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>Other inflammatory conditions (coeliac disease, inflammatory bowel disease)</td>
</tr>
<tr>
<td>Neurological (myasthenia gravis, spinal muscular atrophy)</td>
<td></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).
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 rota.

- 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 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 < 50 × 10^9/litre, may 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 (CMOP) chemotherapy with intrathecal methotrexate and hydrocortisone.

- **Non-Burkitt/non-Hodgkin’s lymphoma:** early stage – surgery plus CMOP 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, ultrasound; 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>
<tr>
<th>TABLE 5.14.1 General side effects of chemotherapy</th>
</tr>
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<tbody>
<tr>
<td><strong>Acute effects</strong></td>
</tr>
<tr>
<td>Bone-marrow suppression</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Anaemia</td>
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<tr>
<td>Nausea and vomiting</td>
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<tr>
<td>Mucositis</td>
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<tr>
<td>Alopecia</td>
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<tr>
<td>Fatigue and cachexia</td>
</tr>
<tr>
<td>Tumour lysis syndrome</td>
</tr>
</tbody>
</table>

| Late effects                                  |
| Infertility                                   |
| Secondary malignancy                          |

| TABLE 5.14.2 Specific side effects of chemotherapy |
|-----------------------------------|-----------------------------------------------|
| **Neurotoxicity**                  | Vincristine (muscle weakness due to peripheral neuropathy, constipation, rarely encephalopathy) |
| **Cardiomyopathy**                 | Doxorubicin/daunorubicin                      |
| **Respiratory system**             | Bleomycin                                     |
| **Urinary tract**                  | Cisplatin (renal), ifosfamide (renal and bladder), cyclophosphamide (bladder) |
| **Liver**                          | Thioguanine, actinomycin D                    |
| **Hearing**                        | Cisplatin                                     |
| **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 $< 1.0 \times 10^9$/litre, and particularly when it is $< 0.2 \times 10^9$/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 $< 1.0 \times 10^9$/litre who develop fever (e.g. $> 38^\circ$C for 2 hours or $> 38.5^\circ$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 amphoterin, 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 $> 40 \times 10^9$/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).
- **5HT 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 flucinazole 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 nausea 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 × 10⁹/litre, hepatosplenomegaly or mediastinal mass, or high LDH).
- Intravenous hydration with potassium-free fluids, at least 2.5–3.0 litres/m²/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/m² 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).
Presentation

This accounts for 15–20% of acute leukaemias in children.

Diagnosis

See above section on acute lymphoblastic leukaemia.

Treatment

This is less successful than for acute lymphoblastic leukaemia. Induction therapy is based on 8–10 days of intensive chemotherapy with drugs such as daunorubicin, etoposide, thioguanine and cytosine. Remission rates of over 80% can be achieved, but these regimens are associated with severe and prolonged myelosuppression, with a significant risk of toxic death. This risk should be carefully considered before curative therapy is attempted. Consolidation therapy is again based on intensive and life-threatening chemotherapy. The risk of CNS relapse is less than with acute lymphoblastic leukaemia. Lumbar puncture with triple intrathecal chemotherapy (methotrexate, hydrocortisone and cytosine) should be given with each course of chemotherapy.

Prognosis

Less than 50% of these children will be expected to survive long term, with a high risk of toxic death following intensive chemotherapy.

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%.

**Supratentorial 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.

**Ependymoma**

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

**Brainstem glioma**

**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.

**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 abdominopelvic mass, often extending across the midline. Paraspinal 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
available), chest X-ray (or CT of the chest for thoracic tumours, if available), abdominal X-ray (calcification is often a feature of primary tumours), 24-hour urine collection or spot urine sample for catecholamine metabolites (secreted in 85% of cases), bone-marrow aspirate and trephine (bilateral) are all helpful. MIBG scan and technetium bone scan are performed to investigate metastasis to the bones. Although the diagnosis can be made without tumour biopsy for patients with classic features of stage IV disease, histological confirmation is required for localised tumours and for advanced disease where the diagnosis is in doubt.

Treatment and prognosis
Patients with stage I and II disease should be treated with surgical excision, which if complete is associated with an 80% or higher survival rate. For stage III patients, the prognosis is around 40%, with treatment including multi-agent chemotherapy with drugs such as cyclophosphamide, vincristine, Adriamycin, etoposide and platinum, followed by surgical excision of the tumour. Stage IV disease has a very poor prognosis, and it is essential to provide palliative care to reduce the suffering of these patients.

Retinoblastoma
Although rare in many countries, retinoblastoma is a common paediatric cancer in many areas, including sub-Saharan Africa, Pakistan and India. Two forms are identified, namely an autosomal-dominant heritable form that may affect one or both eyes, and a sporadic (non-heritable) form that is always unilateral.

Presentation
Most children present within the first few years of life with a white mass in the pupil or with a squint. In patients with a family history, routine surveillance may detect an early lesion. Delayed presentation may result in a protruding fungating orbital mass.

Treatment and prognosis
Enucleation of the involved eye is the standard therapy, and is curative in about 75% of patients with localised disease. Very small tumours may also be effectively treated with a cobalt plaque, local irradiation, light coagulation or cryotherapy. External beam radiotherapy may be curative in early cases, but cataract formation usually results. Extensive spread outside the orbit is usually fatal. Relatively simple chemotherapy (e.g. with carboplatin, vincristine and etoposide) appears to be effective in reducing large tumours, sometimes facilitating preservation of vision and possibly preventing metastatic spread.

Wilms’ tumour (nephroblastoma)
This tumour occurs in nearly all parts of the world, and is one of the most curable of all childhood cancers. Approximately three out of four cases occur in children under 5 years of age.

Presentation
Most patients present with a large and generally painless flank mass with or without haematuria and hypertension. The diagnosis may be confused with the abdominal distension associated with malnutrition and with other flank masses, such as neuroblastoma and splenomegaly 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 confirmation 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 metastatic 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 irradiation (20 Gy), particularly if the lung metastases persist after pre-nephrectomy chemotherapy.

Prognosis
For patients with stage I and II tumours (favourable histology), at least 80% should be cured. Stage III and IV tumours have survival rates of around 60–70% and 50–60%, respectively. 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 abdominal 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 recommended for localised and non-metastatic tumours. The prognosis for patients with these tumours 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 extensively invasive, 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 sacroccygeal 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 ß-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.


**Further reading**


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### 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%

![FIGURE 5.15.1 Eye testing.](image-url)