine, prednisolone (MVPP) – six to eight courses.
- **Burkitt’s lymphoma**: single-agent cyclophosphamide with intrathecal methotrexate and hydrocortisone. Alternatively, cyclophosphamide, vincristine, methotrexate, prednisolone (CCMOP) chemotherapy with intrathecal methotrexate and hydrocortisone.
- **Non-Burkitt/non-Hodgkin’s lymphoma**: early stage – surgery plus CCMOP or cyclophosphamide, Adriamycin, vincristine, prednisolone (CHOP).
- **Brain tumours:**
  - Medulloblastoma and ependymoma (resectable/non-metastatic): surgery followed by radiotherapy.
- **Retinoblastoma**: enucleation (radiotherapy in some cases).
- **Neuroblastoma** (stage I and II): surgery alone.
- **Wilms’ tumour:**
  - Stage I: surgery plus 10 doses of vincristine (at weekly intervals).
  - Stage II (and possibly stage III): surgery plus vincristine/actinomycin for 6 months.
- **Resectable embryonal rhabdomyosarcoma** (certain sites): surgery plus vincristine/actinomycin D (four courses).
- **Germ-cell tumours:**
  - Malignant germ-cell tumours (stage I): surgery alone.

**Specialist cancer centres or units Establishment**

- Specialist cancer centres or units, and the use of standard treatment protocols (discussed below), have both been fundamental to the ever-improving survival of children with cancer in resource-rich countries.
- Cancer is a relatively rare disease and its treatment is usually complex.
- Management requires a dedicated and experienced multidisciplinary team.
- Every country should aim to have at least one adequately equipped and funded centre, and then develop shared care or a satellite centre.

**Advantages of a specialist children’s cancer centre or unit**

- Development of medical, nursing and paramedical expertise.
- Improved supportive care, including pain relief for children.
- Facilities to protect cancer patients from other children suffering from contagious diseases.
- Opportunities for training and retention of staff, leading ultimately to accreditation as a principal care centre in paediatric oncology.
- Improved support, education and counselling of affected children and their families.

- **Stimulus for the development of similar units in the same part of the world.**
- **Improved opportunities for research, including the development of treatment protocols relevant to the particular region or country.**
- **Development of links with national and international oncology units and organisations.**

**Requirements of a specialist children’s cancer centre or unit**

- Dedicated paediatric oncologist(s) and nursing staff supported by nutritionists, psychologists and social care workers.
- General surgeon and neurosurgeon trained in paediatric surgery.
- Access to radiotherapy and services of a radiotherapist.
- Blood and platelet banking facilities.
- Pathologist with experience of paediatric tumours with adequate histology and cytology facilities (immunohistochemistry is desirable; this can be in a centralised laboratory if it provides a service for more than one centre or country).
- Haematology, biochemistry and microbiology laboratories with good quality control.
- Diagnostic imaging: X-ray, ultrasonound; CT imaging is desirable, especially for brain tumours. Families may have to pay for these, which is often a limiting factor that determines whether a child is diagnosed and treated properly. Fine-needle aspiration is important, as are lumbar punctures performed under appropriate analgesia and sedation.
- It is vital to have good supportive care, including regular supplies of medication, good stock-keeping and drug ordering (ensure that drugs are not stolen and sold on the “black market”), IV fluid management systems to avoid tumour lysis syndrome, and good post-operative care.
- Adequate bed capacity. Most units are constantly overcrowded, with two patients per bed, and as units develop it is essential to build the capacity to cope with increasing numbers of patients.
- Computer facilities with Internet connections (for emailing to the link centre, Medline searches, patient database).
- Active involvement in auditing practice and participating in research.

Above all, there must be a keenness of all staff to work together to learn and make the unit successful.

**Centre or unit database**

All centres or units should keep a record of treatment, including details of patient demographics, diagnosis, treatment, side effects and survival. This will aid the identification of specific problems, the development of more effective treatment protocols for treatment and supportive care, and overall healthcare planning and development. The availability of free online and electronic resources such as POND4kids (www.pond4kids.org) makes this feasible.

**Links with other centres or units and organisations**

Provision should be made for communication and transportation for patients from remote areas. Satellite or shared-care centres can be developed by linking with...
healthcare facilities in other areas so that appropriate care can be continued (e.g. district hospitals).

**Links with centres or units in resource-rich countries (twinning)**

Links with an established unit in resource-rich countries can have the following advantages:

- sharing information and experience on how to raise awareness of cancer and reduce delays in diagnosis
- helping to speed up diagnosis and make it more precise
- development of locally affordable supportive, palliative and curative care guidelines
- helping to train and retain staff
- helping to create patient data registration
- help to develop long-term sustainability
- providing support and advice for difficult problems (e.g. by email or web conferencing)
- pathology samples can be couriered for more complex testing (e.g. for immunophenotyping, special staining, VMMA, etc.)
- research collaboration.

In addition, links with international organisations are to be encouraged – for example, with the International Society of Paediatric Oncology (SIOP).

**Principles of the curative treatment of children with cancer as undertaken in a specialised unit or centre**

**Diagnosis**

- A complete history and examination.
- Investigations to confirm histology, determine the extent of the tumour (staging) and identify any tumour-related toxicity (e.g. disturbance of renal, liver and/or bone-marrow function).

**Imaging**

- To define the dimensions of the primary tumour and to determine the degree of tumour spread (staging).
- Good plain posterior–anterior and lateral chest X-rays are generally adequate for chest imaging, while CT scan of the chest may be more definitive if it is available.
- Ultrasonography affords good visualisation of the abdomen and pelvis, although CT of the abdomen and pelvis may have advantages over ultrasonography in some patients.
- Intravenous urography and cavagrams may also be useful in patients with abdominal tumours.
- For the brain, CT scanning is a necessary part of investigation and management. MRI of the brain has advantages over CT, but the availability of this technique is very limited.
- Nuclear imaging can further assist in accurate staging (e.g. technetium bone scan for bone and soft tissue sarcomas, and metaiodobenzylguanidine (MIBG) scan for neuroblastomas).

**Biochemical markers**

These are useful in the diagnosis of a limited number of tumours (e.g. urinary catecholamines in neuroblastoma, and serum alpha-fetoprotein in hepatoblastoma and germ-cell tumours).

**Pathology**

- Good histopathology is essential for the individual, and is the only way to compile accurate incidence figures and survival data and to identify favourable histological subgroups.
- Close involvement of the pathologist is needed before biopsy or surgery so that the surgeon can obtain an optimal specimen in the right fixative.

**Multidisciplinary team meetings**

Following initial clinical assessment and investigation, all children with cancer should ideally be discussed at regular multidisciplinary team meetings that may include the oncologist, radiologist, surgeon and radiotherapist. Such discussions are also recommended at the time of significant events during treatment (e.g. progression or relapse). This ensures that the child benefits from the collective knowledge of the treating team and there is consistency in treatment. However, this can be difficult as staff will be very busy and may require extra funding.

**Treatment protocols**

- Each unit should use a standard protocol for each tumour type, with the necessary variations for tumour stage.
- Protocols should be based on established and effective protocols used by national and international groups.
- Protocols may require modification based on the resources, drug availability, cost and the level of supportive care that can be provided by the unit.
- Such protocols are currently being developed by the SIOP Paediatric Oncology in Developing Countries (PODC) Graduated Intensity Treatment Guidelines Working Group. The first such protocol for acute lymphoblastic leukaemia was recently published.

**Chemotherapy**

- Late diagnosed childhood malignant tumours are almost always disseminated, requiring treatment with systemic chemotherapy.
- Cytotoxic drugs prevent cell division by a variety of mechanisms.
- Although occasionally single-agent therapy is given (e.g. for stage I Wilms’ tumour), the great majority of treatment protocols employ a combination of drugs used synergistically to produce maximal cell kill with acceptable toxicity, and to prevent tumour cell resistance.

**Surgery**

- This is important both for obtaining diagnostic material, and as local therapy to reduce tumour bulk. Surgeons should be specially trained and have experience in oncology.
- It is preferable for surgeons to have received specific training in operating on children and in tumour surgery.
- Operating facilities must be of high quality to reduce the risk of infection.
- There must be adequate support from blood transfusion services.
- Several treatment protocols use pre-operative chemotherapy, which may reduce tumour size, and thus reduce peri-operative risks.
Radiotherapy
- Radiotherapy is used to treat regional tumour extension, including nodal disease, and as part of local tumour control to eradicate local residual microscopic (or sometimes macroscopic) disease following surgery.
- It has a particular role to play in certain brain tumours, and may also be used as curative therapy in early-stage Hodgkin's disease.
- It is also frequently used in the management of bone and soft tissue sarcomas and in the prevention of overt central nervous system disease in acute lymphoblastic leukaemia.
- Megavoltage machines have advantages over the older orthovoltage therapy in giving a more controllable beam and avoiding damage to skin and overlying tissues when administered to deep tissues.
- The whole of the original tumour volume is generally irradiated, plus a safety margin (usually 1–2 cm) of surrounding normal tissue.
- The combination of chemotherapy and radiotherapy can increase late local effects and should be avoided whenever possible.

Procedures
Bone-marrow aspiration
- This is needed in the diagnosis of leukaemia and lymphoma, and also to identify any bone-marrow infiltration with solid tumours such as neuroblastoma.
- It is a painful procedure and must be done under analgesia and sedation (e.g. ketamine 2 mg/kg) (see Section 1.15 and Section 1.24) along with infiltration of the skin and subcutaneous tissues down to periosteal level with a local anaesthetic.
- Aspiration is preferably performed from the posterior iliac crest, but can also be taken from the anterior crest.

Lumbar puncture
- This is needed in the diagnosis of malignant meningitis, especially with leukaemia and lymphoma, but also in certain brain tumours (e.g. medulloblastoma) and other solid tumours, particularly those affecting the head and neck.
- Lumbar puncture is a painful procedure, and in children should be done under analgesia and sedation along with local anaesthetic wherever possible (especially if multiple lumbar punctures are needed).

Venous access
- Venepuncture for administration of chemotherapy and blood sampling is painful and especially difficult in the young child (analgesia and sedative cover may be needed).
- Repeated venepuncture results in loss of venous access due to venous thrombosis, and may significantly compromise therapy.
- Several agents, especially vinca alkaloids, are extremely damaging to tissues when extravasated.
- Short-term percutaneous placement of medium-length or long lines under local anaesthetic may provide an alternative means of venous access.
- The placement of a long-term central venous catheter (e.g. Broviac line, Hickman line) (if available) can be considered in children receiving intravenous chemotherapy. It should be placed by an experienced surgeon, and its use is associated with an increased risk of infection, particularly from skin organisms such as staphylococci.

Psychological support
Cancer and its treatment are frightening experiences for many patients, and every attempt should be made to reduce the child's fears. An explanation of the diagnosis and treatment, including the likely outcome, should be given in clear understandable terms to the child's family and also to the affected child or young adult wherever appropriate. Such information is best delivered over more than one conversation, allowing the family to understand it and come back to ask questions.

All aspects of treatment and associated side effects should be clearly explained, including details of supportive care, such as infection control, the importance of seeking a healthcare worker if a fever develops, mouth care, pain relief, care of lines, and procedures, such as surgery, bone-marrow aspirate and lumbar puncture. These conversations need to continue throughout treatment, thus establishing a relationship with the child and their family. The family must always be fully involved in the patient's care (e.g. by donating blood when it is needed). Parents want their child's doctor to focus on a potential cure and relief of symptoms, and then they can have faith in the doctor and derive hope for the future.

Side effects of the disease and/or its treatment

<table>
<thead>
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<th>TABLE 5.14.1 General side effects of chemotherapy</th>
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<table>
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<th>TABLE 5.14.2 Specific side effects of chemotherapy</th>
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<td><strong>Neurotoxicity</strong></td>
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<tr>
<td><em>Vincristine</em> (muscle weakness due to peripheral neuropathy, constipation, rarely encephalopathy)*</td>
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<td><strong>Cardiomyopathy</strong></td>
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<td><em>Doxorubicin/daunorubicin</em></td>
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<td><em>Cisplatin</em> (renal), ifosfamide (renal and bladder), cyclophosphamide (bladder)*</td>
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<td><strong>Hearing</strong></td>
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<td><em>Cisplatin</em></td>
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Infection
- Neutropenia, both at diagnosis in leukaemia and following most chemotherapy, produces a risk of significant...
bacterial and fungal sepsis derived from the patient’s own flora when the neutrophil count is < 1.0 × 10^9/litre, and particularly when it is < 0.2 × 10^9/litre.

- The greatest risk is from Gram-negative bowel organisms such as E. coli, Proteus, Klebsiella and Pseudomonas.
- Gram-positive organisms from the skin and mucosal surfaces, especially staphylococci, may also cause significant morbidity.

- Life-saving measures include identification of those at risk, close observation, and the empirical administration of intravenous antibiotics to patients with a neutrophil count of < 1.0 × 10^9/litre who develop fever (e.g. > 38°C for 2 hours or > 38.5°C on one occasion).
- The antibiotic regimen should be determined by each centre depending on the prevailing flora and the cost and availability of antibiotics.
- First-line therapy for febrile neutropenia should generally be with a combination of a broad-spectrum beta-lactam antibiotic and an aminoglycoside.
- If the temperature fails to remit, or if Gram-positive organisms are isolated, therapy with vancomycin or teicoplanin is recommended.
- For microbiologically proven septicaemia, antibiotics should be given for 5–7 days, the choice of drug depending on the antibiotic sensitivity of the isolated organism.
- Newer very broad-spectrum antibiotics, such as the carbapenems and quinolones, are best avoided as they are expensive and may promote fungal colonisation and bacterial resistance if commonly or repeatedly used.
- If systemic fungal infection is proven or suspected (e.g. if fever fails to remit after 4–5 days of antibiotics), then intravenous amphotericin, despite its renal toxicity, is still the drug of choice and is widely available. Newer lipid-based formulations of amphotericin are less toxic but very expensive.
- *Pneumocystis carinii* pneumonia, especially in patients with leukaemia, requires prophylaxis with co-trimoxazole (calculated as a dose of 150 mg/m²/day of trimethoprim given twice a week).
- Viral infections are generally tolerated, but chickenpox and measles cause life-threatening infections in immunosuppressed patients. Whenever possible, children must be isolated from direct contact with these infections. Immunoglobulin therapy, including zoster immune globulin, may be life-saving but is rarely available.
- High-dose aciclovir is the treatment of choice for zoster infections, but is expensive and not yet widely available globally.

### Bleeding and anaemia

- Adequate blood banking facilities with availability of blood component therapy such as packed red blood cells and platelets (see Section 1.7) are a fundamental part of therapy. Red blood cell transfusion should be reserved for symptomatic anaemia, or when the haemoglobin falls to a very low level (e.g. < 6 grams/dL).
- Platelets should be reserved for patients with florid petechiae or overt bleeding, or to cover procedures such as lumbar puncture, when a platelet count of > 40 × 10^9/litre is essential.
- Prophylactic platelet transfusions in response to specific platelet counts are not recommended.

- In the presence of fever, bleeding may occur at higher platelet counts than would normally be expected.

### Nausea and vomiting

- Nausea and vomiting are a very unpleasant side effect of chemotherapy and can lead to poor compliance with therapy and additional complications, such as metabolic disturbance, dehydration and oesophageal tears.
- Chemotherapeutic agents vary in their potential to produce vomiting, from very low (e.g. vincristine and etoposide) to very high (e.g. cisplatin). Anti-emetic therapy should be given wherever possible, preferably prophylactically, but certainly to patients with established retching and vomiting.

### Anti-emetic agents

- **Metoclopramide**: this is effective in high dose, but a greater risk of extrapyramidal side effects exists in children. Give 100 micrograms/kg for 1/12 to 1 year, 1–3 years 1 mg, 3–5 years 2 mg, twice daily and 5–9 years 2.5 mg, 9–18 years 5 mg thrice daily orally or slowly (over 2 minutes) by IV injection. Over 60 kg children can have 10 mg three times daily. Avoid the IM route.
- **Chlorpromazine**: orally or IV (the IV route can cause severe hypotension), child 1–12 years 500 micrograms/kg every 4–6 hours, maximum 75 mg daily. For 12–18 years 25–50 mg every 3–4 hours until vomiting stops.
- **Prochlorperazine**: orally or IV slowly over 10 minutes, 250 micrograms/kg 1–12 years every 8–12 hours (only if the child weighs over 10 kg or is over 1 year of age). 12–18 years 5–10 mg three times daily.

The following drugs are generally available but have a high incidence of side effects, including drowsiness. They may be more effective when combined with steroids.

- **Benzodiazepines**: the main effect is sedation and amnesia. These drugs are useful for anticipatory nausea.
- **Steroids**: the main effect is in combination with other agents (prednisolone 0.5 mg/kg every 12 hours).
- **5HT3 antagonists (e.g. ondansetron)**: these are the most effective anti-emetics, especially when combined with steroids. However, they are expensive.

### Ondansetron dosage

Six months–18 years either 5 mg/m² or 150 micrograms/kg (max single dose 8 mg) IV before chemotherapy then repeated every 4 hours for two further doses, then give orally. Oral dose < 10 kg = 2 mg 12 hourly, > 10 kg = 4 mg 12 hourly for up to 5 days.

### Oral mucositis

- This is a common side effect of many cytotoxic agents and also radiotherapy.
- **Scrupulous simple oral hygiene should be maintained.** This can be achieved by regular thorough tooth brushing two to three times a day together with use of a mouthwash such as chlorhexidine if available.
- Oral fluconazole and oral acyclovir may be of benefit in oral mucositis with secondary infection from candida and herpes infection, respectively.
Alopecia
This is inevitable with most chemotherapy, but usually entirely reversible on completion of treatment. Some children are not upset by the appearance of alopecia, but for those who are distressed by it, a light but attractive head covering may be acceptable.

Nutrition
Maintenance of adequate nutrition is essential. ‘Cancer wasting’ or cachexia is a well-recognised complication of paediatric tumours, and is subsequently associated with a decreased tolerance of chemotherapy and its side effects, and possibly an increase in cancer mortality.

Poor nutritional status may result from any of the following:
- stress
- pain
- increased metabolism (due to tumour or infection)
- anorexia
- altered sense of taste and smell
- chemotherapy-induced nausea and mucositis (e.g. stomatitis, oesophagitis)
- radiotherapy-induced mucositis and dry mouth (xerostomia)
- surgery-induced pain, bowel obstruction and appetite suppression.

In addition to this, an unacceptably high number of children in resource-limited countries who do not have cancer are malnourished. The effect of cancer and its treatment can be even more deleterious for such children.

Each child should have a nutritional assessment, including measurement of height or length, weight, mid upper arm circumference and triceps fold thickness (using callipers). Height and weight should be plotted on a standard percentile chart (see Section 9).

Nutritional support should be given to children who consistently show a decrease across percentile lines. It may also be indicated in children with baseline malnourished status. A high-calorie diet with adequate protein should be given to all children with cancer, supplemented if necessary with specific additives to provide additional calories and protein.

If sufficient food cannot be taken orally, enteral feeding via a nasogastric tube (particularly overnight) should be considered. Total parenteral nutrition should be avoided, as it is expensive and associated with a high risk of complications, including infection and metabolic disturbance.

Tumour lysis syndrome (TLS)
This is a life-threatening complication that occurs when the rapid lysis of tumour cells, usually resulting from chemotherapy, leads to the release of excessive quantities of cellular contents into the systemic circulation, resulting in a metabolic disturbance characterised by the following:
- hyperkalaemia
- hyperphosphataemia
- hyperuricaemia
- hypocalcaemia.

This metabolic derangement may lead to acute oliguric renal failure and cardiac arrhythmias.

TLS can occur spontaneously in tumours with a very high proliferative rate, as well as following initiation of treatment. It can be classified as laboratory TLS (with no clinical manifestations) or clinical TLS (with life-threatening clinical abnormalities).

Management of TLS
- Most importantly, anticipate and recognise patients who are at high risk of tumour lysis, i.e. those with leukaemia and lymphoma (particularly T-cell or Burkitt’s phenotype, and those with a high white cell count > 50 x 10^9/litre, hepatosplenomegaly or mediastinal mass, or high LDH).
- Intravenous hydration with potassium-free fluids, at least 2.5–3.0 litres/m^2/day, should be commenced prior to treatment and then continued for the first few days of treatment. Ensure that there is adequate urine output (≥ 1 mL/kg/hour).
- Regular allopurinol, 100 mg/m^2 dose every 8 hours, should be commenced prior to treatment and then continued for the first few days of treatment.
- Clinical and laboratory monitoring should be undertaken, including daily weight, input and output review, and assessment of blood biochemistry, with measurement of uric acid levels up to four times a day if needed.

Infertility
- This mainly occurs in males and is a consequence of specific cytotoxic agents, especially the alkylating agents such as cyclophosphamide, or radiation to the gonads. Girls may suffer from ovarian failure causing a premature menopause after certain therapies.
- Families should receive counselling about infertility, and hormonal treatment may be offered.
- Sperm storage for adolescent boys before the start of treatment can be considered if this service is available.

Second tumours
- Chemotherapy results in a small but important risk of second tumours, especially acute myeloid leukaemia.
- This is particularly associated with alkylating agents such as cyclophosphamide (especially if used with radiotherapy), anthracyclines and topoisomerase-2 inhibitors (e.g. etoposide).

Treatment of individual tumour types
A detailed discussion of the presentation and management of every type of tumour is beyond the scope of this book.

Acute lymphoblastic leukaemia (ALL)
Approximately one-third of all children under 15 years of age with cancer have acute leukaemia, and 75–80% of these have acute lymphoblastic leukaemia, making it the most common childhood cancer in well-resourced countries.

Presentation
- Myelosuppression.
- Anaemia, infection (which can be life-threatening) and thrombocytopenia (bruising, bleeding, petechiae).
- Lymphadenopathy and hepatosplenomegaly.
- Bone pain and limp.

Diagnosis
- Full blood count.
- Blood film can be diagnostic for patients with very high white cell counts.
- Bone-marrow aspirates (these are always required).
Treatment
Rapid tumour lysis, which can sometimes be spontaneous, is a major risk, particularly for patients with high white cell counts leading to biochemical disturbances. Intravenous fluids, allopurinol and close monitoring of renal function are required at the start of treatment. The treatment of acute lymphoblastic leukaemia is divided into a number of phases, as described below.

Induction
The aim is to get the patient into remission (defined as the presence of < 5% blasts in bone marrow). Four weeks of oral prednisolone or dexamethasone with weekly vincristine injections will result in a 90% remission rate, although the addition of a third drug, asparaginase (9–12 doses every 48 hours), is associated with improved long-term survival. If asparaginase is not available or is too expensive, anthracyclines (e.g. doxorubicin) can be substituted.

CNS-directed therapy
This is needed in all patients to prevent CNS relapse. Standard therapy is to give five to six doses of intrathecal methotrexate together with cranial irradiation (18 Gy). For standard-risk (not high-risk) patients, irradiation can be replaced with intrathecal methotrexate at regular intervals throughout the treatment period, although some units may find radiotherapy easier to administer than repeated lumbar punctures.

Intensification therapy
The administration of periods of more intensive therapy (e.g. with drugs such as cyclophosphamide, daunorubicin and cytosine) has been associated with increased survival, although this treatment carries the risk of severe myelosuppression and should be used with caution unless a high level of supportive care is in place.

Continuation (maintenance) therapy
This essential part of treatment generally lasts for 2 to 3 years. Most regimens employ daily oral mercaptopurine and weekly oral methotrexate with vincristine and a short course of steroid given every month.

Prognosis
With current therapy in specialist centres one can expect at least 50% of standard-risk patients (i.e. those with a white cell count at diagnosis of < 50 x 10^9/litre, and aged 2–10 years) to survive.

Acute myeloid leukaemia (AML)
This accounts for 15–20% of acute leukaemias in children.

Presentation
The presentation is the same as for acute lymphoblastic leukaemia, with more likelihood of tissue infiltration:

- gum hypertrophy: monocytic leukaemia
- skin involvement: myeloblastic leukaemia
- disseminated intravascular coagulation: promyelocytic leukaemia.

Diagnosis
See above section on acute lymphoblastic leukaemia.

Non-Hodgkin's lymphoma (NHL)
Childhood NHLs are a heterogeneous group of usually diffuse lymphocytic or lymphoblastic neoplasms arising from both B and T cells. Burkitt's lymphoma, a B-lineage NHL, is the most common childhood malignancy reported from tropical Africa, and is also prevalent in South America and in parts of South-East Asia.

Presentation
Lymphomas can arise in any area of lymphoid tissue, and therefore the presenting features are protean. Patients often have marrow involvement and sometimes CNS disease.

- Burkitt's lymphoma is an aggressive tumour, usually affecting the head and neck, but also arising from several abdominal organs. Progression in size of Burkitt's lymphoma can be rapid, given its 48-hour doubling time. Head tumours usually present with extensive involvement, with swelling of the jaw and tooth loosening, gum expansion, bleeding, ulceration and exophthalmos.

- The majority of non-Burkitt B-cell lymphomas are disseminated at diagnosis, often with diffuse abdominal disease.

- T-cell NHL presents with thymic and/or nodal involvement, often with signs of airway or superior vena cava obstruction.

Diagnosis
The diagnosis is frequently suggested on clinical examination (e.g. classical features of Burkitt's or T-cell lymphoma). The diagnosis is supported by appropriate imaging (X-ray, ultrasound). Bone-marrow aspiration and lumbar puncture should be performed. Biopsy is necessary if the diagnosis cannot be made on a bone-marrow aspiration.
Treatment
Burkitt’s lymphoma
This is an extremely chemosensitive tumour, and a high remission rate can be achieved with a single course of cyclophosphamide. Repeated courses of cyclophosphamide may be successful in some early-stage patients, but the success of therapy is further improved, particularly for patients with advanced disease, by the use of multi-agent chemotherapy using combinations such as COMP (cyclophosphamide, vincristine, methotrexate and prednisolone), for example, given over a 6-month period. This should be accompanied by administration of intrathecal methotrexate and hydrocortisone. As with acute lymphoblastic leukaemia, biochemical disturbance as a result of rapid tumour lysis is a major risk, and intravenous fluids, allopurinol and close monitoring of renal function are required.

Non-Burkitt B-cell NHL
Repeated courses of multi-agent chemotherapy with COMP or CHOP (cyclophosphamide, Adriamycin, vincristine and prednisolone) are often successful, especially for early-stage disease. For advanced disease, more intensive regimens such as the French LMB protocols may result in a high success rate, although the toxicity of these regimens is potentially high.

T-cell NHL
In contrast to B-cell NHL, therapy for T-cell disease is usually based on leukaemia-type therapy (with intensification modules and continuing chemotherapy). CNS-directed therapy with cranial irradiation or moderate-dose methotrexate with ongoing intrathecal methotrexate should be used.

Prognosis
Burkitt’s lymphoma
The prognosis varies according to the stage of disease, although overall at least 85–90% of patients will be cured with modern therapy in well-resourced countries. Where ability to give chemotherapy is restricted, simpler therapy can yield 50–60% survival rates. However, CNS disease is associated with a poor outcome.

Non-Burkitt B-cell NHL
The prognosis is poorer than with Burkitt’s lymphoma, and depends on the stage of disease and the intensity of treatment. In low-stage disease a survival of at least 75% is expected. The prognosis is worse with extensive disease, particularly with bone-marrow or CNS involvement.

T-cell NHL
With modern leukaemia-type therapy, survival rates are around 65–70% or higher.

Hodgkin’s lymphoma
Presentation
Unlike NHL, Hodgkin’s lymphoma tends to be confined to the lymph nodes or spleen, although spread to other sites, such as the lungs, liver and bone, may occur. Most children present with a primary painless neck mass, although any nodal group may be involved. Patients are staged according to the Ann Arbor system, which incorporates an A and B designation for the absence or presence, respectively, of fever, night sweats and weight loss.

Diagnosis
Diagnosis is generally made by lymph-node biopsy. Essential staging investigations include chest X-ray and abdominal ultrasound. Bone-marrow aspirate and trephine should be performed on patients with evidence of advanced disease.

Treatment
In the past, radiotherapy was widely utilised, often using extensive radiation fields (e.g. the ‘mantle’ or ‘inverted Y’ techniques) to cover all known sites of disease. Radiation is still used in localised disease, but generally chemotherapy is preferred for most patients, using regimens such as CHVPP (chlorambucil, vinblastine, procarbazine and prednisolone) or MVPP (with nitrogen mustard replacing chlorambucil). Six to eight courses are given every month. Such chemotherapy may be given on an outpatient basis, and is relatively non-toxic, although the risk of infertility in boys is high. Some of the toxicity can be avoided by alternating CHVPP or MVPP with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), although this may have the potential to cause cardiotoxicity.

Prognosis
Hodgkin’s lymphoma generally carries a good prognosis. For patients with stage I and II tumours, over 80% are expected to be cured. Even with advanced disease, over 50% of patients would be expected to survive.

Brain tumours
These are a heterogeneous collection of several tumours that together represent around 25% of all childhood cancer patients in Europe and North America. The proportion in resource-limited countries is much lower, at least partly due to under-diagnosis as a result of limited availability of neuroimaging (CT and MRI), neurosurgery and neuropathology.

Presentation
About 60% of childhood brain tumours arise in the posterior fossa, and usually present with signs and symptoms of raised intracranial pressure due to obstruction of CSF pathways. A variety of other presenting features may occur, depending on the site and rate of progression of the tumour. These include irritability, behavioural disturbance, cranial nerve palsies, long tract signs (particularly truncal ataxia), endocrine abnormalities, visual disturbance and seizures.

Diagnosis
Modern imaging with CT scanning, or preferably MRI (if available) has revolutionised the management of brain tumours, and should be performed if CNS tumours are suspected. Some tumours have characteristic appearances on imaging (e.g. diffuse brainstem glioma and optic nerve glioma), although most tumours require histological confirmation. Imaging of the spine and examination of the spinal fluid is required to assess for CNS spread in high-grade bone tumours (e.g. medulloblastomas, high-grade gliomas).

Treatment
For most tumours, modern neurosurgery (see Section 5.16.K) is vital to management. Prompt relief of raised intracranial pressure is often required, and may be
life-saving. This is achieved with dexamethasone, which when used peri-operatively has also been shown to significantly reduce operative mortality.

Surgery may also be required to relieve hydrocephalus (e.g. with ventricular peritoneal shunting). The aim of definitive surgery is to provide a histological diagnosis and usually to shrink the tumour as much as possible. Tumour resection is required for most tumours, including all posterior fossa tumours (except the brainstem), tumours of the cerebral hemispheres and craniopharyngiomas. Some tumour types may be cured with surgery alone (e.g. cerebellar low-grade astrocytoma), although others (e.g. medulloblastoma) require adjuvant radiotherapy.

Generally a large dose of radiotherapy is given to the tumour bed, while some tumours (e.g. medulloblastoma) require whole CNS radiotherapy due to the high risk of CSF dissemination. To date chemotherapy has had relatively little impact on the treatment of brain tumours, although it can be used to try to delay radiotherapy in the very young.

Radiotherapy to the whole brain and spine has a very high risk of sequelae, particularly in young children. These include neuropsychological disability, growth failure (growth hormone deficiency and poor spinal growth) and hypothyroidism.

The following is a brief guide to the management and prognosis of individual tumour types.

**Medulloblastoma**

**Prognosis**
The prognosis is around 60% for children with non-metastatic disease and 30% for those with disseminated disease. Children with medulloblastoma aged less than 3 years have a much worse prognosis than older children. Radiotherapy may be curative, but most centres do not advocate this, as radiation therapy to the developing brain is associated with a very high incidence of severe handicap. Prolonged chemotherapy can be used to try to delay radiotherapy, but even then survival is only around 20%.

**Cerebellar low-grade astrocytoma**

**Treatment**
Surgical resection is performed, and post-operative radiotherapy is not required if the resection has been complete.

**Prognosis**
The prognosis is at least 80% following total resection.

**Supratentorial low-grade astrocytoma**

**Treatment**
Surgical resection is performed for accessible lesions, although many of these tumours (e.g. those involving the hypothalamus and optic pathways) are not fully resectable. In these cases, focal radiotherapy should generally be given, particularly in patients with progressive disease.

**Prognosis**
The prognosis is variable, mainly depending on the site of the tumour.

**High-grade glioma**

**Treatment**
Surgical resection (as complete as possible) is performed, and post-operative focal radiotherapy is required.

**Ependymoma**

**Treatment**
Surgical resection (as complete as possible) is performed, and post-operative focal radiotherapy is required.

**Prognosis**
The prognosis is around 30–50%, mainly depending on the degree of tumour resection.

**Brainstem glioma**

**Treatment**
Focal exophytic tumours are treated with surgery followed by focal radiotherapy.

**Prognosis**
The prognosis is around 30–50%, mainly depending on the degree of tumour resection.

**Diffuse (malignant) brainstem gliomas**

**Treatment**
Palliative radiotherapy may possibly be used.

**Prognosis**
These tumours are fatal (less than 5% survival).

**Craniopharyngioma**

**Treatment**
Surgical resection is performed, although there is a high peri-operative mortality rate. Radiotherapy is sometimes used for recurrent tumours.

**Prognosis**
The prognosis is variable. All patients suffer from panhypopituitarism, which requires hormone replacement therapy.

**Neuroblastoma**

This biologically unusual tumour can arise from any part of the sympathetic nervous system, although around 60% originate from the adrenal gland. Localised stage I and stage II disease and the unique stage IV S disease of infancy have a good outlook, although for the 80% of patients who present with advanced tumours the prognosis is very poor.

**Presentation**
A large proportion of patients present with an abdominal (adrenal) or pelvic mass, often extending across the midline. Para-spinal masses that extend into the spinal canal causing cord compression, and thoracic primaries that cause airway obstruction, also occur. Most patients (65%) present with metastatic disease that often causes bone pain and limp, with marrow infiltration mimicking leukaemia, skin infiltration or orbital masses causing proptosis or peri-orbital bruising.

**Diagnosis**
Ultrasound of the abdomen (or CT of the abdomen, if
Section 5.14

The diagnosis may be confused with the abdominal dis- mass, such as neuroblastoma and splenomegaly associ- associated with malaria or haemoglobinopathy.

**Diagnosis**

The presence of a renal tumour can be confirmed by ultrasonography, which should also assess the presence of inferior vena cava involvement. Alternatively, intravenous urogram (with injection into the feet to perform a cavagram) can be used, as can CT scan (with contrast) if available. The diagnosis can be made on the basis of clinical presentation and imaging findings. Histopathological confir- mation is not mandatory, but is advisable, particularly in those under 6 months of age. A chest X-ray should look for evidence of lung metastases.

**Treatment**

The SIOP approach of up-front chemotherapy (4 weeks of vincristine and actinomycin D for non-metastatic tumours, and 6 weeks of the two drugs plus Adriamycin for meta- static tumours) followed by surgery is more suited to resource-limited countries. The duration and type of further chemotherapy after surgery depend on the local staging of the tumour and the response to initial treatment. For stage I tumours, further vincristine and actinomycin may be given for 4 weeks or 6 months depending on the histological response. For stage II disease, vincristine and actinomycin should be given for 6 months, a regimen which may also be used for stage III tumours with the possible addition of radiotherapy. For stage IV tumours and for so-called ‘unfavourable (anaplastic)’ histology groups, all three drugs should be given for 6–12 months. Radiotherapy to the abdomen should only be given if residual bulky disease is present after surgery. Patients with pulmonary metastases at diagnosis should receive lung radiation (20 Gy), particular- ly if the lung metastases persist after pre-nephrectomy chemotherapy.

**Prognosis**

For patients with stage I and II tumours (favourable histol- ogy), at least 80% should be cured. Stage III and IV tumours have survival rates of around 60–70% and 50–60%, respec- tively. However, the prognosis is poor for patients with unfavourable histology.

**Liver tumours**

The two main types of liver tumour are hepatoblastoma and hepatocellular carcinoma (HCC). Although both are rare in Europe and North America, in several parts of the world, such as East Africa and New Guinea, HCC is a relatively frequent childhood malignancy. In children with HCC, as in adults, there is a clear and possibly causative association with hepatitis B infection both in the presence and in the absence of coexisting cirrhosis.

**Presentation**

Hepatoblastoma generally presents in children under 3 years of age, whereas HCC is seen in older children and adolescents. The presentation in both hepatoblastoma and HCC is similar, with most patients presenting with abdomi- nal distension and a right upper quadrant mass. Additional features, particularly for HCC, include abdominal pain, nausea, weight loss, anorexia and jaundice. Features of underlying chronic liver disease may be present with HCC.
Diagnosis
The liver mass may be seen on ultrasound examination of the abdomen and CT scan (if available). The diagnosis should be confirmed by biopsy. Alpha-fetoprotein levels are elevated in nearly all cases of hepatoblastoma and in about 65% of cases of HCC. In these patients, the alpha-fetoprotein level may be used as a tumour marker to monitor progress. A chest X-ray should be taken to look for evidence of lung metastases.

Treatment and prognosis
Surgical excision is the definitive treatment for both tumours. Hepatoblastoma is a chemosensitive tumour, and pre-operative chemotherapy significantly improves the prognosis, facilitating surgical excision and the control of distant metastases. The most active agents are doxorubicin and cisplatin. Cisplatin monotherapy along with surgery is significant and pre-operative chemotherapy significantly improves the prognosis for patients with these tumours. The prognosis for these patients is around 50%, although the surgery is difficult and carries significant risks.

The overall prognosis for HCC is very poor. This disease is much less responsive to chemotherapy than hepatoblastoma, and unfortunately these tumours are often multi-centric or extensive invasiveness, making resection possible in less than 30% of patients. Of these cases, only one-third survive long term.

Soft-tissue sarcomas
These tumours arise from undifferentiated embryonic tissue. The most common of these is rhabdomyosarcoma, a tumour of striated muscle. Rhabdomyosarcomas can arise anywhere where there is such striated muscle or embryonic remnants thereof, but the most common sites include the orbit, head and neck (including the nasopharynx), the genito-urinary tract in both boys and girls, and the extremities. Two main histological types are recognised, namely the more common embryonal type, and the less common alveolar type, which generally carries a much poorer prognosis.

Presentation
Most rhabdomyosarcomas present as diffuse masses, but orbital lesions generally present with proptosis and diplopia, and nasopharyngeal lesions often present with nasal obstruction, epistaxis and pain. At least 25% of sarcomas will have metastases at diagnosis, most commonly to the lungs and lymph nodes.

Diagnosis
Histological confirmation is required by biopsy or excision of the primary tumour. Initial radical surgery should not be performed. Primary tumours should be defined by CT scan (if available) (this is particularly important for head and neck and orbital tumours), although other techniques such as tomography and ultrasound examination may be useful. For head and neck lesions, lumbar puncture with careful CSF examination is required. Parameningeal tumours are those in which CSF invasion is demonstrated or possible due to the proximity of the tumour to the meninges based on CT scanning (if available). Metastatic surveillance includes chest X-ray, abdominal ultrasound examination or CT scanning (if available), and bilateral bone-marrow aspiration.

Treatment
In view of the high rate of local and distal dissemination, chemotherapy is required for all patients. The VAC regimen (vincristine, actinomycin D and cyclophosphamide, four to nine courses), is most commonly used. In more recently devised regimens, ifosfamide has replaced cyclophosphamide (IVA ifosfamide, actinomycin D and vincristine), although ifosfamide carries a far greater risk of side effects, including haemorrhagic cystitis and nephropathy. Unless the tumour can be completely excised, local therapy should generally be performed after cytoreductive chemotherapy (e.g., after three to six courses). Surgery is the usual local therapy for sites such as the extremities and genito-urinary system. For head and neck tumours, surgical excision of the primary tumour is usually extremely difficult, and radiotherapy should be considered.

Radiotherapy is the treatment of choice following chemotherapy for orbital tumours.

For parameningeal tumours, whole CNS radiotherapy and intrathecal methotrexate is advised.

Prognosis
For completely resected tumours, the prognosis is good, with at least 70% survival. For those with regional disease the prognosis is less good, with about 40–50% survival. Survival is particularly poor for patients with metastatic disease (less than 20%) and for parameningeal tumours, so careful consideration is needed before embarking on a curative treatment for these categories. Alveolar histology confers a significantly worse prognosis for all stages and sites.

Kaposi's sarcoma
This tumour has become a major healthcare problem in areas affected by the HIV pandemic. Younger children tend to present with disseminated suppurative lymphadenopathy and conjunctival disease, whereas in older children, skin nodules predominate.

Treatment
Radiotherapy may control locally aggressive tumours. Kaposi's sarcoma may also respond to chemotherapy, including agents such as vincristine, actinomycin D and DTIC.

Bone sarcomas
About 50% of all sarcomas occur in the bone, the predominant types being osteosarcoma and Ewing's sarcoma.

Presentation
A bone sarcoma usually presents as a painful mass which may be hot and tender, mimicking osteomyelitis. Around 95% of osteosarcomas arise in long bones, and about 50% occur in the upper tibia or lower femur. Around 50% of Ewing's sarcomas occur in long bones, usually in the shaft, with the remainder occurring in the pelvis, shoulder, skull and vertebrae. About 20% of patients with Ewing's sarcoma and 10–20% of those with osteosarcoma have metastatic disease at diagnosis.

Diagnosis
The diagnosis is suggested on plain X-ray with osteosarcoma showing bony expansion with osteoblastic and/or lytic activity. Ewing's sarcoma generally appears as an
ill-defined lytic lesion. Diagnosis is confirmed with biopsy, preferably using an open technique under direct vision. Chest X-ray or CT of the chest (if available) is used to detect lung metastases, the lung being the most common metastatic site for both tumours.

**Treatment and prognosis for Ewing’s sarcoma**

Chemotherapy using vincristine, actinomycin D, Adriamycin and cyclophosphamide should be given to control both local and metastatic disease. Local therapy with wide surgical excision should be performed. If this is not possible, high-dose radiotherapy (e.g. 45–50 Gy) should be given, although for long bone sites amputation may be more appropriate.

The overall prognosis is around 40%, but depends on the site and the adequacy of local tumour control. The prognosis for patients with metastatic disease is very poor.

**Treatment and prognosis for osteosarcoma**

Amputation of the long bone containing the primary tumour only gives a cure rate of about 20%. Chemotherapy either before or after local therapy has increased survival to around 50% for non-metastatic patients. Six courses of cisplatinum and doxorubicin (three pre- and three post-surgery) may be feasible in many resource-limited countries. The current American and European protocols use a combination of cisplatinum, doxorubicin and high-dose methotrexate.

Local control is either with amputation or (if available) with tumour resection and endoprosthetic bone replacement or rotation plasty.

**Germ-cell tumours (GCTs)**

Around 3% of tumours in children are GCTs, which are seen mainly in infants and adolescents. They include benign (mature and immature teratoma) and malignant (e.g. yolk sac tumour, germinoma) subtypes.

**Presentation**

In infancy, the usual presentation is a pelvic or sacrococcygeal mass often noticed after birth (or sometimes prior to birth on antenatal scans). In adolescents, GCTs present either as an enlarged mass in the gonads (testicular enlargement or a pelvic mass arising from the ovary) or in the mediastinum with signs of airway or superior vena cava obstruction.

**Diagnosis**

Initial assessment is by X-ray and CT (if available) for mediastinal masses, and ultrasound examination for abdominal and pelvic masses. Assessment of serum alpha-fetoprotein and β-human chorionic gonadotrophin levels can assist in diagnosis and monitoring of the disease.

**Treatment and prognosis**

For mature and immature teratoma as well as malignant GCTs Stage I, surgery alone can be sufficient, with a survival of more than 90%. For more advanced malignant GCTs, four to six cycles of platinum-compound-based chemotherapy in addition to surgery can achieve a survival of around 70%.

**Palliative chemotherapy and radiotherapy**

As stated above, if curative treatment is not possible or has failed, the focus must then be on providing palliative care, particularly symptom control, including adequate pain relief (see Section 1.15 and Section 1.16). Occasionally, palliative chemotherapy may be appropriate, such as the use of steroids with or without vincristine in relapse or incurable acute lymphoblastic leukaemia and lymphomas. Steroids are also used in the control of symptoms such as headache due to certain brain tumours. Palliative radiotherapy may be useful for treating bone pain caused by tumour infiltration (e.g. in neuroblastoma) and by bone tumours themselves, and may be helpful in controlling symptoms caused by compression of nerves (including the spinal cord) or other vital organs.

**Conclusion**

Although in many resource-limited countries the curative treatment of children with cancer may not be achievable currently, children will present with often distressing symptoms, which we must strive to alleviate and palliate. As infections in particular become more controllable in resource-limited settings, cancer starts to emerge as a major cause of morbidity and mortality. Some allocation of resources becomes inevitable, and as paediatric oncology requires a multidisciplinary approach, thinking about and acting on the problems faced by children with cancer can lead to improvement of care for all children in hospital.

**Organisations working to advance paediatric oncology around the world**

World Child Cancer (www.worldchildcancer.org): currently working in Mexico, Colombia, Cameroon, Ghana, Malawi, Mozambique, Bangladesh, the Philippines and the Pacific Islands.

International Confederation of Child Cancer Parent Organisations (ICCCPO) (http://icccpo.org/index.cfm): an international network of parent support groups and survivor networks that provide psychosocial care for children and their families.


St Jude Children’s Research Hospital based in the USA (www.stjude.org): a paediatric treatment and research facility. It develops advanced cures for and means of prevention of paediatric cancer through research and treatment. It is involved worldwide in supporting projects through its International Outreach programme, including twinning. It includes the following:

- Cure4kids (www.cure4kids.org): a free online education and collaboration resource dedicated to supporting the care of children with cancer and other catastrophic diseases worldwide.
- Pond4kids (www.pond4kids.org): provides a free database collecting epidemiological data and including a cancer registry.

International Society of Pediatric Oncology (SIOP) (Société Internationale d’Oncologie Pédiatrique) (www.siop-online.org): this organisation has a special focus on paediatric oncology in developing countries (PODC). Some of the relevant working groups include the following:

- twinning, collaboration and support
- graduated-intensity treatment guidelines
- providing advice and support to low-income countries on the most appropriate protocols to use based on the resources available, including financial resources,
training, supportive care, monitoring and investigations, and infection control

- abandonment of treatment
- palliative care
- essential drugs.

International Network for Cancer Treatment and Research (INCTR) (www.inctr.org): this organisation is dedicated to helping to build capacity for cancer research and treatment in developing countries, and it focuses on palliative care, cancer registration, research, training, nursing and pathology services.

Union for International Cancer Control (UICC) World Cancer Congress (www.uicc.org): this organisation focuses on raising awareness, education, and developing a global network of influence.

Franco-African Pediatric Oncology Group (GFAOP) (www.gfaop.org): this runs projects for children with cancer in Africa, including a recent Wilms' tumour protocol trial.

Further reading

5.15 Eye disorders

BOX 5.15.1 Minimum standards
- Vitamin A.
- Ocular antibiotics.
- Fluorescein.
- Ocular steroids.
- Aciclovir.
- Occlusive pads.
- Glasses and other visual aids.

Introduction
Two of the most important eye disorders in children in resource-limited countries are vitamin A deficiency (xerophthalmia) and trachoma. Both of these can be prevented by appropriate action in the community, which is cheap and very effective for both disorders.

Eye examination and diagnosis: basic equipment
- Vision-testing chart. Show only one letter at a time and get the child to match the letter on a chart (see Figure 5.15.1).
- A bright torch light which can give a focused beam of light.
- An ophthalmoscope:
  - The ophthalmoscope is mainly used for examination of the ocular fundus (i.e. the retina, choroid and optic nerve).
  - It can also be used for examination of the ocular media (i.e. the cornea, lens, and aqueous and vitreous humour). Dial a small positive lens (about +2 or +3) in the ophthalmoscope, and hold it about 20 cm from the patient’s eye. In the healthy eye with a dilated pupil, there will be a clear red glow of light reflected from the retina, called the red reflex, and any opacity in the cornea, lens or aqueous or vitreous humour will appear as a black shadow against this red reflex.
  - The ophthalmoscope can also be used to act like a magnifying lens to examine in detail the conjunctiva, sclera, iris, etc. To do this a very strong positive lens (about +20) is dialled in the ophthalmoscope, which is then held very close to the patient’s eye.
  - An ultra-low-cost ophthalmoscope, otoscope and loupe which is solar powered is now available (www.arclightscope.com).
- Mydriatic drops:
  - Cyclopentolate 1%, or cyclopentolate 0.5% in children less than 6 months old. Atropine 0.5%
Ointment is very long-acting. It can be given to parents to put into the eyes for 2 days prior to a clinic appointment, especially if an initial attempt at refraction and fundus examination has been unsuccessful because of the child becoming distressed when drops were used in the clinic.

- **Local anaesthetic drops:**
  - Proxymetacaine 0.5% is ideal for children because it stings less than other topical anaesthetic drops.
  - Tetracaine 0.5% or 1% is an alternative which is less quickly degraded when not stored in the refrigerator.

- **Sterile fluorescein paper strips.**

- **Binocular telescopic magnifying glasses (loupes) are very useful but not essential. Some magnification will be achieved by using a strong pair of reading glasses (+3.00–4.00 DS) perched as far down your nose as possible.**

- **More sophisticated equipment, such as a tonometer for measuring intra-ocular pressure, a slit lamp and a binocular indirect ophthalmoscope, may only be available in a specialist clinic. However, if available, they greatly add to the diagnosis and treatment that can be offered.**

Gaining the confidence and trust of the child is the most important step in a successful eye examination, which should not be painful or unpleasant, except possibly unavoidably when drops are put in the child’s eye. If the child finds it hard to cooperate, examine the parents’ or older siblings’ eyes first to gain the child’s confidence. A general anaesthetic may sometimes be required in small children where a serious eye problem (e.g. retinoblastoma) is suspected.

**FIGURE 5.15.2** Position in which to examine the eye of a young child.

**Three ways of examining the eyes of young children**

Examining the eyes of babies and young children is often difficult. Patience and encouragement are required to gain the confidence of the child. If it is still difficult to get a good view, the following techniques may be helpful:

1. Let the parent cuddle the child as he or she faces backwards over the parent’s shoulder (see Figure 5.15.2), especially if the parent’s anxiety and sense of obligation to restrain the child is adding to the child’s fears. You may then be able to attract the child’s interest in participating in the examination from this secure position.

2. In the case of infants, wrap the baby in a sheet or blanket, with their head on the examiner’s lap, and their body on their mother’s lap (see Figure 5.15.3). Gently hold open their lids with the fingers and thumb of one hand. The other hand is then free to instil any eye drops, or hold a torch or condensing lens. This is probably the best way to get a satisfactory view of the eye, but it also provokes the greatest resentment from the baby.

3. If it is difficult to get drops into the child’s eye, try lying the child flat on their back, create a puddle of drops at the inner canthus, and wait while the child is held facing upwards (see Figure 5.15.4). The child will eventually open their eye, and the medication in the puddle of drops at the inner canthus will then go into the eye.

4. In difficult cases, where a serious eye condition is suspected, it may be necessary to instil a drop of local anaesthetic, and use a speculum to hold open the eyelids. However, this should only be done by an experienced professional in controlled circumstances, and must not be attempted in the face of determined resistance from any but the smallest child.

**FIGURE 5.15.3** Supine posture for eye examination.

**Presenting symptoms of eye disease**

These include the following:

- red, sore, irritable or discharging eyes
- impairment or loss of vision
- squint.

**Red, sore, irritable or discharging eyes**

- A sticky discharge with no redness, normal cornea and apparently normal vision in a child up to the age of 18 months (and occasionally older) is commonly caused by a blocked tear duct. Teach the mother to express the lacrimal sac with firm pressure to the side of the nose at the inner canthus.

- Bilateral sore red irritable eyes are usually caused by conjunctivitis. If the symptom is unilateral the usual cause is an ulcer or injury to the cornea or iritis. Evert the upper eyelid to inspect the upper tarsal conjunctiva. Apply fluorescein stain to the cornea to diagnose an ulcer or identify a foreign body. The green fluorescein dye will stain the ulcer. A foreign body, especially if lodged under the upper lid, may be associated with staining of the cornea.
Acute bacterial conjunctivitis causes a mucopurulent discharge from the conjunctiva and is usually self-limiting, resolving after a few days. Give topical antibiotics as drops or ointment to speed recovery. Acute bacterial conjunctivitis is dangerous in neonates when caused by sexually transmitted disease. The cornea in a neonate is at much greater risk, and neonates produce less tears to wash away bacteria. Treatment is urgent. The WHO-recommended treatment for severe neonatal conjunctivitis is a single IM injection of either ceftriaxone 50 mg/kg (maximum 125 mg) or kanamycin 25 mg/kg (maximum 75 mg) and hourly tetracycline ointment or chloramphenicol drops or ointment.

In presumed gonococcal infection, empirical treatment for possible co-infection with chlamydia—that is, ceftriaxone and erythromycin to prevent chlamydial pneumonia in the baby—should be strongly considered.

In addition, we recommend diagnosis and treatment of the mother for uro-genital disease due to gonococcus and/or chlamydia in order to prevent salpingitis.

Acute viral conjunctivitis is a self-limiting disease that usually lasts for a week or so. Tear secretions are watery rather than mucopurulent. There is no specific treatment, but it is customary to give antibiotic drops.

Vernal conjunctivitis is a chronic allergic conjunctivitis which is very common and causes recurrent severe itching of the eyes. Affected children are usually atopic (i.e. suffer from asthma and eczema). In addition to itchy eyes, there may be redness, watering, lid swelling and a mucus discharge. Typically there are papillae of the conjunctiva under the upper lid. In some cases these can be massive in size and may be associated with corneal ulceration in the upper third of the cornea. There may be nodular swelling and opacity at the corneo-scleral junction (i.e. the limbus). Anti-inflammatory drops such as cromoglycate relieve the symptoms, but in severe cases use topical steroids (e.g. hydrocortisone 1%, betamethasone 0.1%, or dexamethasone 0.1% eye drops). However, prolonged use of topical steroids has a high risk of causing steroid-induced glaucoma.

**Trachoma**

See Section 6.1.M.

**Corneal ulcers**

- Corneal ulcers are usually unilateral. There is usually pain and photophobia. Staining the eye with fluorescein will show the outline of the ulcer.
- Herpes simplex ulcers are typically branched and irregular. Treat by applying aciclovir ointment 3% every 2 hours until the epithelium has healed.
- Bacterial corneal ulcers are more serious and can rapidly progress to destroy the cornea and the eye. They must be treated as an emergency. If possible, first perform a Gram stain and microscopy of tissue scraped with great care from the edge of the ulcer with a scalpel blade. This will often give helpful information about the cause of the ulcer and so make the treatment more specific. Antibiotic drops should be given hourly or 2-hourly for 48 hours and then four times a day. The choice of antibiotic depends on the availability and also the results of the Gram stain. Ofloxacin (0.3%) or ciprofloxacin (0.3%) both have a good spectrum of activity against Gram-positive and Gram-negative bacteria. In most circumstances one of these is the first choice. Concentrated locally made antibiotic drops are very helpful if pre-prepared drops are not available. These can be made up by diluting antibiotic powder for injection in 5 mL of sterile water or 0.9% saline. These home-made eye drops should only be used for 48 hours, and should then be discarded. The following are the recommended strengths: gentamicin 15 mg/mL or amikacin 50 mg/mL for Gram-negative organisms; cefuroxime, cefazidime or cefazolin 50 mg/mL for Gram-positive organisms. If a Gram stain is not possible, two types of drops can be given alternately every hour. Chloramphenicol (0.5%...
drops and 1% ointment) is a cheap and readily available alternative if none of the above are available.

- **Fungal corneal ulcers** are very common in hot humid climates. The branching filaments of the fungus can be identified on a Gram stain. The treatment is unfortunately very difficult because topical antifungal drugs are hard to obtain and the response to treatment is slow. Natamycin is sometimes available as an eye ointment. Econazol, clotrimazol and ketoconazol are all available as skin creams, and it may be necessary to use either these or systemic antifungal agents in difficult cases.

**Iritis**

Iritis is a less common cause of acute red eye. The pupil is constricted and irregular and there are often deposits known as keratic precipitates on the posterior surface of the cornea. Give intensive topical steroids hourly (prednisolone, betamethasone or dexamethasone drops) and keep the pupil dilated with mydriatics (atropine 0.5–1% twice daily).

**Vitamin A deficiency (xerophthalmia)**

Xerophthalmia usually only affects malnourished children (see Section 5.10.A on vitamin A deficiency).

- In the early stages, the conjunctiva appears dry and wrinkled, but this is not easy to detect.
- As the disease progresses, the cornea also appears dry and then shows signs of corneal ulceration. Ulcers may progress very rapidly to destroy the entire cornea. Eventually the whole eye shrinks or the child may be left with a dense corneal scar.
- In communities where vitamin A deficiency is common, older children are frequently found with corneal scars dating from early childhood. In most cases malnutrition is a chronic problem, and the disease is precipitated by an acute infective illness, which is nearly always measles. Xerophthalmia and measles are particularly important because these ulcers are very frequently bilateral, whereas most other causes of corneal ulceration and scarring usually only affect one eye.

There are three other factors which may precipitate corneal destruction in xerophthalmia:

- **Herpes simplex**: severe and often bilateral herpes simplex ulcers may develop.
- **Traditional eye medicines**: application of toxic substances may cause damage and chemical burns to the conjunctiva and cornea.
- **Exposure**: sick and malnourished children may lie with their eyes open and exposed, so the cornea is not protected by the eyelid.

**Management**

- Apply topical antibiotics and ensure adequate closure of the eyelids. Give local aciclovir if herpes simplex is suspected. Give topical steroids (hydrocortisone 1% or betamethasone 0.1% eye drops or ointment) if a clear history of toxic traditional eye medication is obtained.
- Give vitamin A capsules (200 000 IU/day in children over 1 year of age, 100 000 IU/day for those aged 6–12 months, and 50 000 IU/day for those under 6 months, for 2 days, then another dose in 2 weeks). Systemic antibiotics and rehydration may also be indicated.

**The child who cannot see or who cannot see well**

If only one eye is affected, the child and their family may not be aware of the problem. However, a child with poor vision in one eye only will often develop a squint in that eye (see below).

**Cornea**

Bilateral corneal scarring that is severe enough to cause serious visual impairment is most commonly a consequence of xerophthalmia and measles (both of which are preventable, by giving vitamin A and immunisation). Careful refraction may improve the sight. An optical iridectomy or a corneal graft may also help.

**Cataract**

Cataract is the most common congenital ocular abnormality. It may be present at birth, or may develop in early childhood. It may be complete, presenting as a dense white opacity in the pupil, or be incomplete and less obvious. There will be a normal pupillary light reflex, so that the pupil constricts when a light is shone into the eye. In other causes of a white appearance of the pupil, including retinoblastoma, the reaction of the pupil to a light shone in the affected eye is usually lost.

Congenital cataracts require early expert surgical treatment, otherwise the child will develop nystagmus, which will prevent the development of good vision.

**Congenital glaucoma**

Congenital glaucoma usually presents with photophobia, a hazy cornea and often enlargement of the eye called buphthalmos. Urgent specialist surgery is required to control intra-ocular pressure and save what sight is available, otherwise the child will become irreversibly blind.

**Retinal diseases**

- **Retinopathy of prematurity** is the commonest cause of acquired retinal disease. It is associated with excessive oxygen given to premature babies (see Section 3.4). It is now particularly common in middle-income countries, such as Latin America, Eastern Europe, the Middle East and Asia. In countries with highly developed intensive neonatal care services it is uncommon, and in resource-limited countries most very premature babies do not survive.
- **Retinitis pigmentosa** is the most common congenital disorder of the retina. It affects the peripheral retina and causes night blindness.
- **Vitamin A deficiency** also causes night blindness by affecting rod photoreceptors in the peripheral retina.
- **Retinoblastoma** is important because it is one of the few eye diseases that can be fatal in a child if not properly treated. The tumour can present in one eye or in both eyes as a white mass in the pupil, a squint, a painful inflamed eye or a mass in the orbit. If the eye is removed before the tumour has spread, the child’s life may be saved.

**Optic nerve**

Optic nerve hypoplasia or optic atrophy may be congenital. It may also be acquired following meningitis, or rarely following an infection such as typhoid or measles. There is no effective treatment.
Cortical blindness
Cortical blindness occurs following severe brain insults such as meningitis or cerebral malaria. The pupillary light reflex is normal, but the child cannot see. In some cases the vision gradually improves with time.

Management of blindness
- In the majority of cases, management is with rehabilitation and education rather than medical treatment.
- Cataracts and glaucoma in particular must be recognised and diagnosed early to preserve and save as much sight as possible.
- Most blind children have some sight and should have an opportunity to use low-cost visual aids. Simple aids, manufactured locally, may enable children to read and so transform their opportunities for education. These aids may consist of a strongly positive lens worn as spectacles or used as a stand magnifier.

Squint
Squint, or misalignment of the eyes (also known as strabismus), is common in children. When assessing a child for squint, consider the following:
- Does the child really have a squint? Look at the corneal light reflexes. If the reflection of light is in the same position in each eye, there is no squint, but if one is asymmetrical then that eye is squinting.
- Does the squint alternate? Cover the non-squinting eye. If the squinting eye moves to look at the light or object being held, and if the child can use either eye to fixate, then the squint alternates. This means that the vision is fairly good in each eye, and the treatment of the squint is purely cosmetic.
- If the squint does not alternate, is there any disease in the squinting eye? Test the pupillary light reflex and then dilate the pupils with mydriatic eye drops. Look for diseases such as cataract, retinal scar and in particular retinoblastoma. Refer the child for treatment if you find cataract or an abnormality in the retina. Treatment for retinoblastoma is urgent enucleation.
- Is there a refractive error, such as hypermetropia (long sight) or myopia (short sight)? This requires refraction tests.
- Is the squinting eye amblyopic (i.e. is there poor vision in the squinting eye)? At first, squints cause double vision (diplopia), which the child finds confusing. As time passes, the visual acuity in the squinting eye becomes permanently suppressed. The treatment for amblyopia is to force the child to use the squinting eye by wearing an occlusive patch over the healthy eye for about 1 hour a day for several weeks.

Amblyopia only develops in young children, and it can only be treated in children under 5 years of age. Surgery may be required, but should not be considered until eye disease and refractive errors have been excluded and amblyopia has been treated.